QATAR UNIVERSITY

COLLEGE OF MEDICINE

METABOLIC CHANGES AFTER SURGICAL SUBCUTANEOUS FAT REMOVAL

BY

SAIFEDDIN MOH'D AHMAD BADRAN

A Dissertation submitted to

the College of Medicine

in partial fulfillment of the requirements for the degree of

Doctorate in Clinical Sciences

June 2023

COMMITTEE PAGE

The members of the Committee approve the Dissertation of
Saifeddin Moh'd Ahmad Badran defended on 29/05/2023

Prof. Suhail A. Doi
Thesis/Dissertation Supervisor

Prof. Abdella M. Habib
Committee Member

Prof. Abdul- Badi Abou- Samra
Committee Member

Prof. Moustapha Hamdi
Committee Member

Approved:

Marwan Abu Hijleh, Acting Dean of College of Medicine

ABSTRACT

BADRAN, SAIFEDDIN, M., Doctorate: June: 2023, Doctorate in Clinical Sciences

Title: Metabolic Changes after Surgical Subcutaneous Fat Removal

Supervisor of Dissertation: Suhail, A., Doi.

Background: There is increasing demand for both surgical (SSFR) and non-surgical (NSSFR) subcutaneous fat removal procedures for achieving immediate improvements in physical appearance. However, their metabolic effects remain unclear.

Aims: Firstly, to review the current state of knowledge on the metabolic changes after SSFR and identify any literature gaps. Secondly, to examine the magnitude and sustainability of these changes and explore the impact of prior obesity surgery on changes in glucose homeostasis after SSFR.

Methods: An umbrella review was conducted to identify knowledge gaps, and implications for future research. Then, twin dose response meta-analyses (DRMA) were performed to examine the degree and duration of these metabolic changes after SSFR & NSSFR procedures. This was followed by a commentary paper that highlights the need to examine additional sources of population heterogeneity, which could alter the metabolic trajectory after SSFR. Next, a novel index of glucose excursion was validated which was then used subsequently in a quasi-experimental pilot study to examine changes in glucose homeostasis after SSFR in comparison to the impact of prior obesity surgery.

Results: The umbrella review revealed that current literature is not conclusive; however, they suggest some metabolic benefits without a clear clinical significance. The DRMAs reported that SSFR is safe and may exert a transient metabolic benefit in

body composition, adipokines, inflammation, blood pressure and lipid profile. However, only improvements in insulin sensitivity lasted beyond 6 months. On the other hand, NSSFR exerts a sustained effect on body composition for up to two months, but with a worsening in lipid profile in the first two weeks. The commentary paper highlighted the need to examine the independent metabolic effect of SSFR and history of bariatric surgery (irrespective of their body mass index and diabetic status). The quasi experiment validated Doi's weighted average glucose as a measure of post-load glucose excursion. Also reported that SSFR resulted in improvement in insulin resistance without affecting post-load glucose excursion, but that a history of obesity surgery was associated with an additional effect on glucose excursion, possibly due to sustained improvement of beta-cell function.

Conclusion: SSFR appears to be associated with favorable metabolic changes, particularly an improvement in insulin sensitivity. Further studies that examine these changes from a hormonal perspective can broaden our knowledge of metabolic sequelae associated with sudden removal of subcutaneous fat and help us understand mechanisms underpinning the link between obesity and metabolic diseases. This could potentially identify new therapeutic targets.

DEDICATION

I dedicate my thesis work to my brother Ahmad and my lovely sisters.

A special feeling of gratitude to my loving wife Sara, whose support, and words of encouragement have pushed me through this journey.

Finally, to the soul of my beloved parents, this is for you!

ACKNOWLEDGMENTS

All praise to Allah the one and almighty that gave me the strength throughout this journey. I would like to express my sincere gratitude to everyone who has supported me throughout this valuable and rewarding experience. I would like to acknowledge the tremendous efforts and support of Dr. Suhail A. Doi, my supervisory committee Dr. Abdella M. Habib, Dr. Abdul-Badi Abou-Samra & Dr. Moustapha Hamdi. Special appreciation is also extended to Dr Atallah Hammouda, Dr. Asad Zeidan, Dr Mashael Alshafai, Dr. Mohamed Elrayess, Dr. Feras Alali, Dr Marwan Abu-Hijleh and Ms Sana Al Ajouri for their continuous help throughout my PhD.

Additionally, I would like to pay special acknowledgment to College of Medicine at Qatar University, the Department of Plastic Surgery and Qatar Metabolic Institute at Hamad Medical Corporation for all the knowledge, resources and support that allowed me to complete my PhD program successfully. I also would like to thank the Qatar National Research Fund for funding this project through project fund numbers NPRP13S-0209-200315 and NPRP14S-0406-210153. Finally, I acknowledge the volunteers whose participation made this study possible for their contribution.

TABLE OF CONTENTS

PREFACE

The research presented in this thesis was carried out at the Department of Population Medicine, College of Medicine, Qatar University and the Department of Plastic Surgery and Qatar Metabolic Institute at Hamad Medical Corporation from August 2020 to June 2022. This dissertation is solely the result of my individual work and does not contain any contribution that resulted from the work of others, except as explicitly stated in the acknowledgements section. Furthermore, none of the work included in this thesis has been used in any prior applications for a degree, diploma, or other qualification at any other university.

LIST OF TABLES

LIST OF FIGURES

LIST OF PUBLICATIONS

1. Badran S, Doi SA, Hamdi M, Hammouda A, Alharami S, Clark J, Musa OAH, Abou-Samra AB, Habib AM. Metabolic aspects of surgical subcutaneous fat removal: an umbrella review and implications for future research. Bosn J Basic Med Sci. 2022 Sep 29. Doi: 10.17305/bjbms.2022.8175.

2. Badran S, Habib AM, Aljassem G, Musa OAH, Clark J, Hamdi M, Abou-Samra AB, Glass GE, Doi SA. Metabolic changes after surgical fat removal: A dose-response meta-analysis. J Plast Reconstr Aesthet Surg. 2023 Jan;76:238-250. Doi: 10.1016/j.bjps.2022.10.055.

3. Badran S, Doi SA, Iskeirjeh S, Aljassem G, Jafarian N, Clark J, Habib AM, Glass GE. Metabolic changes after nonsurgical fat removal: A dose response meta-analysis. J Plast Reconstr Aesthet Surg. 2023 Feb;77:68-77. Doi: 10.1016/j.bjps.2022.10.054.

4. Badran, S, Doi SA. Metabolic Changes after Surgical Fat Removal: Current Gaps and Suggestions for Future Studies. J Plast Reconstr Aesthet Surg. 2023. Doi: 10.1016/j.bjps.2023.04.008

5. Badran S, Doi SA, Hammouda A, Musa OAH, Habib AM. Validation of Doi's weighted average glucose as a measure of post-load glucose excursion for clinical use. Biomolecules & Biomedicine, 2023 Mar. Doi: 10.17305/bb.2022.8807.

6. Badran S, Habib AM, Khoogaly H, Hammouda A, Muneer M, Alkasem MJ, Abou-Samra AB, Doi SA. The Impact of Prior Obesity Surgery on Glucose Metabolism After Body Contouring Surgery: A Pilot Study. Biomolecules & Biomedicine, 2023 Mar. Doi: 10.17305/bb.2023.8827

LIST OF ABBREVIATIONS

ASF	Abdominal subcutanous fat
AVF	Abdominal visceral fat
T2D	Type 2 Diabetes
SSFR	Subcutaneous surgical fat removal
HIFU	High intensity focused thermal ultrasound
NSFR	Non-surgical fat removal
GTT	Glucose tolerance test
FPG	Fasting plasma glucose
IGT	Impaired glucose tolerance
dwAG	Doi's weighted average glucose
BMI	Body mass index
AMSTAR-2	A MeaSurement Tool to Assess systematic Reviews-2
MeSH	Medical subject heading
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta Analyses
MASTER	MethodologicAl Standard for Epidemiological Research
SI	Systeme International
FM	Fat Mass
LBM	Lean Body Mass
WC	Waist circumference
HOMA-IR	Homeostatic model assessment for insulin resistance
TNF- α	Tumor necrosis factor alpha
IL-6	Interleukin 6
CRP	C- Reactive protein
LDL	Low-density lipoprotein
HDL	High-density lipoprotein
TG	Triglycerides
TC	Total cholesterol
FFA	Free fatty acids
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
REMR	Robust-error meta-regression
FT	Fat Thickness
VLDL	Very-low-density lipoprotein
AST	Alanine aminotransferase
ALT	Aspartate aminotransferase
ITT	Insulin tolerance test
MAs	Meta-analyeses
SR	Systematic review
CI	Confidence interval
DRMA	Dose response meta-analysis
FABP-4	Fatty Acid binding protein 4
RBP-4	Retinol binding protein 4
ASP	Acylation stimulating protein
LCN2	Lipoclain-2
SSFRP5	Secreted frizzled related protein 5
CT-1	Cardiotrophin-1
DEXA	Dual-energy x-ray absorptiometry

MRI	Magnetic resonance imaging
OGTT	Oral glucose tolerance test
HIFU	High-intensity focused ultrasound
HOMA-S	Homeostatic model assessment for insulin sensitivity
HOMA-B	Homeostatic model assessment for pancreatic beta cell function
GTT	Glucose tolerance test
ADA	American diabetes association
FPG	Fasting plasma glucose
IFG	Impaired fasting glucose
GLP-1	Glucagon-like peptide-1
NPRP 13	National Priorities Research Program 13
NHS	National Health Strategy
MOPH	Ministry of Public Health
GTT	Glucose tolerance test
OGTT	Oral glucose tolerance test
A-GTT	Area under the glucose tolerance test

CHAPTER 1: INTRODUCTION

1.1. Definition of SSFR and NSSFR

1.1.1. Surgical subcutaneous fat removal.

The current drift towards cosmetic plastic surgeries, especially the body contouring surgeries which aim to produce a more attractive body shape by removing excess skin and fat tissue from multiple body areas, is due to several reasons such as the increase in the safety of these procedures, the increase in the availability of these operations and the recent increase in the number of bariatric surgeries. Bariatric surgery is performed for morbidly obese patients to facilitate loss of a significant amount of their body fat mass. Because of the rapid and massive weight loss following bariatric surgery such as sleeve gastrectomy, many patients tend to require body contouring plastic surgery to remove redundant skin and excess body fat 1. Body-contouring surgery is also done for purely cosmetic purposes in patients not undergoing bariatric surgery.

A typical example of these body contouring surgeries is abdominoplasty (also known as Tummy Tuck) surgery which suddenly removes around 2-3kg of abdominal subcutaneous fat (ASF) tissue, and usually is followed by tightening of the abdominal wall muscles, to correct divarication of recti muscles [2]. The other commonly undertaken surgery is suction-assisted lipectomy and, together with abdominoplasty, these represent the commonest plastic surgery procedures that target subcutaneous fat from unwanted areas such as the abdominal wall and flanks. The accelerating demand for these surgical procedures has gradually moved the practice from removing a small amount of intractable fat tissue to the removal of a large volume (more than five liters) of subcutaneous fat tissue, which eventually can result in a significant metabolic effect [3]. However, whether the metabolic effects of these two surgeries are the same or

different is not known. In fact, previous reviews and meta-analyses have combined these two procedures together, which might not be accurate. For example, the repair of the abdominal wall in abdominoplasty might result in an increased intraabdominal pressure with reduced space for the future expansion of intraabdominal fat tissue, which might result in different metabolic effects than liposuction [3,4].

Finally, a distinction needs to be made between SSFR and other modalities of fat loss (such as diet, exercise, or bariatric surgeries) in that non-SSFR modalities result in a gradual decrease in both the subcutaneous and intra-abdominal fat tissue. This gradual reduction occurs through a decrease in the size of the adipocytes while with SSFR there is actual loss of subcutaneous adipocyte numbers, but without impact on intraabdominal adipocytes.

1.1.2. Non-surgical subcutaneous fat removal.

Non-surgical fat removal is one of the fastest areas of growth and innovation within the aesthetics industry. Options include cryolipolysis, laser lipolysis, radiofrequency ablation and high intensity focused thermal ultrasound (HIFU). While the mechanism of action of each method differs, the result is the focused elimination of subcutaneous fat in a non-invasive manner.

1.2. Fat removal sites in SSFR

SSFR classically is from abdominal and thigh areas, although other sites may less commonly be targets for surgery. Abdominal (or upper-fat) distribution is correlated more strongly with obesity-associated metabolic risks and consequences than fat in the gluteo-femoral (or lower-fat distribution in the gluteal and thigh regions) [5]. Fat in the abdomen may be subcutaneous (ASF) or abdominal visceral fat (AVF) tissue and it should be noted that only ASF is the target for abdominal SSFR [2]. AVF is intraperitoneal fat that represents both the mesenteric as well as the omental fat cells [6].

AVF is typically formed of large adipocytes and contains necrotic and inflammatory tissues. There is also retroperitoneal fat in humans of unclear significance.

Central obesity in the abdominal area, represents one of the essential components of metabolic syndrome, along with insulin resistance, elevated serum triglyceride, blood pressure, and low high-density lipoproteins. The distribution of fat deposits in the abdomen (ASF versus AVF) has been thought to determine metabolic outcomes and that AVF tissue is more "pathogenic" [7] and is what has been linked to metabolic syndrome and T2D [8]. Other studies have also proposed that both ASF and AVF play a role in metabolic risk[3] but largely the metabolic risk of obesity has been linked mainly to AVF because it is directly involved in the delivery of free fatty acids as well as inflammatory proteins such as interleukin- 6 (IL-6), to the liver via the portal circulation [9]. It is nevertheless probable that ASF may also play a role given that more than 80% of the free fatty acids and other inflammatory proteins reach the liver via the systemic circulation [10]. This is supported by studies that report that intrahepatic triglyceride rather than AVF is a better marker for obesity-associated metabolic risk [11]. Therefore, it has recently been suggested that the metabolic risk in obesity is a shared effect of molecules secreted by both these compartments. Thus, there is an expectation that SSFR may alter glucose homeostasis and insulin resistance as a direct consequence of surgical ASF removal.

1.3. Background and previous research

Obesity has reached pandemic levels and currently affects all age groups and socioeconomic classes worldwide. Obesity prevalence has almost tripled in the last 50 years according to the World Health Organization and this, in turn, has led to more fatality than malnutrition and being underweight combined [12]. The rising obesity rate has led to a substantial rise in metabolic diseases such as diabetes mellitus type 2 (T2D),

hypertension, cardiovascular disease, non-alcoholic hepato-steatosis, and dyslipidemia [13].

Lipids comprise a wide range of molecules such as phospholipids, fatty acids, and triglycerides [14]. These molecules represent a highly efficient energy resource. Recent studies have advanced our view of adipose tissue from being simply an energy store, into an active endocrine organ, which secretes several metabolically active adipokines such as leptin, adiponectin, and resistin. The latter play an essential role in glucose homeostasis and energy metabolism in our body [13]. These molecules have been thought to have a critical role in energy homeostasis through communication with organs that maintain system-wide metabolic homeostasis such as the liver. Of the adipocyte-derived factors, adiponectin, and leptin are among the essential adipokines. Indeed, adiponectin analogs are now considered one of the promising new therapeutic targets for obesity-linked hyperglycemia, that can mitigate obesity and improve insulin sensitivity [15].

Insulin resistance, as a consequence of such dysregulation associated with obesity, is what links the latter to T2D. Insulin resistance leads to dysregulation of glucose homeostasis via a combination of impaired glucose clearance and elevated glucose production in the liver. Adipose tissue is a major contributor to insulin sensitivity/resistance status. Too little fat mass, as seen in patients with lipodystrophy, results in a severe form of insulin resistance, and too much adipose mass can also result in a similar condition [16]. The primary reason for the latter form of insulin resistance may be hypoxia in adipose tissue that leads to inflammatory lipo-toxicity [17].

Currently it is unknown if the removal of excess subcutaneous fat tissue through surgical subcutaneous fat removal (SSFR; also known as body contouring surgeries such as liposuction or abdominoplasty) ameliorates the mass of hypoxic fat thus

reducing its consequences. Such surgeries have become very common because, although obesity can be prevented, maintaining a normal body weight can be very challenging and difficult and the increase in demand for SSFR has been driven by patients seeking an improved physical appearance [18]. However, the precise effect of sudden removal of a patient's body fat on metabolism is still not fully understood.

In terms of weight reduction, Lifestyle changes are largely ineffective in the long term and there were no efficacious pharmacologic interventions until the recent use of GLP-1 analogues for this purpose. Bariatric surgery aims to induce weight loss by altering intestinal absorption and/or inducing changes in perceived satiety. Categories include gastric bypass, gastric banding and pancreatico-biliary diversion. The efficacy of bariatric surgery in the management of morbid obesity is well established [19]. While bariatric surgery addresses the physiological root causes of obesity, surgical fat removal (SFR) tackles the physical manifestations [20] . Options for SFR include en-bloc excision of skin and fat to the level of the muscle fascia, known as body contouring surgery (e.g. abdominoplasty, belt lipectomy, brachieplasty, thigh lift and breast reduction) and the percutaneous avulsion and aspiration of fat (e.g. liposuction) [21]. Bariatric surgery-induced weight loss results in the depletion of fat stores from both subcutaneous deposits and the viscera (accounting for approximately 20% of fat stores) [22], while SFR selectively depletes the subcutaneous stores.

Fat is an endocrine organ [23]. The long-term metabolic impact of fat loss by bariatric surgery is well documented [19,24]. Attempts have been made to evaluate the comparable metabolic impact of selective loss of subcutaneous fat [25–29] but uncertainties persist owing to the heterogeneity of variables and study parameters. It is important to seek clarity here, for while the metabolic benefits of bariatric surgery are well established, surgical fat removal continues to be considered cosmetic in nature and

subject to healthcare rationing.

Additionally, non-surgical fat removal is one of the fastest areas of growth and innovation within the aesthetics industry. Options, as mentioned previously, include cryolipolysis, laser lipolysis, radiofrequency ablation and high intensity focused thermal ultrasound (HIFU). While the mechanism of action of each method differs, the result is the focused elimination of subcutaneous fat in a non-invasive manner. The question of whether non-surgical fat removal (NSFR) exerts measurable, beneficial metabolic benefits remains unclear.

1.4. Measures of Glucose Homeostasis after SSFR

One test that has commonly been used to diagnose glycemic disorders is the oral glucose tolerance test (GTT) which is extensively used both in research as well as clinically as an indicator of gestational diabetes [30] but has been replaced for the diagnosis of Type 2 diabetes by the fasting plasma glucose (FPG) [31]. In both humans and animals, the GTT provides an indication of the relative roles of insulin secretion and insulin resistance in the progression of glucose intolerance, can provide the best measure of glucose homeostasis and has the potential to diagnose patients with impaired glucose tolerance (IGT) even with normal FPG levels. This is of value because those patients are at higher risk of developing type 2 diabetes as well as cardiovascular diseases [32].

Doi's weighted average glucose (dwAG) is a novel index that represents a single value summary of the glucose excursion under the GTT. The latter is derived from only three time points on the GTT at 0, 60 and 120 minutes and was categorized into four levels in a previous study of gestational diabetes. These four categories differentiated between normal, impaired, abnormal, and severely abnormal glycemic states [30].

Several studies have investigated the metabolic impacts of the large volume subcutaneous fat removal during body contouring surgery, using different tests. The existing studies have been summarized in one systematic review and three meta-analysis, and these syntheses suggest a possible improvement in insulin sensitivity, but a major challenge in interpreting these results is that they did not account for the heterogeneity of patients in terms of baseline body mass index (BMI), diabetic status and prior obesity (bariatric) surgery [33]. This is of high importance to delineate the independent effect of SSFR on glucose homeostasis.

1.5. Potential for Metabolic Sequelae after SSFR

Research has found that even a small weight loss of ten percent can result in a significant improvement of obesity-linked metabolic abnormalities such as insulin resistance, high blood pressure, and abnormal inflammatory marker levels [34,35]. Additionally, increased knowledge of the metabolic consequences of excess body fat and observations after bariatric surgeries [36], have suggested that there could possibly be a similar effect after SSFR. This has been examined in several studies, which measure hormonal changes before and after SSFR at different time points. These studies have been small and heterogeneous and have reported inconsistent effects on metabolic parameters such as insulin resistance, adipokine levels, and inflammation [37–49].

1.6. Rationale of The Thesis

Despite the current drift towards seeking cosmetic plastic surgeries and procedures (SSFR & NSSFR) to improve body shape and image, there is still a lack of knowledge regarding the precise metabolic changes after these procedures, particularly the magnitude and duration of these changes. This includes alterations in body composition, glucose homeostasis and insulin resistance, inflammation, adipokines, blood pressure and lipid profile.

In turn, this will help us not only to confirm the safety of these procedures but also to define if these procedures can be used for metabolic benefit and to broaden our knowledge about the mechanisms underpinning excess ASF and associated metabolic consequences.

1.7. Aims of The Thesis

- To understand the current knowledge and gaps in literature regarding metabolic changes after SSFR.
- To determine the exact magnitude and duration of these metabolic changes after SSFR & NSSFR.
- To validate the Doi's weighted average glucose as a measure of post-load glucose excursion for clinical use.
- To examine changes in glucose homeostasis after SSFR.
- To understand the impact of prior obesity surgery on changes in glucose homeostasis after SSFR.

1.8. Objectives of The Thesis

Each phase of the integrated project has specific objectives outlined below:

Phase 1: Research synthesis

Objective 1: To conduct an umbrella review that focuses on the metabolic sequelae after SSFR interventions for dealing with cosmetic body appearance, aiming to summarize the diversity of possible metabolic changes after SSFR along with gaps in the knowledge and future directions for research and practice.

Phase 2: Dose response meta-analyses

Objective 2: To conduct dose-response meta-analysis, aiming to examine the metabolic impact of SSFR with a view to establishing how these procedures impact patient physiology over time.

Objective 3: To conduct dose-response meta-analysis, aiming to examine the metabolic impact of NSSFR with a view to establishing how these procedures impact patient physiology over time.

Phase 3: Quasi experiment

Objective 4: To validate the Doi's weighted average glucose as a measure of post-load glucose excursion for clinical use.

Objective 5: To examine the changes in glucose homeostasis after SSFR using the Doi's weighted average glucose and HOMA-IR.

Objective 6: To identify the impact of prior obesity surgery on changes observed in objective 5.

CHAPTER 2: DETAILS OF METHODS USED IN THIS PROGRAM OF RESEARCH

2.1. Umbrella review

This synthesis **aims** to examine the current knowledge and gaps in literature regarding metabolic changes after SSFR. This synthesis represents the **first objective (phase 1)** of this thesis, which is to conduct an umbrella review that focuses on the metabolic sequelae after SSFR interventions for dealing with cosmetic body appearance, aiming to summarize the diversity of possible metabolic changes after SSFR along with gaps in the knowledge and future directions for research and practice.

2.1.1. Study inclusion and exclusion criteria.

A search was conducted for evidence syntheses that synthesized data on the metabolic changes after SSFR. PubMed, Embase, and Scopus databases were searched without any date, language, or publication restriction but exclusion of non-English and animal studies, as well as non-surgical body fat removal and bariatric surgeries.

2.1.2. Search strategy

Search was conducted on the 8th of November 2021 by two independent authors using the polyglot Search Translator [50]. The search strings used are given in the supplementary material (Figure S1) for the syntheses that report changes in insulin sensitivity, inflammatory markers, and adipokines levels after SSFR. Data were extracted regarding synthesis type (systematic review or meta-analysis), title and author, year of publication, type of SSFR, a summary of included studies, follow-up duration after SSFR, and possible evidence gaps. Main findings were summarized regarding metabolic changes in terms of potential inflammatory and anti-inflammatory adipokines and other metabolic markers.

2.1.3. Quality assessment

A MeaSurement Tool to Assess systematic Reviews-2 (AMSTAR-2) was used to assess the quality of the included syntheses and each included synthesis was examined against 16 quality safeguards to assess their methodological quality [51] .

2.1.4. Ethical statement

This article does not involve direct contact with human participants or animals performed by any of the authors. Informed consent and ethical approval are not required.

2.1.5. Data synthesis

A structured summary of findings was done for the eligible and included systematic reviews and meta-analyses. Metabolic change findings were assessed in three categories: insulin resistance, inflammatory markers and adipokines. For each of the categories, a separate table of findings was formulated.

2.2. SSFR dose response meta-analysis

This synthesis **aims** to determine the exact magnitude and duration of the metabolic changes after SSFR. This synthesis represents the **second objective (phase 2)** of this thesis, which is to conduct dose-response meta-analysis, aiming to examine the metabolic impact of SSFR with a view to establishing how these procedures impact patient physiology over time. This in turn, establish whether surgical fat removal, similar to bariatric surgery, exerts measurable, lasting metabolic benefits.

2.2.1. Search strategy

A search string was initially designed in PubMed, then translated and run in Embase and Scopus using the Polyglot Search Translator [52]. The search string was designed by an experienced information specialist and was run across all databases on

the 8th of November 2021. The search string was comprised of both medical subject heading (MeSH) terms and free-text terms. Additionally, the online trials registers ClinicalTrials.gov and the national research register were scrutinized for completed, discontinued and ongoing trials relating to body contouring surgery and physiological and/or metabolic parameters. The search strategy was performed in accordance with the Cochrane Highly Sensitive Search Strategy guideline in the Cochrane Handbook for Systematic Reviews of Interventions [53]. The review is reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Full search strings for all databases and PRISMA checklist are available in Supplementary Figures 3 and 4.

2.2.2. Inclusion criteria

Papers were included if they provided quantitative data permitting analyses of the effect of SFR (abdominoplasty or suction lipectomy) on physiology and/or metabolism. Only human studies were considered. No date, language or publication limits were applied to the search.

2.2.3. Exclusion criteria

Non-human (in vivo) studies were excluded from consideration as were studies that used non-surgical fat removal procedures.

2.2.4. Quality assessment

The quality assessment of the eligibly included articles was independently done by two reviewers utilizing the MethodologicAl Standard for Epidemiological Research (MASTER) scale [54]. This scale evaluates each included study against 36 safeguards across seven domains that, if present, may mitigate systematic error in the trial. Then a quality rank for each assessed article was computed and was reported qualitatively. The MASTER scale provided a unified framework for the assessment of the methodological

quality of quasi-experimental and randomized controlled trials included in this synthesis.

2.2.5. Outcome measures

The outcome measures sought encompassed 6 domains. These included anthropometrics/ body composition, serum adipokines, inflammatory cytokines, glucose homeostasis, lipid profile and blood pressure. Data units were unified to the Systeme International d'Unites (SI) units. Specifically, the quantitative data extracted (before and after SFR) included the following:

1. Anthropometrics/ body composition: body mass index (BMI), fat mass (FM), lean body mass (LBM), and waist circumference (WC).
2. Serum adipokines: leptin, adiponectin, and resistin.
3. Markers of glucose homeostasis: fasting plasma glucose (FPG), fasting insulin, and homeostatic model assessment for insulin resistance (HOMA-IR).
4. Inflammatory cytokines: tumor necrosis factor alpha (TNF- α), interleukin 6 (IL-6), and C - reactive protein (CRP).
5. Lipid profile: low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (TG), total cholesterol (TC), and free fatty acids (FFA).
6. Blood pressure: systolic blood pressure (SBP) and diastolic blood pressure (DBP).

Other metabolic variables that were reported in less than 5 studies were excluded such as waist hip ratio, body fat percentage, free fat mass, bone mineral content, interleukin-10, 2-hour post prandial glucose, VLDL-cholesterol, whole-body glucose disposal, glucose oxidative metabolism, nonoxidative glucose metabolism, lipid oxidative metabolism and glycerol.

2.2.6. Data extraction

Data were retrieved from all full text articles by two authors. Where necessary, clarification was sought with the senior author (SD).

2.2.7. Statistical methods

In order to establish an "average" dose-response relationship between the outcome parameters (metabolic changes) and time based on the data of all available studies, the robust-error meta-regression (REMR) model was employed in this study [55]. This is a one-stage approach that treats each study as a cluster and uses robust error variance to address the potential correlations among the within-study effects as these effects share the same reference within the study. A non-linear curve was fitted using restricted cubic splines with three knots. The Wald test was used to test potential non-linearity by assuming the coefficient of the non-linear terms was zero. All analyses were performed using the REMR module in Stata version 15, College Station, TX, USA.

2.3. NSSFR dose response meta-analysis

This synthesis **aims** to determine the exact magnitude and duration of the metabolic changes after NSSFR. This synthesis represents the **third objective (phase 2)** of this thesis, which is to conduct dose-response meta-analysis, aiming to examine the metabolic impact of NSSFR with a view to establishing how these procedures impact patient physiology over time. This in turn, help to establish whether nonsurgical fat removal exerts measurable, lasting metabolic benefits by way of changes to serum lipid profiles.

2.3.1. Search strategy

A search string was designed using relevant MeSH terms in PubMed, Cochrane CENTRAL, and Embase databases, as well as online clinical trials registers using the

Polyglot Search Translator [52]. The search strategy and used strings were designed and conducted by the first author (SB) and an experienced information specialist (JC) and were run across all databases on the 10th of March 2022. The search string included both medical subject heading (MeSH) terms and free-text terms. The online trial registers were searched at ClinicalTrials.gov and the national research register were examined as well for relevant trials relating to non-surgical body contouring procedures targeting the abdominal area and body compositions, and physiological and/or metabolic changes.

The Cochrane Highly Sensitive Search Strategy guideline in the Cochrane Handbook for Systematic Reviews of Interventions was adopted during the search process [53]. The results were reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Full search strings for all databases and the PRISMA checklist are available in Supplementary Figures 6 and 7.

2.3.2. Inclusion criteria

Papers and trials were included if they provided quantitative data permitting analyses of the effect of non-surgical body contouring procedures (Ultrasound, cryolipolysis, radiofrequency, and high intensity electromagnetic) on body compositions, and physiology, and/or metabolism. Only human studies that target the abdominal areas were considered. No search restrictions for a date, language, or publication were applied.

2.3.3. Exclusion criteria

Non-human (in vivo) studies were excluded from consideration as were studies that targeted other anatomical areas (e.g., thighs and arms) and studies on surgical body contouring procedures (eg. Abdominoplasty).

2.3.4. Quality assessment

The quality assessment of the eligibly included articles was independently done by two reviewers (SB and NJ) utilizing the MethodologicAl Standard for Epidemiological Research (MASTER) scale [54]. This scale evaluates each included study against 36 safeguards across seven domains that, if present, may mitigate systematic error in the trial. The MASTER scale delivered a robust framework for assessing the methodological quality of the included quasi-experimental and randomized controlled trials in this paper.

2.3.5. Outcome measures

The outcome measures sought include two domains. These included body compositions/ anthropometrics and lipid profiles. Data units were unified to the Systeme International d'Unites (SI) units. The extracted quantitative data (before and after non-surgical body contouring procedures) included the following markers:

1. Body compositions/ anthropometric: body mass index (BMI), body weight (BW), waist circumference (WC), and abdominal fat thickness (FT).
2. Lipid profile: low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (TG), total cholesterol (TC).

Other body measurements and physiological/metabolic variables that were reported in less than 5 studies were excluded such as other anthropometrics measurements (e.g. hip circumference), fasting glucose, fasting insulin, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), leptin, fatty acids, C-reactive protein, very-low-density lipoprotein (VLDL), alanine aminotransferase (AST), and aspartate aminotransferase (ALT).

2.3.6. Data extraction

Studies screening and data collection were retrieved from all full-text articles by four authors. Where necessary, clarification was sought with the senior author.

2.3.7. Statistical methods

An "average" dose-response relationship between the measured outcome parameters (body compositions and lipid profile) and time elapsed after the body contouring procedure was established using the robust-error meta-regression (REMR) model [55]. Which represents a one-stage approach that treats each study as a cluster. The robust error variance was used in order to address any possible correlations among the within-study effects, because these effects share the same reference within the single study. A non-linear curve was fitted using restricted cubic splines with three knots. The Wald test was used to test potential non-linearity by assuming the coefficient of the non-linear terms was zero. All analyses were performed using the REMR module in Stata version 15, College Station, TX, USA.

2.4. Validation of Doi's weighted average glucose as a measure of post-load glucose excursion for clinical use

The previous aims suggested that insulin resistance is the main metabolic change associated with SSFR and therefore it became necessary to assess both insulin resistance and beta-cell function in relation to these procedures. It became clear that some form of glucose excursion measure needed to be used for subsequent studies in this program of research, and therefore, we began by validating a measure proposed by a member of the research team so it can be used subsequently. This study **aims** to validate the Doi's weighted average glucose "dwAG". This study represents the **fourth objective (phase 3)** of this thesis, which is to validate the dwAG as a measure of glucose excursion. Which is later to be used in examining changes in glucose homeostasis after SSFR. In this study, we examined the performance of the novel index of glucose excursion (the dwAG) in relation to the conventional measure of area

under the oral glucose tolerance test (O-GTT) and the homeostatic model assessment for insulin sensitivity (HOMA-S) and pancreatic beta cell function (HOMA-B). A cross-sectional comparison of the new index was conducted using 66 oral glucose tolerance tests (GTTs) performed at different follow-up times among 27 participants who had undergone surgical subcutaneous fat removal (SSFR).

2.4.1. Subjects

We studied twenty-seven consecutive eligible patients who underwent body contouring surgery at the Department of Plastic Surgery, Hamad General Hospital, in the period between July 2021 and June 2022. Sixteen participants were obese (59%) and four patients were diagnosed with type 2 diabetes mellitus (15%). A GTT was performed at three different time points before and after surgery (visit one: within 1 week before surgery, visit two: 1 week after surgery, and visit three: 6 weeks after surgery). After taking a detailed medical history and complete physical examination, patients with comorbidities were excluded except for type 2 diabetes mellitus who were not on insulin therapy. All subjects signed an informed consent before starting the study, which was approved by the Institutional Review Board at Hamad Medical Corporation and Qatar University (MRC-01-20-466, and QU-IRB 1412-EA/20 respectively), and by the Institutional Bio-safety Committee at Qatar University (QU-IBC-2020/066).

2.4.2. Study design

The research design in this study was a cross-sectional comparison of a standard and new method of assessing glucose excursion under the GTT. The GTT was administered using 75 gm oral glucose with 6 time points of glucose measurements (fasting(gtt0), 15 minutes(gtt15), 30 minutes(gtt30), 45 minutes(gtt45), 60

minutes(gtt60) and 120 minutes(gtt120) in mmol/L). For each of the GTT's, glucose excursion was computed using:

a) standard method: Tai's trapezoidal rule for area under the GTT (A-GTT) [56] expressed as mmol/L/2h using six GTT values (0, 15, 30, 45, 60 and 120 minutes).

b) new method: Doi's weighted average glucose (dwAG) [57] calculated using the formula $(\text{gtt0} \times 0.28) + (\text{gtt60} \times 0.36) + (\text{gtt120} \times 0.36)$ and expressed as actual glucose values in mmol/L. The dwAG represents a single value summary of the glucose excursion under the GTT using only the three time points (0, 60 and 120 minutes) in routine GTT's for diagnostic use [57]. The dwAG value was categorized into four categories: dwAG0 ≤ 6.8, dwAG1 > 6.8 & ≤ 7.5, dwAG2 > 7.5 & ≤ 8.6 and dwAG3 > 8.6 mmol/L based on four levels of risk previously defined for women with gestational diabetes [57]. The four levels of dwAG reflect normal, impaired, abnormal, and severely abnormal dwAG values, respectively.

The Oxford HOMA2 Calculator was used to compute HOMA-IR (anchored at 1 for normal insulin sensitivity) by means of FPG and fasting C-peptide 58. The GTTs were classified into two patterns or shapes that indicate a higher level of beta cell dysfunction:

a) Those that peaked after 30 minutes (Y/N) defined as a maximum value after 30 minutes (or peaked after 45 minutes if the value at this time only exceeded the 30-minute value by <0.25mmol/L) [59].

b) A biphasic GTT which was defined as a GTT with 120 min glucose ≥0.25 mmol/L higher than at 60 minutes [60].

2.4.3. Statistical analysis

Comparisons across categories were made using box plots and the Kruskal-

Wallis one-way ANOVA on ranks which extends the Mann–Whitney U test, which is used for comparing only two groups. Passing-Bablok regression was used to compare both methods of computing glucose excursion and is a linear regression procedure with no special assumptions regarding the distribution of the samples and the measurement errors [61]. The result does not depend on the assignment of the methods for glucose excursion to X and Y. A linear regression model with two categorical predictors (peak after 30 minutes and biphasic GTT) was used to assess mean values of dwAG, A-GTT, HOMA-S and HOMA-B in groups defined by these factors. Finally, the dependence of dwAG on HOMA insulin sensitivity and HOMA beta cell function was modeled in linear regression using restricted cubic splines and using the values of both HOMA-S and HOMA-B indices centered at 100%. Stata version 15 (College Station, TX, USA) was used for all analyses and exact P values were reported throughout.

2.5 Alteration in glucose metabolism after SSFR and the impact of prior obesity surgery

This study **aims** to examine changes in glucose homeostasis after SSFR and to understand the impact of prior obesity surgery on changes in glucose homeostasis after SSFR. This study represents the **fifth & sixth objectives (phase 3)** of this thesis, which is to examine the changes in glucose homeostasis after SSFR using the dwAG and HOMA-IR, and to identify the impact of prior obesity surgery on these changes. In this study we aimed to evaluate the impact of SSFR on glucose excursion and insulin resistance in such patients, by examining them over three visits before and after surgery. The independent impact of SSFR and prior obesity surgery on glucose homeostasis was evaluated, irrespective of patients' BMI and diabetic status.

2.5.1. Subjects

We studied twenty-nine consecutive eligible patient who were planned to undergo abdominoplasty or lower body lift surgery (liposuction cases were excluded) at Hamad General Hospital, in the period between July 2021 and December 2022. All subjects had a stable weight for at least 6 months before the surgery with a fluctuation of less than 3% of body weight. Patients with comorbidities were excluded except for type 2 diabetes mellitus (T2D). Diabetic patients on insulin therapy were excluded. Patients with a history of obesity surgery were excluded if the surgery was less than 2 years before the body contouring surgery. All subjects signed an informed consent before starting the study.

2.5.2. Study design and reporting

The research design in this study was a quasi-experiment with three-time points. A quasi-experimental design lacks individual patient randomization, but it has allocation of treatment by the researcher, and the longitudinal nature of this design means that the same patients act as their own control. This design was chosen because the classical experimental design (randomized controlled trial) is not appropriate for this type of study. Outcome variables of interest were measured at three time-points which were the patient hospital visits (visit one: within 1 week before surgery, visit two: 1 week after surgery, and visit three: 6 weeks after surgery). The TREND reporting guideline for nonrandomized/quasi-experimental study designs was used to guide the reporting in this paper (see supplementary figure 9) [62].

2.5.3. Patient measurements

Collected outcome variables during the three visits included patient age, gender, comorbidities and medications, history of obesity surgery, vital signs, body fat composition measurements using bioelectrical impedance analysis (TANITA®

segmental body composition scale) before and after surgery, details of the surgical procedure including type of surgery and the weight of fat mass removed (in grams), OGTT using 75 gm oral glucose with 6 time points of glucose measurements (fasting(gtt0), 15 minutes(gtt15), 30 minutes(gtt30), 45 minutes(gtt45), 60 minutes(gtt60) and 120 minutes(gtt120) in mmol/L), fasting insulin (pmol/l) and c-peptide (nmol/l), hemoglobin A1c (HBA1c; (%)), lipid profile (LDL, HDL and triglyceride in mmol/l), c-reactive protein (CRP; (mg/l)), interleukin-6 (IL-6; (pg/ml)), vitamin D (ng/ml), and procedure details such as type of surgery and amount of fat mass removed. The HOMA-IR (anchored at 1 for normal insulin sensitivity) was calculated by means of the fasting plasma glucose and fasting c-peptide using the University of Oxford HOMA2 calculator [63]. For each of the GTT's, glucose excursion was computed using Doi's weighted average glucose (dwAG) [57] and was categorized into four categories: dwAG0 ≤ 6.8, dwAG1 > 6.8 & ≤ 7.5, dwAG2 > 7.5 & ≤ 8.6 and dwAG3 > 8.6 mmol/L based on four levels of risk previously defined for women with gestational diabetes [57]. The four levels of dwAG reflect normal, impaired, abnormal, and severely abnormal dwAG, respectively. The dwAG has been validated [64] against the area under the GTT curve.

2.5.4. Blood Samples and assays

Fasting blood samples were collected, immediately processed, and stored frozen at -80OC pending analysis. All assays were performed at the central laboratory of Hamad Medical Corporation, a laboratory accredited by the College of American Pathologist (CAP) and Joint Commission International (JCI).

Plasma glucose was measured using a hexokinase-based enzymatic method, the coefficient of variation for the assay was 1.2% at a mean glucose value of 5.3 mmol/L during the study period. Total cholesterol, triglycerides, and high-density lipoprotein

cholesterol (HDL-C) levels were measured enzymatically. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation. Serum 25(OH)D concentration (included both vitamin D2 and vitamin D3 fractions) was measured using electrochemiluminescence immunoassay (Vitamin D Total II, Roche, North America, USA). Plasma insulin and C peptide concentrations were measured on EDTA plasma (0.1 mL) using a sandwich-based assay on microparticles detected by fluorescence according to the manufacturer recommendations (insulin and C peptide Elecsys kits, Roche, North America, USA). The detection ranges were between 0.2-1000 mIU/mL and 0.01-40 ng/mL, for insulin and c peptide, respectively. The intra-assay and inter-assay variations were less than 5% for both assays. The plasma concentration of C-reactive protein (CRP) was measured using a particle enhanced immunoturbidimetric assay following the manufacturer recommendation (cobas CRP Test, Roche Diagnostics, North America, USA); the CRP in the diluted plasma binds with the CRP antibody on latex particles; the concentration of CRP is calculated as a function of the changed absorbance measured at 525 nm and 625 nm which is in relation to the amount of agglutination. The detection range is 3.0-400 mg/L and intra- and inter-assay variations are less than 4%. Interleukin 6 (IL-6) was measured by a non-competitive (sandwich) chemiluminescent immunoassay (Elecsys® IL-6, Roche Diagnostic, North America USA). The assay measures a range of 1.5−5000 pg/mL, with an inter-assay precision of 17.4 % (at 1.82 pg/mL) and 2.0 % (at 4461 pg/mL) and a stated reference value <7 pg/mL.

All subjects had an oral glucose tolerance test (OGTT) with a 75 gram glucose challenge and blood sampling at 0, 15, 30, 60, 90 and 120 min. Blood samples during the OGTT were collected in plain microtubes, rapidly centrifuged in a micro-centrifuge, and the supernatant serum was assayed for glucose concentrations using Analox

(Analox Instrument Ltd, GM9, UK).

2.5.5. Statistical analysis

Descriptive statistics were computed (median and interquartile range or number and percent) to report patient variables across time-points. Because the data collected over time (three-time points) are correlated, the methods used for longitudinal data analysis accounted for the correlated nature of the data. A cluster robust error logistic regression analysis was conducted to assess predictors of glucose excursion with the clusters being the individual patient. Two outcomes were analyzed in two separate analyses, with outcomes being either upper tertile HOMA-IR (model 1) or severely abnormal glucose excursion (measured through the dwAG; model 2). Only patient characteristics deemed important prognostically for these outcomes were adjusted for in these models. The mass of fat removed was not included in the models because it was a proxy for degree of obesity. Predictive margins from the logistic model were computed as a way of presenting model results in the scale of interest (probability), not in the estimation scale (logit) as the latter is more informative than odds ratios. A predictive margin is a generalization of an adjusted mean applied to the nonlinear model (logistic regression model) thus using the estimated model to make predictions on different values of a covariate to evaluate its effect on the outcome. Stata version 15 (College Station, TX, USA) was used for all analyses and exact P values were reported throughout.

CHAPTER 3: METABOLIC CONSEQUENCES OF SSFR

3.1. Main objectives and methods summary

This study is an umbrella review of metabolic sequelae after SSFR interventions for dealing with cosmetic body appearance. The purpose of this review is to examine the existing literature to develop a clearer understanding of potential changes after SSFR, such as insulin resistance, adipokine levels, inflammatory markers, appetite, and satiety as well as to identify existing gaps in knowledge.

To address the main objectives above, a search was conducted for evidence syntheses that synthesized data on the metabolic changes after SSFR. PubMed, Embase, and Scopus databases were searched without any date, language, or publication restriction but exclusion of non-English and animal studies, as well as non-surgical body fat removal and bariatric surgeries. A structured summary of findings was done for the eligible and included systematic reviews and meta-analyses. Metabolic change findings were assessed in three categories: insulin resistance, inflammatory markers and adipokines. For each of the categories, a separate table of findings was formulated. Further details of the methods used are discussed in Chapter 2.

3.2. Results

3.2.1. Study selection

A search in the three databases; PubMed, Embase, and Scopus on (08/11/2021) resulted in 444 studies. A total of 186 duplicate studies were excluded. The remaining 258 articles were screened by title and manuscript for eligibility of which six met inclusion criteria. One synthesis was in French and was excluded from this umbrella review [65], while another was excluded as it reported changes in weight and fat mass only [66]. There were thus three meta-analyses and one systematic review

included, and (Figure 1) depicts the PRISMA flow diagram for the selection of studies.

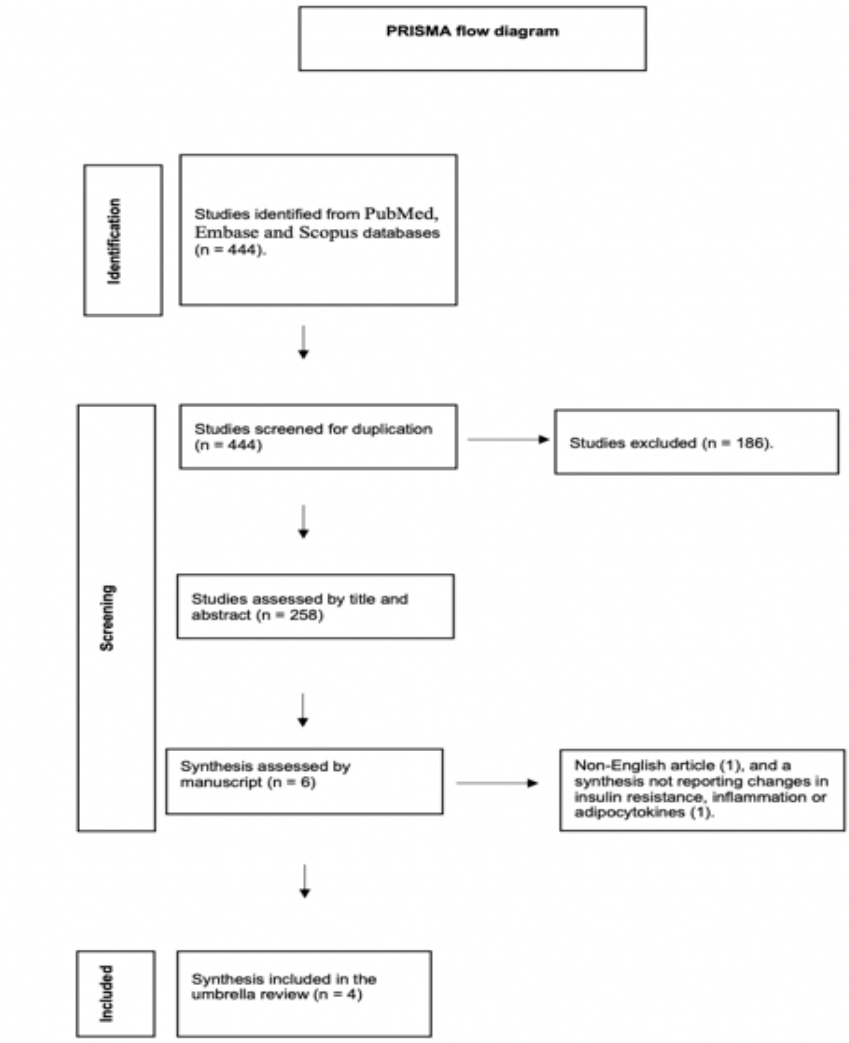


Figure 1. PRISMA flow diagram of the study selection process.

The first synthesis was conducted in 2013 [67], and since then, another three syntheses have been published [3,4,68]. None of the four included syntheses (fifteen, fourteen, twelve, and eleven studies included) examined the time trend after SSFR, and thus they looked at metabolic changes through quantitative analyses (if any) did not consider the heterogeneity in follow-up duration across studies. This umbrella review summarizes the changes reported in three categories: insulin resistance, inflammatory

markers, and adipokines levels. Quality assessment of the included syntheses demonstrated that most of them included PICO components in the review, explanation of inclusion criteria, justification for the excluded studies, use of a satisfactory quality assessment tool in studies included in the review and adequate description of the included studies. See supplementary material Figure S2.

3.2.2. Impact of SSFR on Insulin resistance

Several studies had measured changes in insulin resistance status after SSFR using different tests such as measuring fasting glucose, fasting insulin, and the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) [46,49,69], insulin tolerance test (ITT) [70], oral glucose tolerance test [45,71], and the gold standard glucose clamp test [44,72]. Apart from the glucose clamp test, most of these tests are not accurate in assessing the change in insulin sensitivity, and the studies that used the glucose clamp test had a small sample size and a lot of variability among participants in terms of diabetic status, and degree of obesity. The challenge behind using accurate tests such as the hyper insulinemic glucose clamp and the intravenous glucose tolerance test is the fact that they are very demanding [73].

Across three meta-analyses (MAs) and one systematic review (SR) examining the effect of SSFR on insulin sensitivity, most of the evidence suggests a possible improvement in obesity-associated insulin resistance, however, there was a lack of clarity regarding the extent of the effect and clinical significance. This was because there were major problems in the design and analysis of the MAs and therefore results couldn't be interpreted. There was also no clarity on the extent of the changes across the studies since there was a focus on statistical significance only. In summary, syntheses were inconsistent, there was a trend towards improvement in insulin sensitivity, and the clinical extent or duration of any improvement remained unclear.

The impact of SSFR on insulin resistance thus remained unknown given the data reported in (Table 3.1) and we recommended that a dose response meta-analysis was needed to answer this question.

Table 3.1. Syntheses That Report Changes in Insulin Sensitivity After SSFR

	Synthesis author and year	Synthesis type	Type of SSFR	Included studies	follow up	Main finding	Remaining evidence gaps
1.	Sailon et al. 2017 3	SR	Liposuction	Ten prospective studies (346 participants), which examined large volume liposuction (>3.5 liters).	3 weeks - 6 months.	Author reported conflicting results but stated that surgical fat removal by large volume liposuction can improve insulin sensitivity. No clear extend of change was reported.	This SR focused examining the statistical significance of these changes post SSFR, without reporting the extent of change, or its clinical importance. The review had substantial heterogeneity in terms of participants baseline characteristics, included studies sample size, and different assessment tools for insulin resistance.
2.	Seretis et al. 2015 4	MA	Liposuction + Abdominoplasty	Four studies (140 participants).	2 months-2 years.	Fasting glucose levels changes after SSFR were not statistically significant (1.42, 95% CI: −1.57, 4.40). Changes in insulin sensitivity were also assessed either by insulin tolerance test or HOMA index, however the result reported lack of significant change after SSFR (0.14, 95% CI -0.69-0.96).	This MA included studies that were so contrived in terms of control group that no conclusion was possible. The small number of studies limited its validity and prevented subgroup analysis according to certain confounders such as age or BMI.

	Synthesis author and year	Synthesis type	Type of SSFR	Included studies	follow up	Main finding	Remaining evidence gaps
4.	Danilla et al., 2013 67	MA	Liposuction	Five quasi experiment studies (111 participants).	3 weeks - 1 year.	Analysis reported that SSFR result in decreased fasting insulin levels, and the amount of reduction was associated with the amount of aspirated fat, independent with the baseline BMI. No significant change was reported in HOMA-IR levels after SSFR.	Although this MA studied the effect of time on the SSFR induces changes in insulin resistance, the sample size of the included studies was small.

SSFR; surgical subcutaneous fat removal. SR; systemic review. MA: meta-analysis. CI; confidence interval. BMI; body mass index. HOMA-IR; Homeostatic Model Assessment for Insulin Resistance.

3.2.3. Impact of SSFR on Inflammation

Obesity is associated with chronic low-grade inflammation. This is a result of the increased influx of immune cells to the fat tissue, as well as the increased secretion of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-a) [13]. Adipocytes have an equal proinflammatory effect on the macrophages [74]. This inflammatory status is thought to be the mechanism behind most of the obesity-linked metabolic disorders [13].

One SR and one MA examined the effect of SSFR on multiple inflammatory markers such as TNF-a, C-reactive protein (CRP), and Interleukin-6 (IL-6), and the findings are detailed in (Table 3.2). In summary, the syntheses combined heterogeneous studies with different follow-up times. Conclusions varied between no change after SSFR or lower levels of IL-6 and TNF-a after surgery. However, the extent and time-trend were not reported, thus a dose response meta-analysis remained a needed future task.

Table 3.2. Syntheses That Report Changes in Inflammatory Markers After SSFR

	Synthesis author and year	Synthesis type	Type of SSFR	Included studies	Follow up	Main finding	Remaining evidence gaps
1.	Sailon et al. 2017 [3]	SR	Liposuction	Four prospective studies (210 participants). The review examined the effect of large volume liposuction (more than 3.5 liters) on IL-6 and TNF-α.	10 weeks - 6 months.	Two studies reported a statistically significant decrease in plasma IL-6 and TNF-α levels.	Neither a clear extend of change, nor the clinical significance was reported.
2.	Danilla et al. 2013 [67]	MA	Liposuction	Eight prospective studies (239 participants) examined the changes in CRP (4 studies), IL-6 (3 studies), and TNF-a (3 studies).	1 - 6 months.	No association between the amount of aspirated fat and serum levels of CRP, IL-6, and TNF-a.	No clear report on the results, rather than just a general conclusion of no association.

SR; systemic review. MA: meta-analysis. CI; confidence interval. CRP; c-reactive protein. IL-6; interleukin 6. TNF-a; tumour necrosis factor-alpha.

3.2.4. Impact of SSFR on adipokine levels

Changes in the adipokines have been examined by only one SR and one MA, and both reported a reduction of leptin levels after SSFR. However, there was heterogeneity in the reported changes in other adipokines such as adiponectin and resistin (Table 3.2).

Table 3.3. Syntheses That Report Changes in Adipokines After SSFR

	Synthesis author and year	Synthesis Type	Type of SSFR	Included studies	Follow up	Main finding	Remaining evidence gaps
1.	Sailon et al. 2017 [3]	SR	Liposuction	Five prospective studies (225 participants) examined the effect of large volume liposuction (> 3.5 liters) on adipokines levels (namely leptin and adiponectin).	10 weeks- 6 months.	Leptin was examined by 4 studies, which all reported a statistically significant reduction. Adiponectin was assessed in all studies, two of which reported a significant increase.	Neither a clear extend of change, nor the clinical significance was reported. Other adipokines were not assessed.
2.	Danilla et al. 2013 [67]	MA	Liposuction	Six quasi experiment studies (191 participants) examined the effect of SSFR on leptin levels.	6 weeks - 6 months.	The MA showed a statistically significant reduction in leptin levels (Coefficient: 0.18). This reduction was proportional to the amount of aspirated fat, and patient BMI.	The study didn't report the changes in other adipokines, nor the clinical significance of the reported changes.

SR; systemic review. MA: meta-analysis. SSFR; surgical subcutaneous fat removal. BMI; body mass index.

3.2.5. Summary of findings

This umbrella review summarizes four attempts at evidence synthesis on the metabolic changes after surgical fat removal, with a total of 29 unique studies included and 759 total participants. There was a possible improvement in obesity-associated insulin resistance, however, there was a lack of clarity regarding the extent of the effect and clinical significance. Nevertheless, it seems likely that ASF removal is associated with improved insulin sensitivity. In terms of inflammation, one of the two syntheses reported that ASF removal results in a lower degree of IL-6 and TNF-a, and thus potentially a more favorable metabolic risk profile. These syntheses also reported a reduction of leptin levels after ASF removal through surgery. There was heterogeneity in the reported changes in other adipokines such as adiponectin and resistin. Clearly, the data from previous studies are not conclusive, nevertheless, it seems likely that SSFR is associated with improved insulin sensitivity and lower levels of inflammatory cytokines.

3.3. Current gaps in the literature

It is true that existing studies were of small sample size, heterogeneous in terms of baseline body mass index (BMI), type and amount of SSFR, gender differences, as well as participants behavior in terms of diet and exercise [75]. While this has a bearing on the results of this paper, a meta-analysis generates an average effect over the multiple studies and those till date [76–81] have failed to generate consensus because they did not address the heterogeneity in follow up duration among the included studies. Our dose response meta-analysis (DRMA) [82] aimed not only to pool previous studies to reach a bigger sample size and stronger conclusion, but also to account for differences in follow-up time. Thus, regardless of the existing heterogeneity in patient characteristics, there was a metabolic effect demonstrable for SSFR and these results are consistent

with the observation that even a small amount of fat reduction can have a significant metabolic benefit on insulin sensitivity, inflammation, and blood pressure [83,84].

With the current advancement in our understanding regarding fat tissue being an active endocrine organ rather than an energy store, as well as the accelerating increase in demand for such body contouring surgeries (that lead to SSFR) to improve body shape quickly, it is essential to further investigate the metabolic changes after these surgeries, not only to confirm the safety of these procedures, but also to help us to understand the mechanisms underpinning the link between obesity and metabolic diseases and the impact of various patient differences on metabolic sequalae. Our meta-analysis is reassuring in that metabolic safety seems plausible and therefore the focus now needs to be on additional sources of population heterogeneity such as existing comorbidities such as diabetes mellitus and history of previous bariatric surgery, which could alter the metabolic trajectory after SSFR. As Seretis aptly concludes, future controlled studies with homogenous samples, proper methodology, and adequate follow-up remain of high importance to clarify the role of different patient factors on metabolism after surgical [82]nd non-surgical [85] fat removal.

3.4. Implications for future research

3.4.1. The role of ASF versus AVF in human metabolism

Central obesity in the abdominal area represents one of the essential components of metabolic syndrome, along with insulin resistance, elevated serum triglyceride, blood pressure, and low high-density lipoproteins, and it is distributed between the ASF and AVF compartments [4] Although some studies have linked the metabolic risk of obesity mainly to the AVF tissue [9,86], others have proposed that both AVF and ASF play a role in metabolic risk [3]. Generally, subcutaneous fat mass is more than twice the visceral fat mass, especially among females [87]. As a result, 85% of bloodstream free

fatty acids come from the subcutaneous fat stores, which is a major contributor to systemic insulin resistance by inhibiting glucose uptake by skeletal muscles [88]. There is evidence from some studies among healthy men [89] and those with T2DM [90] that ASF may be more strongly correlated with insulin resistance than AVF. There has also been a report from a study of a healthy cohort of mixed genders that ASF correlates with insulin resistance independently of AVF, but not the other way around [91]. To sum this up, there is some evidence from the umbrella review as well as other studies suggesting that ASF may make an important contribution to obesity-related metabolic change, and this thus can be a mechanism through which SSFR can create a more favorable metabolic profile.

When studies have looked directly at the added impact of AVF on metabolism, by examining the effect of adding omentectomy to bariatric procedures, results were inconsistent. Some studies reported that it could result in better glucose homeostasis and lower inflammatory markers [92,93]. Conversely, others reported a lack of clinical improvement in the metabolic profile [94–96]. Many open questions remain therefore about the role of AVF versus ASF and part of the problem lies in their study design, for example the lack of clarity regarding patient selection, determining the type of surgery, the parameters that needed to be measured, and accounting for patient factors [97]. In addition, there were also technical limitations of older studies regarding advanced imaging technologies to measure visceral adipose tissue accurately. At a more fundamental level, improved knowledge of all aspects of adipose biology, including adipose tissue cellular heterogeneity [98,99] as well as divergent responses to metabolic and endocrine stimuli that will be required to make significant advances and resolve the problem highlighted above [100]. In addition, a recent genome-wide association study also shows the contribution of genetics to visceral adiposity and its relation to

ethnicities and gender in the context of metabolic disease. In particular, the study suggests that increased AVF is more harmful compared with ASF, but it is not clear why this should be the case 101.

3.4.2. Adipokines

To determine why SSFR impacts adipokines levels, one needs to understand the roles of adipocyte-derived factors, as well as their effects on intermediary metabolism. Adipocyte-derived factors need to be understood in terms of source, relation to obesity, and main function. (Tables 4 & 5) summarize the inflammatory and anti-inflammatory adipokines, the most well-known candidates are leptin, and interleukin-6 (IL-6).

Table 3.4. Description of The Potential Inflammatory Adpokines

	Hormone	Source	Observed changes in obesity	Main function
1.	Leptin [102]	Mainly from adipocytes.	It is a well-known marker of obesity.	It is a satiety hormone, that regulate body weight by suppressing the feeling of hunger, inhibit fat storage, and promote fatty acid oxidization. It also promotes inflammation.
2.	Resistin [103]	Adipocytes, monocytes, and macrophages.	Increased in obesity, insulin resistance, and diabetic patients.	It is a pro-inflammatory adipokine. It is thought to play a role in insulin resistance.
3.	Fatty acid binding protein- 4 (FABP-4) [105]	Adipocytes and macrophages.	Increased in obesity, insulin resistance, and diabetic patients.	Play a role insulin resistance and inflammation.
4.	Retinol binding protein (RBP-4) [105]	Adipocytes (especially visceral fat), macrophages, and liver.	Increased in obesity, insulin resistance, and diabetic patients. Associated with hypertension, and dyslipidemia.	Act as a transporter for retinol and play a role in insulin resistance development.
5.	Acylation stimulating protein (ASP) [106]	Adipocyte	Increased in obesity and dyslipidemia patients.	Autocrine function that leads to increasing triglyceride synthesis.
6.	Lipocalin-2 (LCN2) [107]	Adipose tissue, liver, kidney, lung, macrophages, and neutrophils.	Increased in obesity (specially in severely obese females).	Play a role in inflammation and insulin resistance.
7.	Chemerin [108]dipose tissue, liver, as well as innate immune cells.	Elevated with obesity and diabetic patients.	Play a role in insulin resistance, adipocyte metabolism, and diabetic induced cardiovascular disease.	

	Hormone	Source	Observed changes in obesity	Main function
9.	Vaspin [110]	Adipose tissue, liver, pancreas, stomach, muscles and skin.	Increased in obesity, insulin resistance and diabetic patients.	Act as a member of the serine protease inhibitor family
10.	Apelin [111]	Adipose tissue, hypothalamus, heart, and skeletal muscles.	Increased in obesity, insulin resistance and diabetic patients.	Play a role in regulating glucose metabolism, by inducing glucose uptake.
11.	Gremlin-1 [112]	Preadipocytes.	Increased in obesity.	Act as an inhibitor of bone morphogenetic protein (BMP), which is one of the transforming growth factor-beta family.

Table 3.5. Description of The Potential Anti-Inflammatory Adipokines

	Hormone	Source	Observed changes in obesity	Main function
1.	Adiponectin [113]	Adipose tissue and skeletal muscles.	Lower levels in diabetic patients.	Anti-obesity, anti-atherogenic, anti-inflammatory, and anti-diabetic effects.
2.	Omentin-1 [114]	Visceral adipose tissue.	Lower levels in obese and diabetic patients	anti-inflammatory, anti-obesity, anti-diabetic properties, and insulin sensitizing effect.
3.	Secreted frizzled related protein 5 (SSFRP5) [115,116]	Adipose tissue.	Lower levels in obese and diabetic patients.	anti-inflammatory and insulin sensitizing effect.
4.	Cardiotrophin-1 (CT-1) [116]	Adipose tissue, liver, kidney, muscle, heart, and lung, brain and testis.	Controversial results regarding the changes in serum levels of obese patients.	One of the IL-6 cytokine family, play a role in glucose and lipid metabolism, has an insulin sensitizing potential effect.

IL-6; interleukin 6.

3.4.3. Leptin, ASF and insulin sensitivity

Leptin is a 167-residue peptide hormone encoded by the *Ob* gene, and it is secreted mainly by the adipocytes but also from the gastric epithelium and other tissues [117]. Since its identification in 1994 by positional cloning [118], leptin has gained much recognition as a crucial peripheral and central signaling molecule associated with energy balance. This, in turn, has contributed to changing the perception of the adipose tissue from being a form of passive energy depot (primarily in the form of energy-rich triglycerides (9 kilocalories per gram) to that of an active endocrine organ that actively modulates food intake and systemic energy metabolism.

Leptin levels are positively associated with BMI, HOMA-IR and serum triglycerides and negatively with serum HDL in mostly normal weight health individuals suggesting that leptin increases with BMI as well as in those with insulin resistance [119]. The latter study suggests that leptin was coming mainly from ASF given correlation with hip and waist circumference but not with waist-hip ratio [119]. Under normal physiological conditions, bloodstream levels of leptin are proportional to fat mass for a given individual [120] suggesting that the increase in leptin is driven by fat mass and that both leptin and insulin resistance are consequences of an increase in fat mass. Nevertheless, basal plasma leptin concentrations are significantly lower in insulin-sensitive than in insulin-resistant men (1.90 +/- 0.4 vs. 4.35 +/- 1.21 ng/ml, $P < 0.05$) of identical body fat composition [121] suggesting either that excess leptin may also lead to increases in insulin resistance independent of adiposity or that leptin production increases in insulin resistant men in response to unknown feedback mechanisms in an effort to ameliorate the insulin resistance. The latter seems more plausible given that a direct action of leptin on its hypothalamic neuronal target is required to maintain normal glucose homeostasis data and insulin sensitivity [122,123] and therefore the rising leptin

level *and* insulin resistance in obesity lends plausibility to the conclusion that another fat derived molecule required for the leptin effect on glucose homeostasis may be downregulated in obesity for this paradoxical observation to hold. It remains to be determined if this molecule does indeed exist and what it could be.

3.4.4. Interleukin-6 (IL-6), ASF and inflammation

Interleukin-6 is a 212-residue protein cytokine encoded by the IL-6 gene [124]. Since its identification in 1986 by molecular cloning of B-cell stimulatory Factor-2 [125], IL-6 has been recognized as a cytokine with various biological activities implicated with a detrimental role in a wide range of inflammation-associated disease states, including susceptibility to diabetes mellitus [126]. IL-6 is synthesized by various cell types of which white adipocytes are responsible for one-third of basal serum levels in humans [127].

The IL-6 level is probably the single most important factor associated with the hepatic acute-phase response and this is a response to tissue damage or infection that initiates host defense mechanisms and whose goal is to eliminate the threat and facilitate tissue repair [128]. Obesity however is associated with chronic low-grade inflammation possibly from hypoxia in adipocytes, resulting in the release of IL-6 and activation of other factors that positively feedback and amplify IL-6 release [129]. This leads to the metabolic syndrome and similar to leptin, in vitro studies have shown that ASF produces more IL-6 than VSF [130] making the link between ASF and metabolic syndrome stronger than that for VSF [131].

3.4.5. Leptin, IL6 and the SSFR- bariatric surgery interaction

It is important to note that some SSFR patients tend to have had bariatric surgery, which is associated with enhanced postprandial gut hormone release, particularly GLP-1, a hormone interlinked with factors released from adipose tissue,

e.g. leptin and IL-6 highlighted above. However, what remains unclear is whether or to what extent this crosstalk gets perturbed in patients undergoing SSFR and/or bariatric surgery. Furthermore, what are the long-term metabolic sequelae? Thus, a robust examination of the changes of IL-6 after the sudden removal of fat surgically by body contouring procedures might widen our understanding of the mechanisms behind these metabolic changes.

3.4.6. Other considerations and future tasks

Apart from the potentially favorable effects of SSFR on metabolism and adipokines discussed above, many studies also support the effectiveness of bariatric surgery for treating obesity and weight-related disease [36,132]. However, the question about the combined impacts of these surgical interventions has been relatively under-studied, and the results remain inconclusive. Future studies that can link the metabolic improvement after bariatric surgery and bariatric medications such as Semaglutide to the preferential loss of AVF or ASF will be of great benefit. Additionally, a dose response meta-analyses is needed to examine the time trend of the metabolic changes after SSFR, which can answer important questions regarding the durability and extent of changes induced by these procedures over time.

When a negative energy balance is induced by interventions such as SSFR, resulting in a moderate initial reduction of 5 to 10% from baseline body weight, the physiological adaptations certainly favour weight regain; thus, most people recover weight post-SSFR or at the end of lifestyle interventions. With the common SSFR procedures, this loss is of abdominal fat that constitutes ~15% of total adipose tissue [133], with the main component of the latter being ASF.

Given that fat distribution is one parameter that modifies the impact of obesity on health, knowledge about whether fat tissue removed through SSFR is replaced by

new fat tissue and if this occurs in the same or at different anatomical sites is important since the latter may have worse effects. Previous studies reported that the fat could return to sites other than that from which fat has been removed, such as the breast, hip, and thigh regions [134,135], but this is not always the case [136]. There is also the possibility that new fat may accumulate at sites where fat does not commonly accumulate (ectopic fat) and such ectopic adipose tissues may deposit in several organs/tissues (intramuscular/cardiac/hepatic) in the body with adverse consequences [137,138]. However, recent studies of the heart [139,140] have suggested that ectopic fat is protective against the risk of developing cardiovascular complications by increasing glycolysis, as a physiological healing response. In the context of SSFR, it is unclear to what extent the redistributed fat contributes to the ectopic fat accumulation in tissues such as intramuscular, intrahepatic, and myocardial fat and if it has a protective or detrimental effect. Furthermore, it is unclear if and how or which specific factors drive the fat redistribution to ectopic regions in preference to the rest of the body spatiotemporally. Identifying such factors can be helpful surrogate biomarkers for predicting potential risk factors in epidemiological studies. However, it should be noted that rodent models of fat biology do not adequately represent what happens in humans, and higher mammals such as baboons may be a better model that closely resembles human adipocyte function [141].

Thus far, results from studies designed to identify the factors that address the regulation of energetics and body fat redistribution/ regeneration post-SSFR in rats, mice or hamsters have limited contribution in closing the knowledge gap because of insufficient mechanistic data, inadequate sample size, or lack of proper statistical tests reported [142]. Therefore, future studies in appropriate animal models or human clinical trials should account for the biological consequences of ectopic fat redistribution

following weight gain post-SSFR. However, there is a need to ascertain the beneficial or detrimental nature of fat redistribution at specific anatomical sites, in relation to its quantity, rate, and time of accumulation following weight gain post-SSFR.

3.5. Conclusion

We conclude that there is a gap in terms of the probability of weight gain or accumulation of fat post-SSFR, but there is data that in the short term there might be a metabolic benefit of excess ASF removal. Longer-term data are needed to determine if this benefit is sustained in the longer term. Patients going for SSFR, represent a unique population with a sudden removal of their ASF. However, the metabolic changes after these procedures are still unclear, and existing studies suggest a trend towards benefit rather than harm. There is thus no immediate harm from these procedures but there is a need for properly designed dose-response meta-analyses as well as well-conducted prospective clinical studies to unravel these putative changes. In turn, this will help us not only to confirm the safety of these procedures but also to define if these procedures can be used for metabolic benefit and to broaden our knowledge about the mechanisms underpinning excess ASF and associated metabolic consequences.

CHAPTER 4: DURABILITY OF METABOLIC CHANGES AFTER SSFR

4.1. Main objectives and methods summary

This study describes a systematic review and dose-response meta-analysis (DRMA) of observational studies pertaining to the metabolic impact of body contouring surgery with a view to establishing how these procedures impact patient physiology over time.

To address the main objectives above, PubMed, Embase and Scopus databases were searched using the Polyglot Search Translator to find studies examining quantitative expression of metabolic markers. The latter included anthropometrics/ body composition, serum adipokines, inflammatory cytokines, glucose homeostasis, lipid profile and blood pressure. Further details of the methodology used in this study are detailed in Chapter 2.

4.2. Results

The literature review yielded a total of 444 studies. Duplicate studies were excluded leaving 258 studies, of which 236 were excluded by abstract review. Eventually 22 studies with a total of 493 participants, were selected as relevant to this synthesis [143–164]. The conduct of the literature review is summarized in Figure 2.

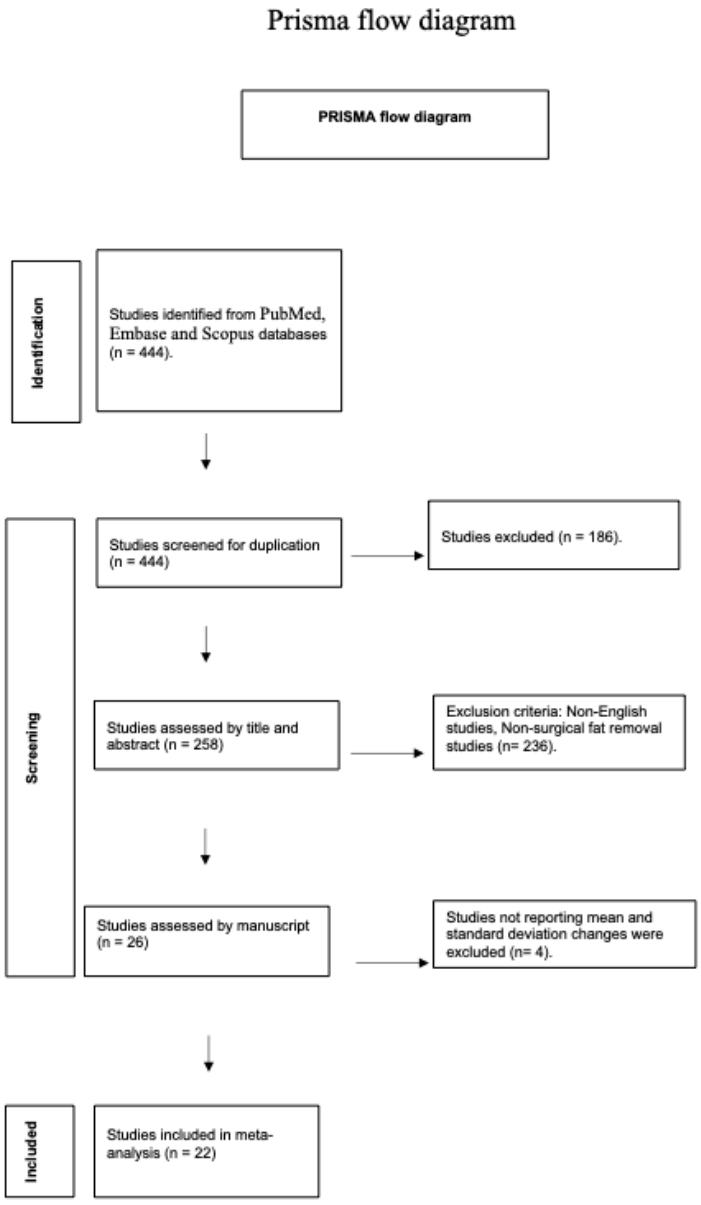


Figure 2. PRISMA flow diagram for selection of studies (SSFR-DRMA study).

4.2.1. Characteristics of included studies

Characteristics of the selected studies are summarized in (Table 4.1) and include study identifier, country, design, number of participants (sample size), population demographics, preoperative (baseline) body mass index, type of surgical fat removal

(abdominoplasty versus liposuction), follow up time points after surgery (in days), and fat mass (in Kgs) removed in abdominoplasty or lipo-aspirate (in liters) (which consists of infiltrated solution plus removed fat mass) in liposuction procedures.

Table 4.1 Characteristics of Included Studies For The SSFR-DRMA

Study	Country	Study design	No. of subjects	Population (Gender, age, comorbidities)	Base -line BMI (kg/m^2)	Type of SFR	Outcome measures	Follow up time points (days)	Average fat mass (kg) or lipoaspirate (L) removed
Vinci et al, 2016	Italy	Case-control	13	-males - age (18- 55) yrs	30.3 ± 3.06	abdomino-plasty	Adiponectin, IL6, CRP, TNF-a, FBG, LDL, HDL, TG, TC	0 40	NR
Gibas-dorna et al, 2016	Poland	Case-control	17	-males - age (37.15 ± 9.60) yrs -35% are diabetic type 2	29.16 ± 4.02	lipo-suction	BMI, WC, leptin, adiponectin, FBG, insulin, HOMA-IR	0 60 180	2.208 ± 0.562 L
Cuomo et al, 2015	Italy	Quasi-experiment	64	-females -age (32-48) yrs	33.44 ± 2.3	abdomino-plasty	Leptin, adiponectin, resistin, FBG, insulin, TG, TC	0 180 360	1.6 kg
Solis et al, 2014	Brazil	RCT	18	-females -age (20 -35) yrs	23.1 ± 1.6	lipo-suction	FM, LBM, leptin, adiponectin, IL6, TNF-a, FBG, insulin.	0 60 180	1.240 ± 0.363 L
Ramos-gallardo et al, 2013	Mexico	Quasi-experiment	26	-female -age (26 -56 yrs - all are dyslipidemic	27.4± 1.1	abdomino-plasty	BMI, FBG, insulin, HOMA-IR, LDL, HDL, TG, TC	0 90	1.7 kg
Benatti et al, 2012	Brazil	RCT	18	-females -ages (20-35) yrs	23.2± 1.3	lipo-suction	FM, LBM	0 60 180	1.240 ± 0.363 L

Study	Country	Study design	No. of subjects	Population (Gender, age, comorbidities)	Base -line BMI (kg/m^2)	Type of SFR	Outcome measures	Follow up time points (days)	Average fat mass (kg) or lipoaspirate (L) removed
Mohammed et al, 2008	USA	Quasi-experiment	7	-females - 43% diabetic type 2	39± 2	lipo-suction	BMI, FM, FBG, HOMA-IR, LDL,HDL, TG, SBP, DBP	0 70 189	18 L
Robles-cervantes et al, 2007	Mexico	RCT	6	-females -age (30- 40) yrs	31.9± 1.2	lipo-suction	Leptin, FBG, HDL, TG, TC	0 30	NR
Chang et al, 2007	USA	Quasi-experiment	15	-females -age (21 - 39) yrs	18- 25	lipo-suction	Leptin, adiponectin, IL6, CRP	0 1	NR
Martinez-abundis et al, 2007	Mexico	RCT	6	-females -age (20 - 50) yrs	30.7 ± 0.9	abdomino-plasty	Leptin, LDL, HDL, TG, TC	0 21	3.2 kg
Busetto et al, 2006	Italy	Quasi-experiment	15	- females -pre-menopausal	30.7 - 53.6	lipo-suction	FM,LBM, leptin, adiponectin, resistin, IL6, CRP, FBG, insulin, HOMA-IR, FFA	0 1 3 28 180	16.3 ± 4.3 L
Hong et al, 2006	Korea	Quasi-experiment	11	-age (19 -40) yrs	23.8 ± 4.4	lipo-suction	BMI, LDL, HDL, TC	0 60	6,790 L
Andrea et al, 2005	Italy	Quasi-experiment	123	-females -age (32 - 40) yrs	32.8 ± 0.8	lipo-suction	BMI, leptin, adiponectin, resistin, IL6, TNF-a, FBG, insulin, HOMA-IR, TG, TC, FFA, SBP, DBP	0 21 90	4.984 ± 0.821 L

Study	Country	Study design	No. of subjects	Population (Gender, age, comorbidities)	Base -line BMI (kg/m^2)	Type of SFR	Outcome measures	Follow up time points (days)	Average fat mass (kg) or lipoaspirate (L) removed
Davis et al, 2005	USA	Quasi-experiment	15	-females -age (23–45) yrs	25–35	lipo-suction	BMI, leptin, adiponectin, IL6, TNF-a, FBG, insulin, HOMA-IR, TG, FFA	0 1 30	1.88 ± 0.213 L
Klein et al, 2004	USA	Quasi-experiment	15	-females -46% diabetic type 2	nonDM 35.1 ± 2.4, DM 39.9 ± 5.6	lipo-suction	BMI, WC, FM, leptin, adiponectin, IL6, CRP, TNF-a, FBS, insulin, LDL, HDL, TG, TC, SBP, DBP	0 84	17±2
Robles-cervantes et al, 2004	Mexico	Quasi-experiment	15	-females -age (28.8) yrs	26.35	lipo-suction	BMI, FBG, insulin, HOMA-IR, TC	0 21	3.570 ± 1.543 L
Esposito et al, 2004	Italy	Quasi-experiment	45	-females -pre-menopausal	35.1 ±2.9	lipo-suction	BMI, WC, adiponectin, HOMA- IR, TG, TC	0 90 180	NR
Gonzalez-Ortiz et al, 2002	Mexico	RCT	6	-females -age (20 - 40) yrs	31.7 ± 1.7	lipo-suction	BMI, FBG, insulin, LDL, HDL, TG, TC	0 28	4.308 ± 1.126 L
Chen et al, 2001	China	Case series	4	-females - age (34.0± 3.7) yrs.	23.6 - 42.7	lipo-suction	leptin	0 1 2 14	range 1.25 - 12.78 L

RCT; randomized controlled trial. *BMI;* body mass index. *FM*; fat mass. *LBM*; lean body mass. *WC;* waist circumference. *TNF- α*; tumor necrosis factor alpha. *CRP*; C - reactive protein. *IL6*; interleukin 6. *FBG*; fasting blood glucose. *HOMA-IR*; homeostatic model assessment for insulin resistance. *SBP;* systolic blood pressure. *DBP;* diastolic blood pressure. *LDL;* low-density lipoprotein cholesterol. *HDL*; high-density lipoprotein cholesterol. *TC*; total cholesterol. *FFA*; free fatty acids. *L*; liters. *NR*; not reported.

4.2.2. Metabolic changes after SFR

A. Anthropometrics / body composition

Body mass index (kg/m2), fat mass (kg), waist circumference (cm), and lean body mass (kg) were measured. There was significant heterogeneity in BMI and fat mass changes across studies, however, the DRMA suggested that post-surgical weight reduction was maximal at fifty days (2 BMI units, and 3 kg of fat mass respectively), after which there was a return towards the average pre-surgical weight (Figure 3). Due to the paucity of studies, confidence intervals were wide, and the trend could not be confirmed more precisely as this was driven by the bigger studies. Nevertheless, the effect of SFR on BMI and related parameters persisted for at least 50 days. The waist circumference showed a clear reduction of around 5 cm after surgery, which was maintained till end of follow-up. Lean body mass showed no significant change after SFR.

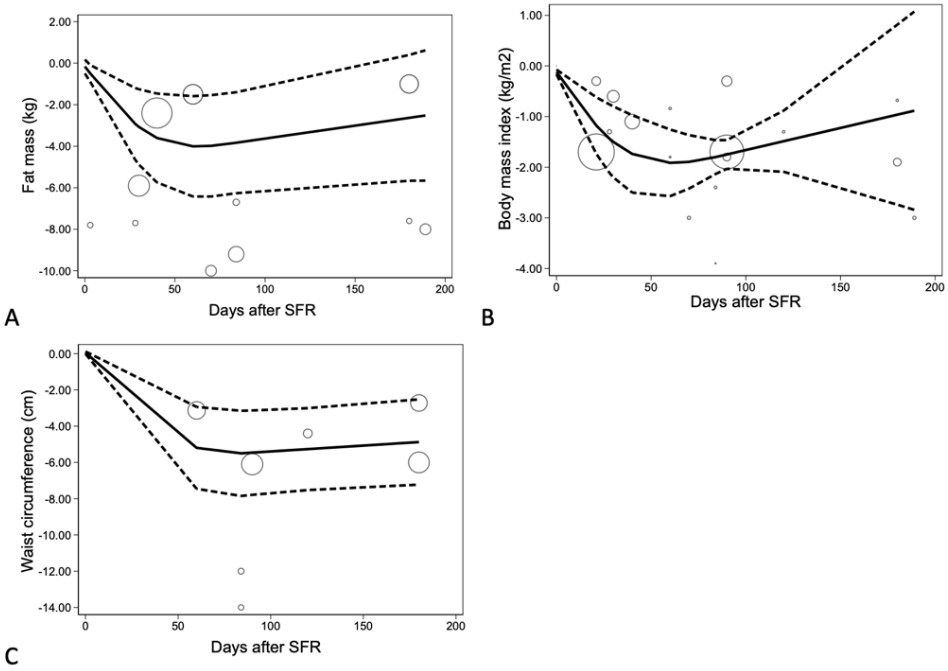


Figure 3. Change in (A) Body mass index, (B) Fat mass, (C) Waist circumference over time since surgical fat removal (SFR)

The “dose” is time in days after surgical fat removal (SFR). The circles represent the weighted mean difference in each individual study at this time-point with the marker size reflecting the weight of corresponding study.

B. Serum adipokines

Serum leptin (µg/L), adiponectin (µg/ml), and resistin (µg/L) were measured before and after SFR. Leptin exhibited a significant post-operative reduction that peaked at post-operative day 50 (average of 15 µg/L) and returned to preoperative levels by day 180 (Figure 4). The DRMA yielded no significant differences in serum adiponectin and resistin over time.

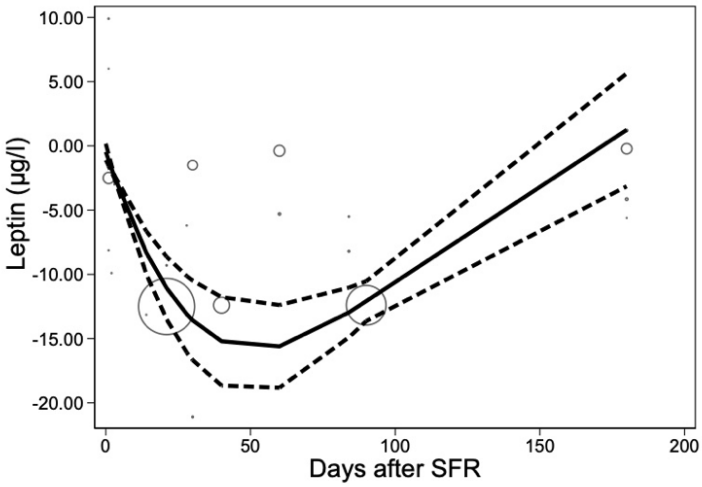


Figure 4. Change in Leptin over time since SFR.

The “dose” is time in days after surgical fat removal (SFR). The circles represent the weighted mean difference in each individual study at this time-point with the marker size reflecting the weight of corresponding study.

C. Markers of glucose homeostasis

Fasting blood glucose (mmol/L), fasting insulin (pmol/L), and HOMA-IR levels were measured. The DRMA suggested that post-surgical insulin resistance reduction was a lasting feature of SFR for the duration of the study. Peak reductions were 17 pmol/L and 1 point for fasting insulin and HOMA-IR respectively. There was no change seen with fasting blood glucose (Figure 5).

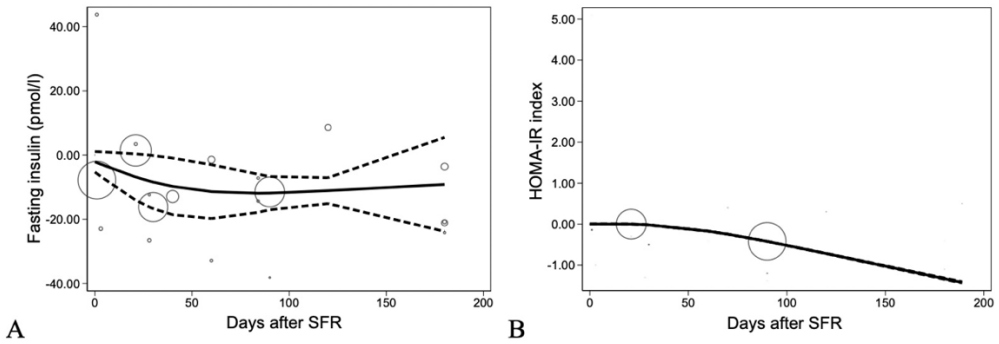


Figure 5. Change in (A) Fasting insulin, (B) Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) over time since SFR.

The "dose" is time in days after surgical fat removal (SFR). The circles represent the weighted mean difference in each individual study at this time-point with the marker size reflecting the weight of corresponding study.

D. Inflammatory markers

Tumor necrosis factor alpha (TNF-α) (pg/ml), Interleukin-6 (IL-6) (pg/ml) and C - reactive protein (c-RP) (mg/L) and were measured. While there was substantial heterogeneity across studies, the DRMA suggested that post-surgical reduction in serum TNF-α peaked at day 50 (0.75 pg/ml) and thereafter exhibited a return to pre-surgical levels (Figure 6). No significant differences were observed in serum levels of

IL-6 or c-RP over the course of the study.

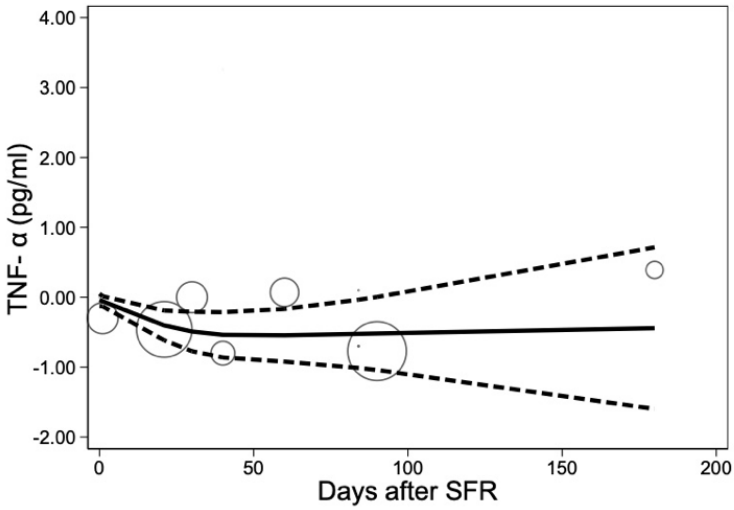


Figure 6. Change in Tumor Necrosis Factor alpha (TNF- α) over time since SFR. The "dose" is time in days after surgical fat removal (SFR). The circles represent the weighted mean difference in each individual study at this time-point with the marker size reflecting the weight of corresponding study

E. Lipid Profile

Low-density lipoprotein cholesterol (LDL in mmol/L), high-density lipoprotein cholesterol (HDL in mmol/L), serum fasting triglycerides (mmol/L), total cholesterol (mmol/L) and free fatty acids (g/L) were measured. Serum HDL increased post-surgically, peaking at day 50. However, by day 100 expression had returned to the baseline and thereafter continued to fall to the end of the study period at day 180. Total cholesterol fell by 0.25mmol/L post-surgically to day 50, however the trend thereafter is obscured by wide confidence intervals owing to paucity of data (Figure 7). No significant differences were observed in serum levels of triglyceride, low density

lipoproteins and free fatty acids.

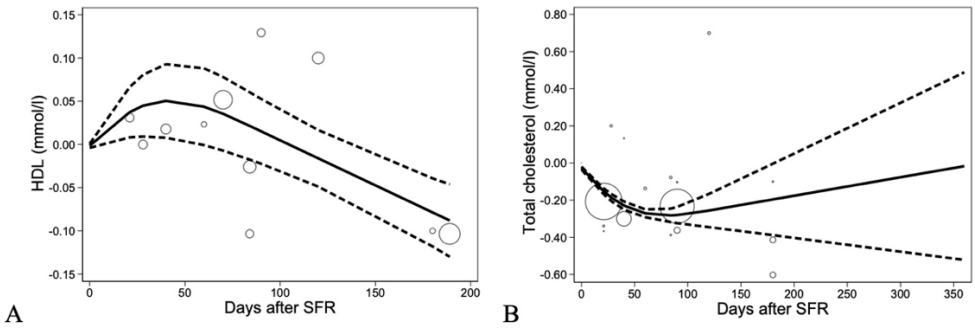


Figure 7. Change in (A) High-density lipoprotein (HDL) cholesterol and (B) Total cholesterol over time since SFR.

The circles represent the weighted mean difference in each individual study at this time-point with the marker size reflecting the weight of the corresponding study.

F. Blood Pressure

Following SFR, there was a mean reduction in both SBP and DBP of 3.5mmHg by day 50 which thereafter exhibited a return to pre-surgical levels at day 180 (Figure 8).

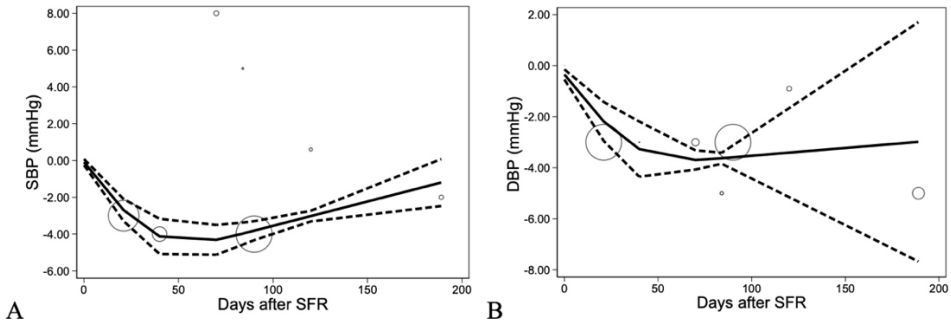


Figure 8. Change in (A) Systolic Blood Pressure (SBP), (B) Diastolic Blood Pressure (DBP) over time since SFR.

The “dose” is time in days after surgical fat removal (SFR). The circles represent the weighted mean difference in each individual study at this time-point with the marker size reflecting the weight of corresponding study.

4.2.3. Quality assessment of included studies

Most of the studies were ranked in the 4th quartile of the count of safeguards. Moreover, the most deficient standards across articles were equal ascertainment and equal prognosis. On the other hand, equal implementation, equal recruitment, equal retention, sufficient analysis, and temporal precedence were found to be the least deficient standards. See Supplementary Figure 5.

4.3. Discussion

We examined the influence of surgical fat removal (SFR) during body contouring surgery on body anthropometrics/ body composition measurements, serum adipokines and inflammatory cytokines, glucose homeostasis, lipid profile and blood pressure by means of a systematic review of clinical data and subjected these data to dose-response meta-analysis. We observed that SFR resulted in a significant and lasting improvement in insulin resistance as evidenced by serum fasting insulin and homeostatic model assessment for insulin resistance (HOMA-IR) index and transient improvements in body mass index, fat mass, systolic and diastolic blood pressure and in serum leptin, TNF-α, high density lipoprotein and total cholesterol concentrations. There were no observable improvements in lean body mass, serum adiponectin, resistin, IL-6, C - reactive protein, low density lipoprotein, free fatty acids, or fasting blood glucose.

Weight loss after SFR peaked at day 50 post-surgery but thereafter weight gain was observed with BMI and fat mass returning to near pre-operative levels after a period of 6 months. This might be due to the loss of the negative energy balance after surgery, or increased energy intake, especially if it was not accompanied by physical exercise after SFR [26,29]. Another possibility is that this return towards baseline has an underlying hormonal basis such as residual fat cells hypertrophy [165–167]. This has also been noted on similar animal studies, where surgical fat reduction was followed weeks to months by a compensatory increase in the fat mass elsewhere [168,169]. Using dual-energy x-ray absorptiometry (DEXA) scans and magnetic resonance imaging (MRI), a clinical trial observed compensatory abdominal fat mass deposition in a 12-month period after thigh liposuction [170]. Other retrospective human studies reported an increase in breast size after abdomen and thigh liposuction surgeries, which was postulated to be due to an altered ratio of androgen to estrogen levels [165–167] but this may not be the only explanation.

Leptin was the only hormone derived from adipose tissue that exhibited and expression pattern altered by SFR. This was similar to the findings of a meta-analysis on the effect of large-volume liposuction on serum leptin and adiponectin levels. In this study too, leptin, but not adiponectin was reduced after SFR. Since, leptin is secreted mainly from fat cells and correlates with fat mass,[171] the transient fall in serum leptin levels is understood in the context of the post-surgical reduction in fat mass. More interestingly, we may speculate that the rebound rise in serum leptin back to pre-surgical levels may involve hypersecretion and/or hypertrophy by the residual fat mass [165–167]. The physiological adaptation underpinning this phenomenon remains obscure but the fact that the post-surgical BMI mirrors the post-surgical temporal expression profile of leptin (which governs satiety) suggests a homeostatic mechanism.

There is no clear relationship in the literature between SFR and variations in the expression profiles of the inflammatory cytokines TNF-α and IL-6 [26,28,172]. That said, the transient reduction in serum TNF-α identified in the present study has been observed before [172]. In comparison to leptin, the synthesis of TNF-α occurs mainly in the monocyte lineage [174]. The accumulation of resident macrophages in the adipose tissue correlates with the degree of obesity [175,176]. Animal models suggest that, in morbid obesity, macrophages (responsible for most of the overall secretion of TNF-α) may account for up to 40% of the cellular mass of adipose tissue [177]. Our analysis suggests that SFR mediated removal of the resident macrophages in the adipose tissue results in the initial reduction in TNF-α levels. The underlying mechanisms for the recovery in TNF-α level after the first two months of the SFR remains unclear. However, toll-like receptors induced synthesis of TNF-α from existing resident macrophages and/or through recruitment of circulating myeloid-derived blood monocytes that give rise to adipose tissue-resident macrophages are potential pathways for TNF-α recovery.

Accumulation of adipose tissue resident-macrophages is facilitated by IL-6 secreted from adipocyte, and obesity is associated with elevated circulating IL-6 levels [178,179]. During the inflammatory phase, macrophages promote the return to homeostasis by removing apoptotic cells and cell debris and contributing to damage repair [180]. Circulating IL-6 plays an important role in mediating inflammation and is a central stimulus for the acute phase inflammation response [181]. Our analysis found no significant changes in serum IL-6 and CRP (a known marker for acute inflammation), suggesting the absence of systemic inflammatory response after SFR. IL-6 stimulates CRP synthesis in the liver [181] and thus the stable serum CRP level after SFR is consistent with a stable IL-6 level for the same period. Our analysis couldn't exclude the possibility of an increase in IL-6 levels at the surgery site.

Several syntheses have examined the changes in insulin sensitivity after SFR and a trend towards improvement in insulin sensitivity has been described without elucidation of the magnitude of effect or clinical significance thereof [26–29]. Moreover, results were inconsistent due to the heterogeneity in the design and analysis of studies. The present synthesis demonstrates a gradual and steady decrease in the fasting insulin which reaches an average decline of 17 pmol/L by 6 months. The HOMA-IR showed a similar trend with a 1-unit reduction by 6 months. There have so far been reports of more accurate measurements for insulin sensitivity, such as the oral glucose tolerance test (OGTT) [183]. Interestingly, the return of BMI towards baseline after 50 days, as shown above, was not coupled with a similar return in insulin sensitivity towards baseline values. This finding may reflect extra-abdominal post-surgical fat deposition, which might be less harmful [184].

There is a strong positive relationship between body mass and blood pressure. A reduction in body mass of between 5 and 10% can reduce blood pressure in both hypertensive and normotensive cohorts [184]. Indeed, a reduction of 1 kg of body mass in obese patients results in a sustained decrease of 1.2 mmHg and 1 mmHg in systolic and diastolic blood pressure, respectively [186]. Additionally, chronic hyperleptinemia as seen among obese population is also correlated with blood pressure [187]. Loss of function mutations in leptin and leptin receptors are associated with decreased blood pressure despite severe obesity [188]. The effect of leptin is mediated by the neurons in the dorsomedial hypothalamus. Inhibiting leptin receptor expressing neuronal activity in the hypothalamus leads to a rapid decrease of blood pressure in obese mice, independent of changes in body mass [187]. In the present study, the correlation between post-surgical blood pressure and serum leptin may be understood in these terms.

Subcutaneous fat mass plays a causative role in obesity-linked dyslipidemia [189].

Thus, SFR may have a positive effect on lipid profile [165] especially in the absence of morbid obesity [190] . However, the present study failed to demonstrate a clinically significant clear correlation between SFR and post-surgical lipid profile. Several small and heterogenous studies have measured changes in body composition, adipokines and inflammatory marker [143–164], and have been followed by systematic reviews and meta-analyses in an attempt to examine the effect of SFR on body metabolism. Only one synthesis looked at these changes in terms of time since surgery [30] , but even then, the latter study only reported the differences in physical biometrics such as body weight and fat mass. The remaining syntheses combined several heterogenous studies with different follow up durations [26–29], resulting in contradicting and unclear conclusions regarding the metabolic benefit or harm of SFR. The ideal approach to the synthesis of the existing body of evidence required a dose-response meta-analysis (DRMA) since this is the only way to reduce the existing clinical heterogeneity.

A major limitation with this study is the small number of eligible studies, many of which had recruited a small number of patients. Thus, when the margin for error was taken into consideration, few obvious trends emerged. While we considered the inclusion of different types of surgical fat removal to be a strength of our meta-analysis it is possible that the technical differences of each approach bequeathed unique and dissimilar physiological legacies on the patient that manifest as different changes in post-surgical metabolic parameters. For example, abdominoplasty surgery for obesity or weight loss often includes, as an operative step, correction of divarication of the rectus muscles. This, in turn, results in an increase in the abdominal pressure, myocardial preload and compresses visceral fat [191] It is clear from this synthesis that metabolic changes after SFR needs further study in a well-designed prospective design, and this in turn will help us not only to identify the changes and the safety of these

procedures, but also broaden our knowledge about the metabolic effects of obesity.

4.4. Conclusion

This study shows that body contouring surgery correlates with enhanced insulin sensitivity for at least 6 months after surgery. Transient benefits were observed in body mass index, blood pressure, serum leptin and TNF-α. An evaluation of the metabolic benefits of body contouring surgery beyond 6 months is hampered by lack of data.

CHAPTER 5: DURABILITY OF METABOLIC CHANGES AFTER NSSFR

5.1. Main objectives and methods summary

This study describes a systematic review and dose-response meta-analysis (DRMA) of observational studies pertaining to the metabolic impact of NSFR. To address the main objectives above, PubMed, Embase and Scopus databases were searched using the Polyglot Search Translator to find studies examining quantitative expression of metabolic markers. The outcome measures sought include two domains. These included body compositions/ anthropometrics and lipid profiles. Further details of the methodology used in this study are detailed in Chapter 2.

5.2. Results

The conducted literature review resulted in a total of 818 articles and 33 registered trials (a total of 851 studies). Duplicate studies (252 studies) were excluded leaving 599 studies, of which 534 were excluded by title and abstract. The remaining 65 studies were examined by manuscript and 46 studies were excluded due to a lack of clear statement of the metabolic changes' magnitude and/or the precise time of assessment after surgery. Eventually, 19 studies with a total of 601 participants, were selected as relevant to this synthesis [191–209]. The conduct of the literature review is summarized by the PRISMA flow chart in Figure 9.

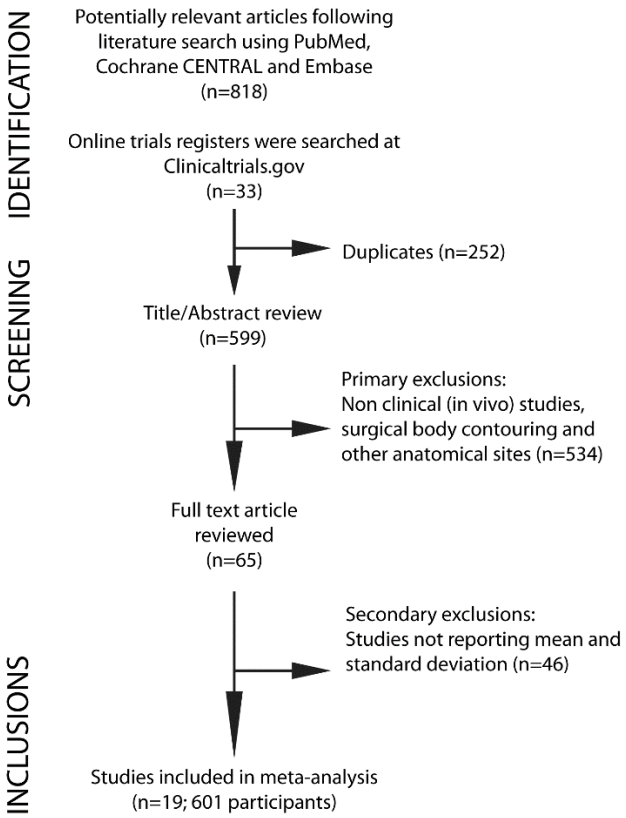


Figure 9: PRISMA flow diagram for selection of studies (NSSFR DRMA study).

5.2.1. Characteristics of included studies

Characteristics of the selected studies are summarized in (Table 5.1) and include study identifier, country, design, number of participants (sample size), population demographics, preoperative (baseline) body mass index, type of non-surgical body contouring procedure (Ultrasound (HIFU), cryolipolysis, radiofrequency, high intensity electromagnetic), outcome measures (BMI, BW, WC, FT, LDL, HDL, TG, and TC), and follow up time points after surgery (in days).

Table 5.1 Characteristics of Included Studies For The NSSFR-DRMA

Study number	Study identifier	Country/ Region	Study design	Number of subjects	Population demographics	Baseline BMI (kg/m2)	Procedure	Outcome measures	Follow up time points (days)
1	Brightman et al, 2009	USA	quasi-experiment	10	Age 28- 70 years, all females	NA	radiofrequency + laser	WC	0, 30, 90
2	Shek et al, 2009	China & Japan)	quasi-experiment	53	51 females and 2 males, age range 26 – 69 years	N/A	ultrasound	FT, WC	0, 30
3	Choi et al, 2018	Korea	quasi-experiment	24	21 females and 3 males, age 20 - 60 years	23.97 +- 2.64	radiofrequency	FT, WC	0, 28, 56
4	Shek et al, 2014	China	quasi-experiment	12	9 females and 3 males, age 27- 56 years	25.230 ± 2.0310	ultrasound (HIFU)	WC, WT	0, 28, 56, 84
5	Boisnic et al, 2014	France	quasi-experiment	21	all females, age 31- 59 years	N/A	radiofrequency	FT, WC, WT	0, 30, 90
6	Tonucci et al, 2014	Brazil	quasi-experiment	20	all females, ages 18–60 years	25.85 ± 4.07	ultrasound	BMI, TC, HDL, LDL, TG, WC, WT	0, 14

Study number	Study identifier	Country/ Region	Study design	Number of subjects	Population demographics	Baseline BMI (kg/m2)	Procedure	Outcome measures	Follow up time points (days)
7	Katz et al, 2019	USA	quasi-experiment	33	age 21- 65 years	20.0 - 30.0	high intensity electromagnetic	FT	0, 30, 90
8	Hong et al, 2019	Korea	quasi-experiment	20	17 females, 3 males,	27.34 +-6 1.82	ultrasound (HIFU)	FT	0, 28, 56
9	Fonsea et al, 2018	Brazil	quasi-experiment	31	Females, age 20- 40 years	≥ 30.0	ultrasound	TC, HDL, LDL, TG	0, 10
10	Arabpour-Dahoue et al, 2019	Iran	RCT	25	50 females, age 35.32 ± 8.70 years, DM, hyperlipidemia	16.1 - 56.7	radiofrequency+ US	TC, HDL, LDL, TG	0, 1
11	Moreno-Moraga et al, 2007	Spain	quasi-experiment	10	22 females and 8male, age 18 – 62 years	N/A	ultrasound	WC	0, 1
12	ELdesoky et al, 2015	Middle east	RCT	20	5 males and 15 females, age 34.1 ± 4.95 years	32.67± 0.91	ultrasound	BMI, FT, WC, WT	0, 60

Study number	Study identifier	Country/ Region	Study design	Number of subjects	Population demographics	Baseline BMI (kg/m2)	Procedure	Outcome measures	Follow up time points (days)
13	ELdesoky et al, 2015	Middle east	RCT	20	6 males and 14 females, age 33.3 ± 5.33 years	32.4 ± 1.0	cryolipolysis	BMI, FT, WC, WT	0, 60
14	Katz et al, 2019	USA	quasi-experiment	33	mean age 40.8 years	20.0 to 30.0	high intensity electromagnetic	FT	0, 30, 90
15	Robinson et al, 2014	USA	quasi-experiment	118	males and females, median age: 45.2 years	24.7 +- 2.6	ultrasound	WT	0, 28, 56, 84
16	Solish et al, 2011	Canada	quasi-experiment	45	majority females, age 42 -44 years	25.0 - 27.0	ultrasound	WT	0, 28, 56, 84
17	Verner et al, 2021	Middle east	quasi-experiment	15	females, mean age 45.5 ± 5.0 years	≤26	ultrasound	WC	0, 7, 30, 84
18	Khedmatgozar et al, 2020	Iran	quasi-experiment	30	females, age 18-65	29.55 ± 3.08	cryolipolysis	BMI, WC, WT	0, 56

Study number	Study identifier	Country/ Region	Study design	Number of subjects	Population demographics	Baseline BMI (kg/m2)	Procedure	Outcome measures	Follow up time points (days)
19	Khedmatgozar et al, 2020	Iran	quasi-experiment	30	females, age 18-65 years	30.43 ± 4.38	Ultrasound cavitation, cryolipolysis, and diet	BMI, WC, WT	0, 56
20	Dhillon et al, 2018	United Kingdom	quasi-experiment	20	17 females 3 males, mean age 37.6±7.11 years	25.1± 3.80	ultrasound	WC	0, 90
21	Fritz et al, 2017	Germany	quasi-experiment	20	18 females, 2 males	25.78 ±2.37	ultrasound	WT, WC	0, 30
22	Guth et al, 2017	Brazil	quasi-experiment	24	males, age 18-59 years	≤ 30	ultrasound (HIFU)	TC, HDL, LDL, TG	0, 1
23	Fonseca et al, 2018	Brazil	quasi-experiment	31	Females, age 20- 40 years	≥ 30.0	ultrasound	TC, HDL, LDL, TG	0, 10

24	Boisnic et al, 2014	France	quasi-experiment	21	age 31 -59 years	N/A	radiofrequency	FT, WC, WT	0, 30, 90

RCT; randomized controlled trial. *BMI;* body mass index. *FM*; fat mass. *LBM*; lean body mass. *WC;* waist circumference. *TNF- α*; tumor necrosis factor alpha. *CRP*; C - reactive protein. *IL6*; interleukin 6. *FBG*; fasting blood glucose. *HOMA-IR*; homeostatic model assessment for insulin resistance. *SBP;* systolic blood pressure. *DBP;* diastolic blood pressure. *LDL;* low-density lipoprotein cholesterol. *HDL*; high-density lipoprotein cholesterol. *TC*; total cholesterol. *FFA*; free fatty acids. *L*; liters. *NR*; not reported.

5.2.2. Metabolic changes after NSSFR

A. Anthropometrics / body compositions

Change in (A) Body mass index, (B) Body Weight, (C) Waist circumference and (D) Fat thickness were measured over time in days since the body contouring procedure. A clear drop of 2 units in the body mass index, 1 kilogram in the body weight, 5 centimeters in waist circumference, and 1.5 centimeters in abdominal fat thickness was noted up to 60 days after the procedure. Fat thickness continued to decrease up to 90 days after the procedure. A moderate heterogeneity in the last three outcome variables was noted across studies, and the confidence intervals were wide due to the paucity of studies and the effect of bigger studies. However, the meta-analysis showed that the effect of body contouring procedures on BMI and related parameters persisted for at least 60 days. The fat thickness showed a clear continuous reduction up to 90 days after the procedure, see Figure 10: A-D.

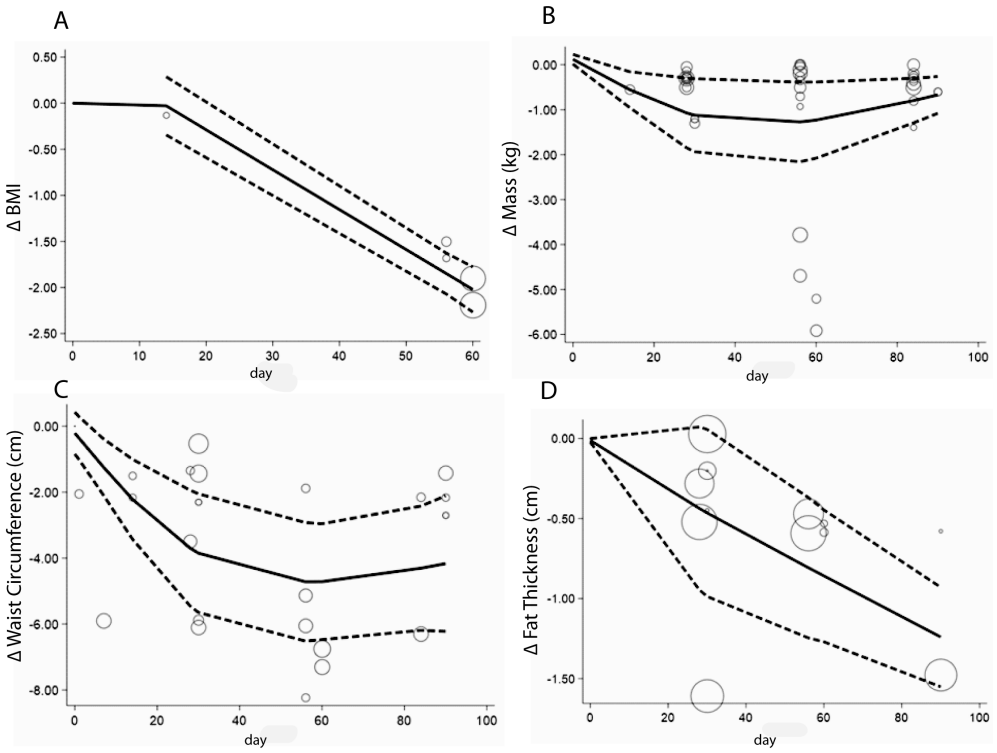


Figure 10. Change in (A) Body mass index, (B) Body Weight, (C) Waist circumference, and (D) Fat thickness over time since body contouring procedure. The "dose" is time in days after the procedure. The circles represent the weighted mean difference in each individual study at this time-point with the marker size reflecting the weight of corresponding study.

B. Lipid Profile

Changes in low-density lipoprotein, (B) high-density lipoprotein, (C) triglycerides, and (D) total cholesterol were measured over time in days since the body contouring procedure. A serum increase of 15 mg/dL in LDL, 10 mg/dl in TG, and 15 mg/dl in TC were noted up to two weeks after the procedure. No significant change was noted in serum HDL. Due to the paucity of studies, confidence intervals were wide, and the trend could not be confirmed more precisely as this was driven by the bigger studies, see Figure 11: A-D.

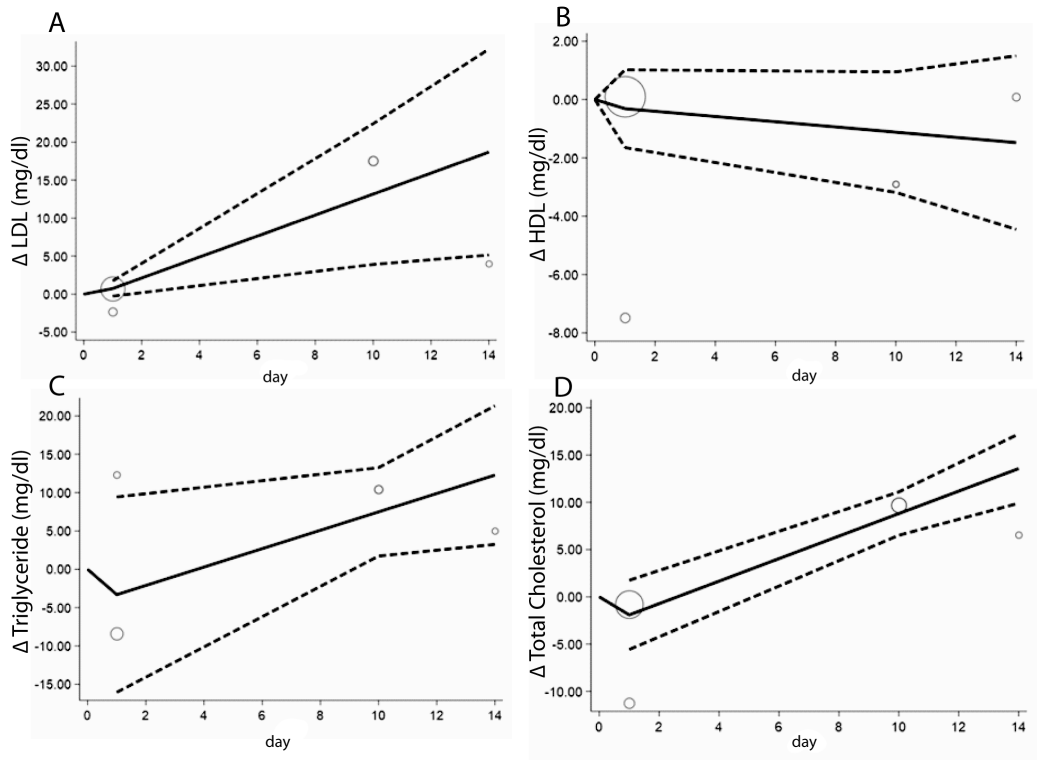


Figure 11. Change in (A) low-density lipoprotein, (B) high-density lipoprotein, (C) triglycerides, and (D) total cholesterol over time since body contouring procedure. The "dose" is time in days after the procedure. The circles represent the weighted mean difference in each individual study at this time-point with the marker size reflecting the weight of corresponding study.

5.2.3. Quality assessment of included studies

The majority of the included studies were ranked in the 4th quartile of the safeguards' count. Additionally, the most deficient safeguard standards were equal ascertainment and equal prognosis. On the other hand, the remaining standard safeguards were found to be less deficient. See Supplementary Figure 8.

5.3. Discussion

We examined the influence of non-surgical body contouring procedures on body anthropometrics/ body composition measurements and lipid profile using a systematic review of clinical data and subjected these data to a dose-response meta-

analysis. Transient increases in serum low-density lipoproteins (LDL), triglycerides (TG), and total cholesterol were observed up to two weeks following exposure to non-surgical fat removal. In the longer term, no significant differences were observed. Anthropometric data confirmed a reduction in fat thickness over the treated area which persisted throughout the observation period (day 90). Taken as a whole, these data suggest that non-surgical fat removal is efficacious, and that evidence of fat lysis may be inferred by transient rises in serum lipid profiles in the weeks following exposure to non-surgical fat removal. However, no firm conclusions about the effect of non-surgical fat removal on serum lipid profiles in the long term were permissible. This is in contrast to the results obtained when these analyses were performed for surgical fat removal. Here, the data confirmed that the surgical removal of fat by aspiration (liposuction) or excision (body contouring) resulted in favorable changes to the serum lipid profiles in the long term (Badran et al- in press). Most likely, there were simply insufficient data to be able to conclude.

The pre-clinical and clinical evidence for favorable metabolic changes associated with cryolipolysis is variable. Using a porcine model, Kwon and colleagues [211].The study raises several important questions about the role of non-surgical fat removal as an endocrinological, as opposed to purely aesthetic, intervention. With a rising tide of obesity owing to calorie-rich diets and sedentary lifestyles, the desire for fat removal has fueled burgeoning surgical and non-surgical aesthetics industries tailored to the pursuit of anthropometric ideals. Interestingly, however, these industries have neglected the potential health benefits of fat removal. Adipocytes regulate energy homeostasis by the synthesis and secretion of metabolic hormones known as adipokines [220,221]. It is hypothesized that circulating free fatty acids induce insulin-mediated triglyceride storage in adipose tissue, skeletal muscle, and liver.

Chronic insulin overstimulation causes a stress response in each of these tissues with a synthesis of pro-inflammatory cytokines, recruitment of inflammatory cells, systemic inflammation, and insulin resistance via negative feedback controls. Many clinical studies have demonstrated that insulin sensitivity and lipid profiles may be improved merely by the removal of subcutaneous adipocytes [222,223]. It is interesting to speculate on whether evidence of metabolic benefits would influence the industry that has built up around non-surgical fat removal. On one hand, such evidence would be a powerful refutation of critics who espouse the view that there are no inherent health benefits to non-surgical fat removal. On the other hand, more data are needed before authoritative conclusions can be reached.

A major limitation with this study is the small number of eligible studies, many of which had recruited a small number of patients. Thus, when the margin for error was taken into consideration, few obvious trends emerged. The lack of compelling source data reflects the fact that, on the whole, aesthetic practitioners are less interested in the potential health benefits of non-surgical fat removal than in the commercial potential of the pursuit of anthropometric ideals. If nothing else, this study highlights the pressing need for more metabolic data. Moreover, we included a number of different methods of non-surgical fat removal. This inevitably leads to concerns that our data are heterogeneous and that, as such, our conclusions mean little for any one specific commercial device. The third limitation is the relatively limited number of metabolic parameters and the narrow metabolic window studied. Again, we are limited by the data available from the source material.

5.4. Conclusion

This study shows that non-surgical body contouring procedures correlates with a sustained improvement in anthropometrics and body compositions for at least two

months after procedure. A transient deterioration in lipid profile is observed over the first two weeks, consistent with lipolysis. The long-term metabolic effects of non-surgical fat removal remain uncertain.

CHAPTER 6: MEASURING GLUCOSE EXCURSION AFTER SSFR

6.1. Main objectives and methods summary

In this study we examine the performance of the Doi's weighted average glucose (dwAG) value in comparison to the area under the GTT and homeostatic model assessment for insulin sensitivity (HOMA-S) and pancreatic beta cell function (HOMA-B) in a group of participants undergoing surgical subcutaneous fat removal (SSFR). The aim was to validate the dwAG as a measure of post-load glucose excursion for measuring glucose excursion after SSFR. To address the main objectives above, A cross-sectional comparison of the new index was conducted using 66 oral glucose tolerance tests (GTT's) performed at different follow-up times among twenty-seven participants who had undergone surgical subcutaneous fat removal (SSFR). Further details of the methodology used in this study are detailed in Chapter 2.

6.2. Results

There was a total of 66 complete GTTs and of these, 47 (71.2%) had peak values after 30 minutes and 9 (13.6%) were biphasic (8/9 also had a peak after 30 minutes). Glucose excursion was computed using the two measures indicated in the methods and a Passing-Bablok regression model suggested a cutoff for normal values for the A-GTT of 15.14 mmol/L·$2h^{-1}$ as the equivalent cutoff to the dwAG value of 6.8 mmol/L). For every 1 mmol/L·$2h^{-1}$ increase in A-GTT, the dwAG value increased by 0.473 mmol/L (Figure 12).

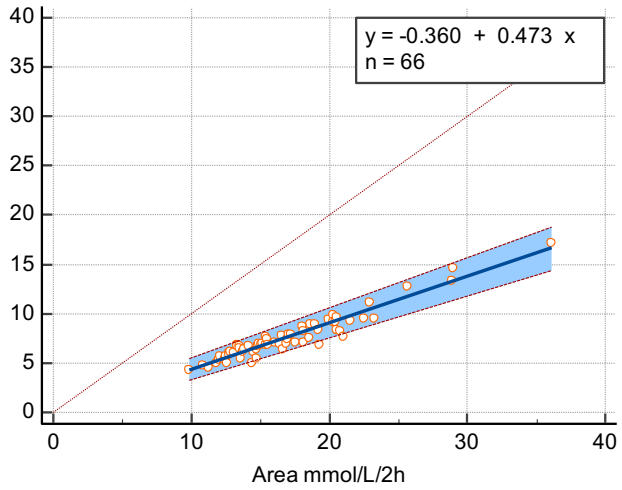


Figure 12. Passing-Bablok regression plot showing data and fit for the weighted average glucose measure of glucose excursion predicted from area under the GTT (glucose)

GTT: glucose tolerance test.

Cusum test for linearity, No significant deviation from linearity (P=0.83); Spearman rank correlation coefficient 0.934 (95% CI 0.894 to 0.959)

The glucose area under the curve correlated well with the dwAG level (four groups), with the levels having a different A-GTT (KW Chi2= 52.8(df=3), P<0.001). The median A-GTT in each dwAG category was 13.2, 15.9, 18.3 and 21.0 mmol/L·2h^{-1} in the normal, impaired, abnormal, and severely abnormal dwAG groups respectively (Figure 13).

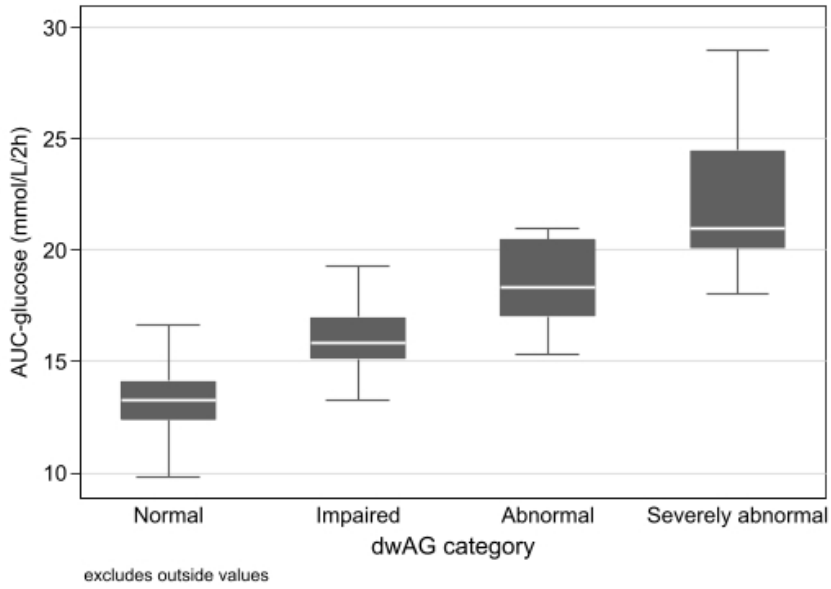


Figure 13. Association between the area under the GTT and the weighted average glucose category measure of glucose excursion.

GTT: glucose tolerance test.

The HOMA-S tertiles were associated with different levels of glucose excursion measured through both the dwAG value (KW Chi2= 11.4 (df=2), P=0.003) and A-GTT value (KW Chi2= 13.1 (df=2), P=0.001) and this is depicted in Figure 14. The IQR for the dwAG across the insulin sensitivity tertiles were 6.8 to 9.4, 6.1 to 7.6 and 5.3 to 7.0 mmol/L respectively. For area under the GTT curve, the IQR's were 15.4 to 21.5, 13.3 to 18.5 and 12.2 to 16.5 mmol/L·2h^{-1} respectively. The impact on glucose excursion is seen more prominently once insulin sensitivity is lowest (in the first tertile; HOMA-S median -53.35%, IQR -69.7% to - 49.1%).

HOMA-B alone (in a nonlinear regression model) explained 42% of the variation in dwAG values while HOMA insulin sensitivity explained 9% of the variation in dwAG values in a similar model. The combination of both HOMA B and HOMA-S in a non-linear regression model (using restricted cubic splines) contributed to explaining 66% of the variation in dwAG values suggesting that the combination

was what defined the bulk of the variation in dwAG values. This is depicted graphically in Figure 15 which depicts that the dwAG depends on both beta cell function as well as insulin sensitivity and that dwAG increases as insulin sensitivity and beta cell function both decline.

The mean dwAG value in those GTTs with a peak at 30 minutes and that were monophasic was 6.4 mmol/L. There was a mean increase in dwAG of 1.4 mmol/L (P=0.032) in those GTTs with a peak after 30 min but no biphasic shape and a mean increase of 3.0 mmol/L in GTTs with both a later peak and biphasic shape (P=0.002). With the A-GTT the mean changes followed a similar trend but with less statistical evidence against the model hypothesis at this sample size. HOMA-B declined on average by 19.8% (P=0.262) in the late peak only group and by 29.3% (P=0.285) in the combined late peak and biphasic group. The respective changes in HOMA-S for these groups was -3% and -3.7% respectively suggesting that these shape changes reflected beta-cell function. No GTTs coming from a patient with a history of bariatric surgery demonstrated a biphasic pattern (P=0.028, Fishers exact test) but a peak after 30 minutes occurred with the same frequency in those with or without bariatric surgery history.

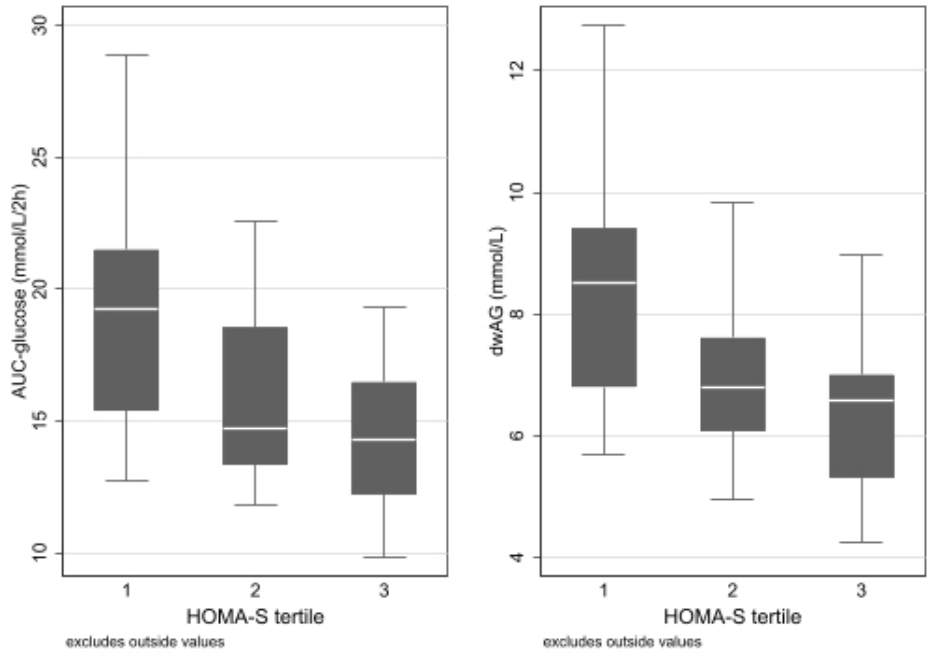


Figure 14. Association between glucose excursion (Tai's area under the GTT, left panel; Doi's weighted average glucose, right panel) and Insulin sensitivity tertile.

*HOMA-S tertile: Homeostatic Model Assessment for insulin sensitivity tertiles 1, 2 and 3.

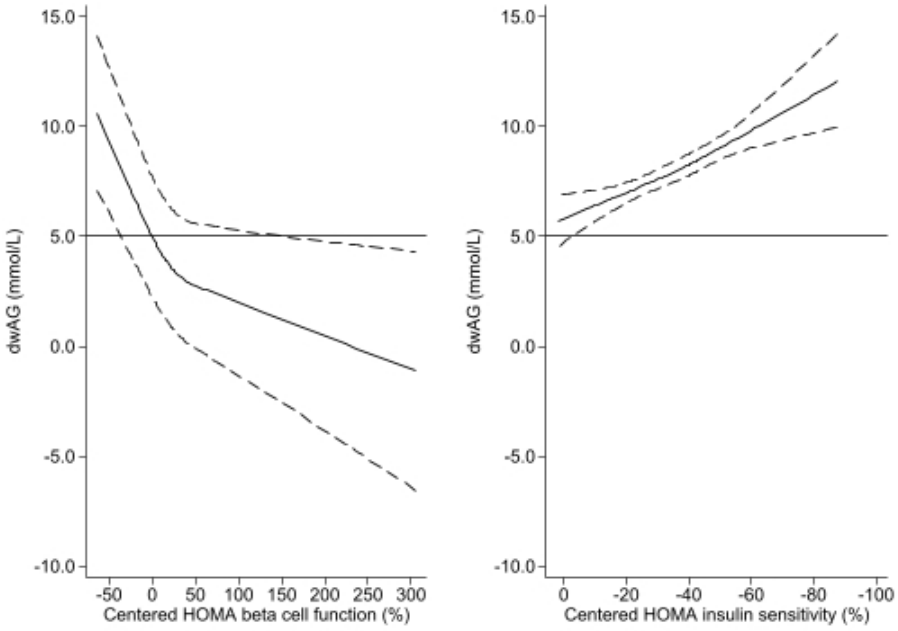


Figure 15. Relationship of HOMA insulin sensitivity (%) and HOMA beta cell function (%) to the dwAG (mmol/L) demonstrating that both are important in determining the dwAG value.

The values of HOMA are centered at 100% and when both are normal (0%) the dwAG value is about 5 mmol/L. As HOMA insulin sensitivity decreases the dwAG rises linearly and this is mitigated by an increase in beta cell function which drops the dwAG value.

6.3. Discussion

This study provides firm support to the dwAG as an alternative to the formal assessment of glucose excursion under the GTT. While it was developed for gestational diabetes [58] it is shown here that it can have wider use. This study confirms that the same groupings from normal to severely abnormal glucose excursion hold in this population of adults outside of pregnancy and correlate with HOMA insulin sensitivity.

In the past, the GTT used to be the mainstay in diabetes diagnosis. However,

the new recommendation by the American Diabetes Association (ADA) has shifted to simpler tests [223]. The rationale behind this was that the complexity of the GTT, the fact that it is time consuming and not well tolerated by the patients as well as its reproducibility [225]. Thus, adopting the fasting plasma glucose (FPG) with a lower criteria (7 mmol/L (126 mg/dl) for diabetes and 5.6 mmol/L (100mg/dl) for impaired fasting glucose (IFG)) would lead to more efficient diagnosis [224]. This study also confirms that in those with abnormal dwAG values (dwAG2) the mean FPG was 5.6 mmol/L. The latter coincides with the ADA threshold for an impaired fasting glucose (IFG) and therefore one could consider these two (dwAG and IFG) to represent an equivalent intermediate level of dysglycemia. While substituting the GTT with FPG may seem to be more convenient clinically, but these two tests do not provide the same level of glucose homeostasis assessment because the GTT combines information from both insulin sensitivity and beta-cell function [226] while the FPG is responsive mainly to insulin secretion relative to the level of insulin resistance and reflects the duration and magnitude of insulin resistance [227].

In our study, the dwAG served as an easy tool to define normality in glucose homeostasis in this non-pregnant population, demonstrated an excellent correlation with the A-GTT and was well discriminated by tertiles of HOMA-S. The implication here is that the dwAG, which combines fasting (FPG), 1h and 2h glucose values is a sufficient criterion to measure glucose excursion in other adults, which in this paper specifically refers to a group of non-pregnant adults who underwent body contouring surgery. The dwAG was responsive to GTTs with peaks after 30 minutes or with a biphasic shape and this was not so clearly evident with the A-GTT. The time to glucose peak >30 minutes has previously been shown to be an independent indicator of prediabetes and lower β-cell function in an otherwise healthy multi-ethnic adult cohort

[228]. It is known that the glucose peak occurs most frequently at 30 minutes (60.5%) and is accompanied by a synchronous peak of insulin [229]. Thus, both a later peak and a biphasic shape indicate worse beta-cell function [230,231].

It was noted that none of the GTT's showed a biphasic pattern in those subjects who had a prior history of bariatric surgery, and this is not surprising given the fact that meal-induced glucagon-like peptide-1 (GLP-1) secretion could be up to ten-folds higher in patients after gastric bypass or sleeve gastrectomy surgeries compared to non-surgical individuals. One possible mechanism (among others) that has been put forward is an accelerated nutrient transit from stomach to the gut leading to enhanced secretion of GLP-1 [231]. The latter is specific to bariatric surgery and occurs before weight loss ensues and, given that our patients had bariatric surgery more than 18 months preceding the GTT, the effect is sustained. The latter is different from the favorable effects of bariatric surgery on peripheral insulin sensitivity which is shared with those of calorie restriction [233] and is only improved in proportion to weight loss [234,235] .

The implication from the observations in these patients with or without a bariatric surgery history is that the measure of glucose excursion using the dwAG value shares elements of the two major metabolic impairments associated with glucose homeostasis; namely an increase in insulin resistance and impaired beta cell function [236], and this was demonstrated in this study (Figure 15) where the dwAG was about 5 mmol/L when both HOMA indices were normal (100%). There was a linear increase in dwAG when insulin sensitivity declines and a non-linear increase in dwAG when beta cell function declines. This explains why the dwAG or area under the GTT curve may be a better indicator of transitioning to T2D [236] or future cardiovascular disease and mortality [237] than with insulin resistance alone. As indicated in our results, the

dwAG correlates better with shape parameters than with the A-GTT and this was evident in post-bariatric subjects with much better beta-cell function.

The strengths of the present study include a first-time comparison of the A-GTT to a novel index of glucose excursion using the conventional GTT used in clinical practice, the computation of the A-GTT from six time-points of the GTT, and the comparison of both the conventional and novel indices to HOMA beta cell function and insulin sensitivity in the same model. Potential limitation include use of a single GTT for the comparisons in individuals, which may have less duplicability but, on the positive side, mimics the clinical use of these indices in practice.

6.4. Conclusion

The dwAG represents a single value summary of glucose excursion under the GTT and serves as a simple but accurate tool that can be used for glucose homeostasis interpretation. It was initially conceived as a tool that could be used to define glucose homeostasis in pregnancy and, in that study, correlated with adverse perinatal outcomes. It has now been independently validated as equivalent to the conventional A-GTT (based on six time-points) measure of glucose excursion in this study in a different population of non-pregnant adults and correlates well with both HOMA insulin sensitivity and HOMA beta cell function.

CHAPTER 7: ALTERATIONS IN GLUCOSE METABOLISM AFTER SSFR

7.1 Main objectives and methods summary

This study aimed to evaluate the changes in glucose excursion and insulin resistance in patients undergoing SSFR, specifically abdominoplasty (with or without a history of obesity surgery). To address the main objectives above, a quasi-experiment was implemented. This involve examining the patients over three visits (within 1 week before surgery, 1 week after surgery and 6 weeks after surgery) using Doi's weighted average glucose (dwAG) under the oral glucose tolerance test (GTT) and HOMA-IR respectively. Further details of the methodology used in this study are detailed in Chapter 2.

7.2. Results

7.2.1. Patients studied

The study included 29 patients (22 females and 7 males), all patients had at least one post operative visit (15 patients completed both second and third visit, 7 patients completed second visit only, and 7 patients completed third visit only). Ten patients (37%) had a history of obesity surgery (6 sleeve gastrectomy, 2 bypass surgery, 2 sleeve plus bypass surgery). Eleven patients (38%) were either lean or overweight, and the remaining eighteen patients (62%) were obese. Five patients (17%) had type 2 diabetes (T2D) on oral medications, and none were on insulin therapy. A detailed medical history and complete physical examination revealed no other serious comorbidities or organ dysfunction in any participant. Average abdominal subcutaneous fat removed during surgery was 2400 (range 1300 – 3600) grams. Preoperatively, the median dwAG value was 7.0 mmol/L (interquartile range (IQR) 6.4 - 8.3), and median HOMA-IR was 1.6 (IQR 1.3 - 2.1). The Tanita full body composition analysis, complete lipid profile, and basic laboratory results are depicted

in Table 7.1 While the mean fat% and fat mass remain unchanged, on average, across visits, in a paired-difference linear regression analysis we find that for every percent difference in fat% the excised tissue in body contouring surgeries increased by 206.1g (95% CI 26.1g, 386.1g).

Table 7.1 Characteristics of Study Population (Quasi Experiment Pilot Study)

Factor	Level	visit 1	visit 2	visit 3
Number of participants		29	22	22
Age		43.0(38.0,50.0)	41.0(37.0,50.0)	43.0(38.0,51.0)
Sex	M	7 (24.1%)	6 (27.3%)	5 (22.7%)
	F	22 (75.9%)	16 (72.7%)	17 (77.3%)
Diabetic status	No	24 (83%)	20 (91%)	18 (82%)
	yes	5 (17%)	2 (9%)	4 (18%)
dwAG value* (mmol/L)		7.0 (6.4, 8.3)	6.9 (6.4, 8.7)	7.1 (5.7, 8.2)
AUC glucose* (mmol/L/2h)		16.6(13.5,20.4)	15.8(14.4,19.0)	15.4(12.9,18.2)
HOMA-IR^		1.6 (1.3, 2.1)	1.7 (1.3, 2.0)	1.5 (1.2, 1.7)
History of bariatric surgery	yes	10 (34%)	9 (41%)	7 (32%)
	no	19 (66%)	13 (59%)	15 (68%)
BMI category	< 30	11 (38%)	9 (41%)	7 (32%)
	≥ 30	18 (62%)	13 (59%)	15 (68%)
BMI*		31.7(29.1,33.6)	31.7 (29.1, 34.2)	32.0 (29.3, 34.2)
Fat percent*		37 (33.6, 42.2)	37 (32.9, 42.9)	38.9 (34.1, 44.0)
Fat mass*		32.4(26.6,37.4)	32.1 (26.6, 40.3)	32.5 (26.9, 37.4)
Free fat*		47.9(45.1,54.8)	47.6 (45.1, 55.7)	48.3 (45.1, 55.7)
Total body weight*		33.3(32.0,39.9)	33.7 (32, 40.5)	33.7 (32.0, 40.5)
Total body fat percent*		44.4(41.4,47.1)	44.4 (41.4, 47.2)	43.8 (40.8, 46.1)
Basal metabolic rate*		5933(5644,655)	5897.5(5523,6556)	6070.5(5653,7130)
Metabolic age*		54 (46, 60)	53.5 (44, 60)	55.5 (48, 61)
Visceral fat rate*		9 (6, 11)	8.5 (6, 12)	9 (6, 12)
Obesity*		42.5 (30.1,52.7)	42.5 (30.1, 55.7)	43.8 (31.1, 55.7)

Factor	Level	visit 1	visit 2	visit 3
HbA1c*		5.4 (5.2, 5.6)	5.4 (5.2, 5.6)	5.3 (5.2, 5.6)
CRP*		1 (1, 2.8)	1 (1, 2.9)	1 (1, 2.8)
IL-6*		3 (1, 5)	3.5 (2, 5)	3 (1, 4)
Vitamin D*		26 (19, 36)	26.5 (21, 40)	25 (18, 40)
Cholesterol*		4.3 (3.8, 4.9)	4.3 (3.8, 4.8)	4.4 (3.7, 4.8)
Triglyceride*		0.8 (0.6, 1)	0.9 (0.6, 1)	0.8 (0.6, 1)
HDL*		1.3 (1.1, 1.7)	1.3 (1.1, 1.6)	1.2 (1.1, 1.7)
LDL*		2.8 (1.9, 3.4)	2.8 (1.9, 3.4)	2.8 (1.9, 3.3)

7.2.2. Model 1 (HOMA-IR): Predictors of insulin resistance

The risk of insulin resistance (defined as having having a severely abnormal HOMA-IR level (upper tertile)) was assessed in relation to SSFR, history of bariatric surgery, diabetic status and baseline BMI independently (Table 9). The median HOMA-IR in the upper tertile HOMA-IR group across all time points was 2.18 (IQR 1.96 – 3.30).

The odds of having upper tertile HOMA-IR (independent of the diabetic status, BMI, and history of obesity surgery) was 30% higher (OR 1.30; p=0.688) in the first week after SSFR but had dropped 78% below base value (OR 0.22; p=0.042) by 6-weeks after SSFR (Table 3.2). The interpretation of the latter is that at 1 week after surgery the estimated OR suggested some worsening of HOMA-IR due to post-operative inflammatory status [238] but the evidence was weak at this sample size (p=0.688). However, at 6 weeks, there was a clinically and statistically significant drop in HOMA-IR (OR 0.22; p=0.042) and therefore the odds of upper tertile HOMA-IR dropped by an almost five-folds over the baseline.

On the contrary, those with a history of obesity surgery (irrespective of SSFR, BMI and T2D status) had a 56% decrease in odds of upper tertile HOMA-IR (OR 0.44) compared to those without prior obesity surgery, but the evidence was weak at this

sample size (p=0.142).

Diabetic status showed a four-folds higher odds of having upper tertile HOMA-IR (OR 3.99; p=0.086), despite the limited statistical evidence at this sample size. However, BMI had weak correlation with insulin resistance status (OR 1.38; p=0.615). The interpretation of the latter could be that the visceral fat mass as well as the adipose fat dysfunction are stronger predictors of insulin resistance status, rather than total fat mass and BMI [239]. This model showed goodness of link (linktest in Stata) and goodness of fit (Area under ROC curve= 0.709, McFadden's R2= 0.096).

7.2.3. Model 2 (dwAG3): Predictors of abnormal glucose excursion

The risk of having a severely abnormal glucose excursion on the GTT, defined as severely abnormal dwAG level (the fourth dwAG category), was assessed in relation to SSFR, history of bariatric surgery, as well as diabetic and obesity status independently (Table 9). The median dwAG in this severely abnormal group across all time points was 9.51 (IQR 9.15 – 11.93).

The odds of having severely abnormal dwAG (independent of the diabetic status, BMI, and history of obesity surgery) was 2-fold higher (OR 2.2; p=0.256) in the first week after SSFR but had returned to base value (OR 1.05; p=0.956) by 6-weeks after SSFR. The interpretation of the latter is that at 1 week after surgery the estimated OR suggested some worsening due to post-operative inflammatory status [239] but there was weak evidence (p=0.256) against the model hypothesis at this sample size. On the contrary, those with prior obesity surgery had an almost 10-fold decrease in odds of a severely abnormal dwAG status (OR 0.09; p=0.031) compared to those without prior obesity surgery (irrespective of SSFR, obesity and T2D status).

Diabetic status as expected showed an extremely high odds of having severely abnormal dwAG (OR 66.01; p= 0.001). However, obesity status showed very weak

evidence for an association with the risk of having a severely abnormal glucose excursion on the GTT (OR 0.78; p= 0.795). This finding also supports the theory that visceral fat mass and adipose fat dysfunction are stronger predictors of insulin resistance status, rather than total fat mass [239]. This model showed goodness of link (linktest in Stata) and goodness of fit (Area under ROC curve= 0.764, McFadden's R2= 0.246).

Table 7.2 Predictors of Insulin Resistance (Model 1: HOMA-IR) Or Abnormal Glucose Excursion (Model 2: dwAG3)

Variable	Model 1 (HOMA-IR) ** OR (95% CI)	P values	Model 2 (dwAG3) ** OR (95% CI)	P values
Time post SSFR				
1 week after surgery*	1.30 (0.36, 4.67)	0.688	2.20 (0.56, 8.56)	0.256
6 weeks after surgery*	0.22 (0.05, 0.95)	0.042	1.05 (0.17, 6.34)	0.956
Risk factors				
History of bariatric surgery	0.44 (0.14, 1.32)	0.142	0.09 (0.01, 0.80)	0.031
Diabetes mellitus	3.99 (0.82, 19.34)	0.086	66.01 (6.61, 435.47)	<0.001
Obese	1.38 (0.40, 4.78)	0.615	0.78 (0.12, 4.94)	0.795

* Compared to pre-surgery.

** Model 1: OR of upper tertile HOMA-IR; Model 2: OR of severely abnormal dwAG

7.3. Discussion

Obesity surgery is an efficient treatment for obesity and related metabolic diseases [240]. Because of the rapid and massive weight loss following the surgery, many patients tend to require body contouring plastic surgery to remove redundant abdominal skin and excess subcutaneous abdominal fat for aesthetic purposes. The precise mechanisms by which obesity surgery affords the protections and the consequences of surgical (and non-surgical) fat removal on human metabolism is not fully clear yet [33,85,241,242].

This study answered a few of the pertinent questions through examination of the early post-operative changes in glucose homeostasis after SSFR at three time points. A clear protective effect of prior obesity surgery on glucose excursion during the GTT was demonstrated using a novel index, the dwAG. This effect was found to be independent of time post SSFR, BMI and diabetic status. Abnormal glucose excursion has been associated with different metabolic risk profiles and increased future risk of T2D [223,242]. Therefore, our results suggest that obesity surgery offers this protection, independent of BMI.

The mechanism underpinning this protection on abnormal glucose excursion seems to work through both effects on insulin resistance as well as pancreatic β cell function because the OGTT combines both insulin resistance and the β cell function status. The implication is that glucose excursion under the OGTT curve provides a predictive test for future development of T2D, independent of BMI. The latter is related to the overall shape of the glucose excursion curve and thus the slower the glucose curve returns to the fasting glucose level, the worse the metabolic profile with

greater insulin resistance and/or worse pancreatic β cell function, and higher risk of future development of T2D [242].

7.4. Conclusion

This study demonstrates an improvement in insulin resistance after SSFR, independent of BMI, diabetic status, or obesity surgery status. The benefit on insulin resistance in this study was first seen at 6 weeks post-surgery, which is consistent with our findings in our SSFR DRMA (chapter 4). The expected duration of this effect is unknown, but our DRMA suggested that it lasts at least for 6 months.

CHAPTER 8: IMPACT OF PRIOR OBESITY SURGERY ON GLUCOSE METABOLISM AFTER SSFR

8.1 Main objectives and methods summary

This study aimed to evaluate the impact of prior obesity surgery on glucose metabolism (including both glucose excursion and insulin resistance) after SSFR. This involve examining the patients over three visits (within 1 week before surgery, 1 week after surgery and 6 weeks after surgery) using Doi's weighted average glucose (dwAG) under the oral glucose tolerance test (GTT) and HOMA-IR respectively. To address the main objectives above, a cluster robust-error logistic regression was undertaken to examine the independent impact history of obesity surgery on glucose homeostasis. Further details of the methodology used in this study are detailed in Chapter 2.

8.2. Results

The impact of prior bariatric surgery on changes in glucose homeostasis (both insulin resistance and glucose excursion under the GTT) after SSFR were examined using predictive margins after logistic regression from models 1 & 2. Figure 12 depicts the proportions under the models in sections 3.2 & 3.3. This analysis aims to compare the changes in proportions with either insulin resistance or glucose excursion under the GTT in those with history of bariatric surgery versus bariatric surgery naïve participants. The left panel depicts insulin resistance (model 1; HOMA-IR) and the right panel depicts glucose excursion under the GTT (model 2; dwAG).

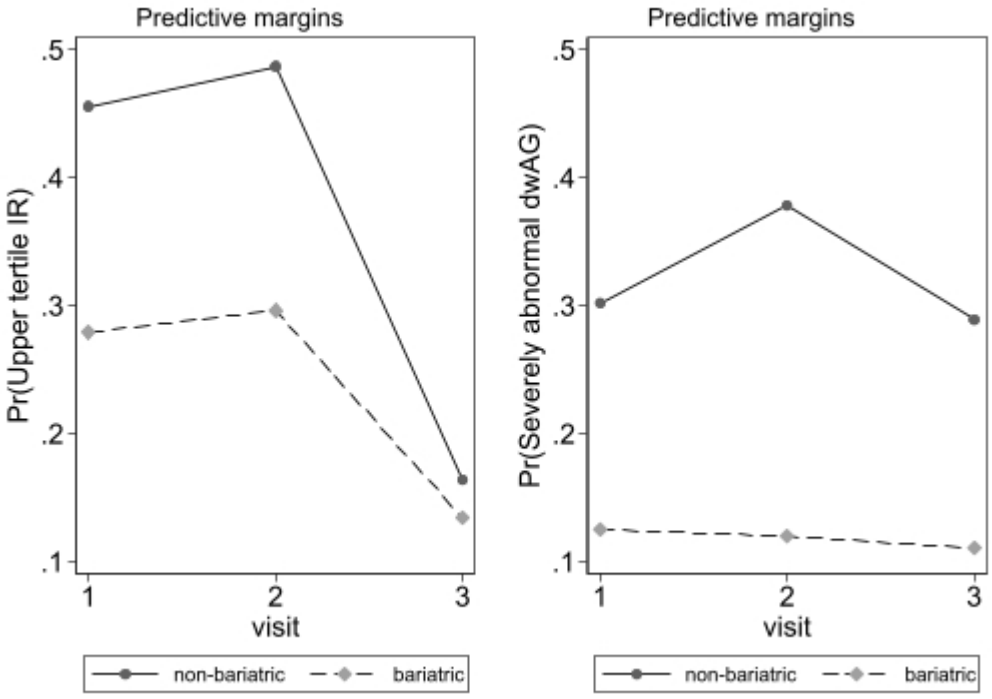


FIGURE 12. Predictive margins after logistic regression in Table 7.2

The left panel depicts insulin resistance (model 1; HOMA-IR) and right panel depicts glucose excursion under the GTT (model 2; dwAG).

In the left panel, there is an increase in proportions (the change in proportions is depicted in Figure 12) with gross insulin resistance (defined as upper tertile HOMA-IR) by visit 2 and this is seen in both those with and without a bariatric surgery history. Marked improvement in proportion (difference in proportions depicted in Figure 12) with severe insulin resistance is seen by visit 3 (again in both groups with and without a history of bariatric surgery) suggesting that insulin sensitivity has improved markedly by 6 weeks (more so in bariatric surgery naïve participants). This also correlates with the previous finding in section 3.2, where SSFR resulted in a transient worsening in insulin resistance at visit 2 (1 week after surgery) possibly due to post operative hyper-inflammatory status [238], followed by significant improvement at visit 3 (6 weeks after surgery).

The right panel in Figure 12 depicts the proportions in relation to severely abnormal glucose excursion (defined as severely abnormal dwAG) and here this picture is different. Those with a history of bariatric surgery have no real change in probability of this degree of glucose excursion over time while those without a prior history of bariatric surgery demonstrate a rise in the proportion with severely abnormal glucose excursion by visit 2 (which parallels the increase in HOMA-IR) and then returns to baseline by visit 3.

In both the left and right panels, those with a history of bariatric surgery have both lower proportions with gross insulin resistance as well as with severely abnormal glucose excursion at all time points. It is clear that the main impact of SSFR is on insulin resistance (HOMA-IR) in all subjects, but that glucose excursion effect is markedly diminished in those with a history of bariatric surgery.

These results clearly suggest that SSFR improves insulin sensitivity in those with or without bariatric surgery, but only improves glucose excursion under the GTT in bariatric surgery naïve participants, suggesting that bariatric surgery results in sustained improvements in beta-cell function (and less so in terms of HOMA-IR) [256].

8.3. Discussion

Insulin resistance, which is defined as a suboptimal response to normal blood levels of insulin, is what links overweight and obesity to worsening pancreatic β cell dysfunction, T2D and its associated metabolic consequences such as cardiovascular diseases. In this study, subjects with a history of obesity surgery had a markedly lower glucose excursion even at visit 2 when HOMA-IR increased, strongly suggesting that the obesity surgery effect is mediated through sustained improvement in pancreatic β cell function. This is interesting because obesity surgery is known to improve glucose homeostasis before significant weight loss ensues [257,258] and this also occurs with

calorie restriction [259]. The mechanisms by which pancreatic cell health and function are improved remain unknown [261] though it has been suggested that gut hormones, especially glucagon like peptide-1 [262], may modulate this effect. Better understanding of what happens in the aftermath of obesity surgery will provide novel insights into our understanding of the management of chronic metabolic sequalae of obesity, especially T2D.

The removal of about 2-3 kg of abdominal subcutaneous fat (through SSFR) was associated with a net benefit in terms of insulin resistance post SSFR as indicated in Table 7.2 and Figure 12 at six weeks. This finding is consistent with our finding in the SSFR DRMA, where insulin sensitivity improved gradually with a maximum reduction in fasting insulin and homeostatic model assessment for insulin resistance of 17 pmol/L and 1 point, respectively, up to six months after surgery. The DRMA also showed that peak metabolic benefits manifested at six weeks after surgery as a reduction of 2 units in body mass index, 3 kg of fat mass, 5 cm of waist circumference, 15 μg/L of serum leptin, 0.75 pg/ml of tumor necrosis factor-alpha, 0.25 mmol/L of total cholesterol, and 3.5 mmHg of systolic and diastolic blood pressure, but were followed by a return to preoperative levels by six months (except for the improvement in insulin sensitivity).

This improvement in insulin resistance may be linked to SSFR associated changes in secretion of certain adipokines such as leptin [263], which secreted from subcutaneous fat stores rather than the visceral fat stores, due to their larger mass and higher secretion rate [248] . It acts centrally (in the hypothalamus) and peripherally in various tissues such as adipocytes, pancreas, liver, and skeletal muscles [249] to promote insulin action and sensitivity, thereby maintaining glucose homeostasis. However, the impact of leptin may be influenced by other factors, particularly in cases of elevated

leptin levels in obesity, and these additional factors may counteract the favorable effects of leptin [251]. Leptin exerts an insulin sensitizing effect in those with low leptin states, including lipoatrophy states [252]. Thus, a decrease in leptin levels is expected after SSFR, but the underlying mechanism for improved insulin sensitivity remains unknown. One explanation could be that leptin resistance is a consequence of another adipokine that is elevated in obesity and falls with SSFR. This would ease leptin from its resistant state, even as its own levels decrease. This hypothesis is supported by the association of hypoleptinaemic states with insulin resistance which can be ameliorated by leptin treatment [1,251,254] mechanisms involved however need further investigation to establish a link with main adipokine; leptin, which is the most abundant adipokine secreted from white adipose tissue [263].

8.4. Conclusion

This study sheds new light on the possibility that the long-term impact of obesity surgery may primarily target improvement in pancreatic β-cell function, regardless of SSFR. However, the intricate interplay between SSFR and obesity surgery in obesity and T2D remain to be fully elucidated.

CHAPTER 9: SUMMARY OF RESEARCH OUTCOME, IMPACT AND FUTURE DIRECTIONS

9.1. Summary of research outcome and their integration

Patients going for SSFR, represent a unique population as they experience a sudden loss of their ASF. However, the metabolic changes after these procedures are still unclear. The first stage of this project conducted an umbrella review, which summarized four attempts at evidence synthesis on the metabolic changes after surgical fat removal, with a total of 29 unique studies included and 759 total participants. Results showed a possible improvement in obesity-associated insulin resistance, however, there was a lack of clarity regarding the extent of the effect and clinical significance. Nevertheless, it seems likely that ASF removal is associated with improved insulin sensitivity. In terms of inflammation, one of the two syntheses reported that ASF removal results in a lower degree of IL-6 and TNF-a, and thus potentially a more favorable metabolic risk profile. These syntheses also reported a reduction of leptin levels after ASF removal through surgery. There was heterogeneity in the reported changes in other adipokines such as adiponectin and resistin. Clearly, the data from previous studies are not conclusive, nevertheless, it seems likely that SSFR is associated with improved insulin sensitivity and lower levels of inflammatory cytokines.

To have a clear understanding of the degree and duration of these metabolic changes, the second phase of this research project conducted a DRMA to examine the durability of these changes after SSFR. Twenty-two studies with 493 participants were included. Insulin sensitivity improved gradually with a maximum reduction of fasting insulin and HOMA-IR of 17 pmol/L and 1 point respectively at post-operative day

180. Peak metabolic benefits manifest as a reduction of 2 units in body mass index, 3 kg of fat mass, 5 cm of waist circumference, 15 μg/L of serum leptin, 0.75 pg/ml of tumor necrosis factor alpha, 0.25mmol/L total cholesterol and 3.5 mmHg of systolic and diastolic blood pressure were observed at 50 days but were followed by a return to preoperative levels by day 180. Serum concentration of high-density lipoproteins rose to a peak at 50 days post-surgery, before falling below the baseline. No significant changes were observed in lean body mass, serum adiponectin, resistin, interleukin 6, C- reactive protein, triglyceride, low density lipoproteins, free fatty acids and in fasting blood glucose. In conclusion, this paper showed that body contouring surgery exerts several metabolic benefits in the short term but only improvements in insulin sensitivity last at least for 6 months.

To compare these finding with the metabolic changes after NSSFR, a second DRMA was conducted. Twenty-two studies with a total of 676 participants were included. Peak body compositions measures manifest as a reduction of 2 units in the body mass index, 1 kilogram in the body weight, 5 centimeters in waist circumference and 1.5 centimeters in abdominal fat thickness. The effect was sustained up to 60 days after procedure. Fat thickness continued to decrease up to 90 days after procedure. Lipid profile deteriorated up to 14 days after procedure with a serum increase of 15 mg/dL in low-density lipoprotein (LDL), 10 mg/dl in triglycerides (TG), and 15 mg/dl in total cholesterol (TC). No significant change was observed in serum high-density lipoprotein (HDL). In conclusion, this paper showed that non-surgical fat removal exerts a similar effect on body mass index and related parameters up to 60 days after procedure, while the lipid profile deteriorated in the first two weeks.

The third phase of this project aimed to validate the Doi's weighted average glucose (dwAG) as a novel index of glucose excursion after oral glucose tolerance test

OGTT. Then to combine this index along with the HOMA index (a measure for insulin resistance/sensitivity status) in examining the changes in glucose homeostasis after SSFR.

The results showed that the glucose area under the curve correlated well with the four defined dwAG categories, with one of the categories having a different area under the GTT curve (KW Chi2= 52.8(df=3), P<0.001). The HOMA-S tertiles were also associated with a significantly different level of glucose excursion measured through both the dwAG measure (KW Chi2= 11.4 (df=2), P=0.003) and A-GTT measure (KW Chi2= 13.1 (df=2), P=0.001). It was concluded that the dwAG value (and categories) serve as a simple tool that can be used for glucose homeostasis interpretation. It correlated well with the conventional A-GTT and the HOMA-S tertiles.

Utilizing these indexes (the dwAG and HOMA) on measuring the changes in glucose homeostasis after SSFR, showed that SSFR led to a gross improvement in insulin resistance by 6-weeks after SSFR in all patients irrespective of BMI, diabetic status or history of bariatric surgery (OR 0.22; P=0.042), however, no effect was observed on glucose excursion except for a transient increase at visit 2 (1st week after surgery) in those without prior obesity surgery. Participants with history of bariatric surgery had approximately half the odds of upper tertile HOMA-IR (OR 0.44; p=0.142) and ten-folds lower odds of severely abnormal (dwAG3) glucose excursion (OR 0.09; p=0.031), irrespective of their BMI, diabetic status or time post SSFR. In conclusion, this study showed that body contouring related SSFR resulted in (at least) short-term improvement in insulin resistance (independent of BMI, diabetic status and history of obesity surgery) without affecting glucose excursion under the GTT. On the contrary, obesity surgery resulted in a long-term effect on glucose excursion, possibly

due to sustained improvement of beta-cell function.

In summary, it seems that SSFR results in favorable metabolic changes, particularly improving insulin sensitivity. However, there is a need for properly and well-conducted prospective clinical studies to unravel these putative changes. In turn, this will help us not only to confirm the safety of these procedures but also to define if these procedures can be used for metabolic benefit and to broaden our knowledge about the mechanisms underpinning excess ASF and associated metabolic consequences.

9.2. Research impact, significance and future directions

9.2.1. Advances on state of the art

This research aimed to target the uncertainties in the metabolic changes after a sudden reduction in the amount of subcutaneous fat tissue by surgical methods. This in turn helps to understand the underlying mechanism behind the insulin resistance trajectories among overweight and obese patients which is a major cause of morbidities and mortalities among the Qatari population and on the global level as well.

This research output aims ultimately to increase our knowledge and improve our clinical practice in managing obesity-associated insulin resistance and other metabolic complications, which has a direct consequence for the health system by potentially suggesting ways through which higher accuracy and specificity in the treatment and detection of these diseases can proceed. Eventually, this will have a positive impact on the cost burden of treating these obesity-related diseases and complications. The innovation in this program of work outlined in this research is not limited to theory-driven data, but the aim is to be clinically translated.

9.2.2. Alignment to the national research priority

This research falls within the National Priorities Research Program 13 (NPRP

13) biomedical and health pillar priority theme of non-communicable diseases. This optimizes effective delivery of health care and related systems and services and improve the health and wellbeing of the Qatar population through better use of research output.

There is a pressing need to ensure that we expand research input to cope with the high impact of such metabolic disorders and to study the metabolic effect of these body contouring surgeries which is gaining accelerating popularity in Qatar. This, in turn, provide an opportunity to improve our clinical practice so that Qataris can continue to enjoy a productive and fulfilling life with the best efficiencies for support and health services, and on the budget. Importantly, it provides robust evidence that can be used to guide health modeling. As such it contributes to major health care advances thereby providing a better quality of life for the population.

9.2.3. Social, health, economic and environmental impact

Based on the previous literature it was not clear if surgical fat removal for cosmetic reasons has a neutral, adverse or beneficial impact on metabolic health of a patient. This is a critical question that has been answered for Qatar because this is a common procedure amongst the Qatari population, given the free access to this surgical procedure. There is of high importance in order to ensure that patients are not harmed by this procedure. In addition, the metabolic changes observed can have potential implications for type 2 diabetes in terms of understanding interaction with fat tissue related hormones and further our medical knowledge of the interaction between fat mass and various hormonal regulation.

Additionally, Qatar University (QU) intends to become the most research-intensive university in the region. Qatar University (QU) has been ranked 332nd in the QS World University Rankings 2019, among the top 1,000 universities in the world,

and 36th in the “QS Top 50 Under 50” 2019 ranking. It has been steadily increasing in rank across reputable international rankings. QU-CMED facilitates national and international collaboration with world research leaders and fosters the career development of staff through providing opportunities for training (e.g. academic leadership) and funding for attendance at national and international conferences. The current research is integrated within QU's broader strategic recognition of core responsibilities around providing research leadership, addressing complex problems, and extending benefits to the community that accompanies the development and maintenance of a pervasive research culture. QU has systematically and deliberately invested in the development of a health cluster across the colleges of Medicine, Health Sciences and Pharmacy. The present research fits with existing QU research strengths in terms of advancing the fields of diabetes & metabolic diseases, clinical epidemiology and the field of molecular medicine.

The funding sought in the current research through several research grants, provides the required level of research support for the principal supervisor of this dissertation, Professor Suhail A. Doi, in his capacity as an academic staff member and Head of the Department of Population Medicine, to deliver on the mission of this research-intensive Department located within the QU-CMED and thus strengthen Qatar’s research infrastructure. It also supports the role of QU-CMED in post-graduate education.

Key elements of the mission of the College of Medicine, in line with Hamad Medical Corporation's priorities, are to better the health of the population through leveraging research findings and to promote and improve the physical image as well as the physiological state and wellbeing of the Qatari population. This research project contributes directly to this mission through better evidence generation across a

multitude of unanswered questions to generate new data that will link clinical, biochemical and molecular parameters after these body contouring surgeries. In so doing, the capacity for informed decision making through leveraging of research output becomes more robust and reliable contributing to our ability to make the best use and interpretation of knowledge in the country, potentially informing policy and practice.

This research project provides a very strong platform for the continuation, consolidation, and expansion of this work, with the potential to impact the National Health Strategy (NHS) of Qatar, as outlined by the Ministry of Public Health (MOPH). Research translation is a key aspect of the MOPH health strategy as that is what guides policy and practice and is evidenced by being a key element within the NHS. In addition to its direct alignment with the strategic priorities of Qatar Foundation, the proposed research will allow existing national and international collaborative relationships with other research institutions to be strengthened through collaborative analyses of large datasets. This project also influences research translation in this area of national importance thus creating further opportunities for collaborative research translation activities to be initiated and developed within CMED and these outputs will be invaluable to the various researchers in these streams. This outcome would also be valuable to researchers across QU such as in Biomedical Sciences, Public Health, Academic Departments of Surgery & Medicine and therefore this project has strategic importance well beyond CMED thereby contributing to cross- and inter-disciplinary research at QU. The funding obtained for this project also support the strategic requirements of both the CMED and QU by providing access to opportunities that can leverage for the broader interest of the Qatari research community.

9.2.4. Communication and exploitation of results

Results of this research project are currently being disseminated to update the health system (surgical departments) regarding the non-cosmetic impact on patients and may serve to modify selection criteria for this procedure, to those who would benefit most, or avoid harm. Dissemination of results based on the data through peer-reviewed publications and conference presentations. Given the importance of this research, particular attention will be focused on the wider dissemination of the research findings. Where possible open access options have been chosen and results has been communicated to the broader community through public seminars and talks to interest groups and leaders especially within the NHS of the MOPH in Qatar.

Special advantages of this research project are to use it as a promotion for further collaborative studies among the involved parties, as well as an opportunity to advertise QU-postgraduate projects that include masters and PhD. programs at Qatar University. This aims to generate not only advanced clinical knowledge but also will help the development of future researchers that will continue to support the health advancement of this country.

A. PubMed

("Insulin Resistance"[Mesh] OR "Adipokines"[Mesh] OR "Insulin sensitivity"[tiab] OR "Adipose tissue"[tiab] OR "Visceral fat"[tiab] OR "Plasma leptin"[tiab] OR "Lipid profile"[tiab]) AND ("Lipectomy"[Mesh] OR Liposuction[tiab] OR Lipectomy[tiab] OR Abdominoplasty[tiab] OR Megalipoplasty[tiab] OR "Mega Lipoplasty"[tiab]) AND ("Metabolism"[Mesh] OR "Body Mass Index"[Mesh] OR Metabolic[tiab] OR Metabolism[tiab] OR "Adipokine secretion"[tiab]) AND ("Postoperative Period"[Mesh] OR Surgery[sh] OR Surgery[tiab] OR Surgical[tiab] OR Surgically[tiab] OR Postoperative[tiab]).

B. Embase

("Insulin Resistance"/exp/mj OR adipocytokine/exp/mj OR "Insulin sensitivity":ti,ab OR "Adipose tissue":ti,ab OR "Visceral fat":ti,ab OR "Plasma leptin":ti,ab OR "Lipid profile":ti,ab) AND (Lipectomy/exp/mj OR Liposuction:ti,ab OR Lipectomy:ti,ab OR Abdominoplasty:ti,ab OR Megalipoplasty:ti,ab OR "Mega Lipoplasty":ti,ab) AND (Metabolism/exp/mj OR "body mass"/exp OR Metabolic:ti,ab OR Metabolism:ti,ab OR "Adipokine secretion":ti,ab) AND ("Postoperative Period"/exp/mj OR Surgery:ti,ab OR Surgical:ti,ab OR Surgically:ti,ab OR Postoperative:ti,ab).

C. Scopus

(INDEXTERMS("Insulin Resistance") OR INDEXTERMS(Adipokines) OR TITLE-ABS("Insulin sensitivity") OR TITLE-ABS("Adipose tissue") OR TITLE-ABS("Visceral fat") OR TITLE-ABS("Plasma leptin") OR TITLE-ABS("Lipid profile")) AND (INDEXTERMS(Lipectomy) OR TITLE-ABS(Liposuction) OR TITLE-ABS(Lipectomy) OR TITLE-ABS(Abdominoplasty) OR TITLE-ABS(Megalipoplasty) OR TITLE-ABS("Mega Lipoplasty")) AND (INDEXTERMS(Metabolism) OR INDEXTERMS("Body Mass Index") OR TITLE-ABS(Metabolic) OR TITLE-ABS(Metabolism) OR TITLE-ABS("Adipokine secretion")) AND (INDEXTERMS("Postoperative Period") OR TITLE-ABS(Surgery) OR TITLE-ABS(Surgical) OR TITLE-ABS(Surgically) OR TITLE-ABS(Postoperative)).

Figure S1. Search strings for the umbrella review study.

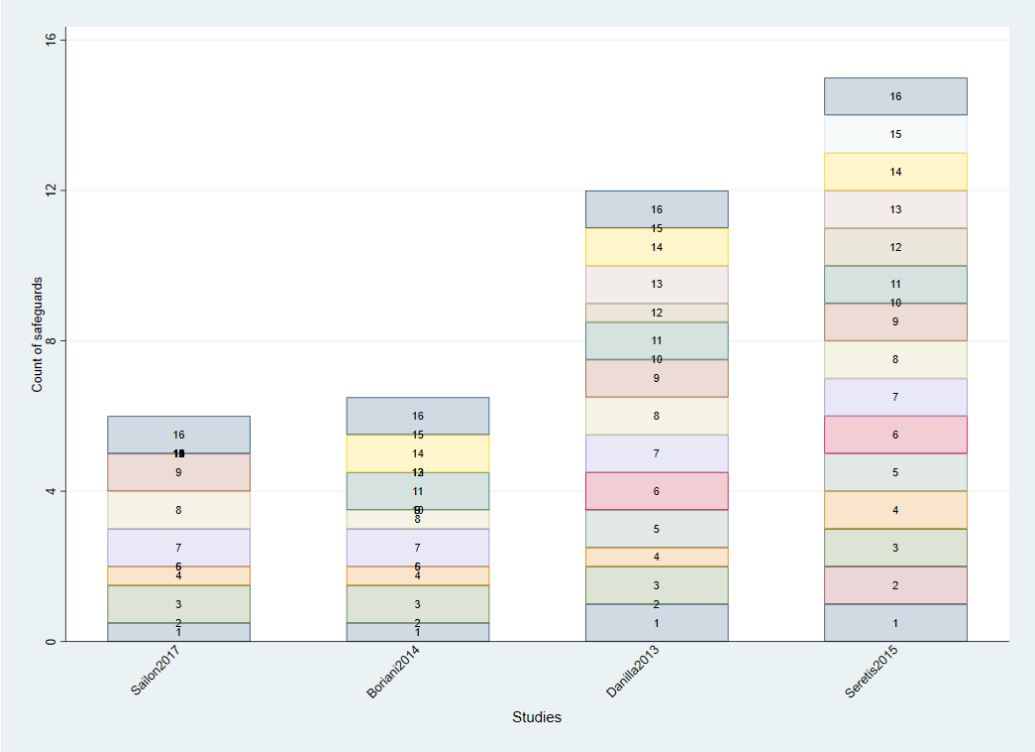


Figure S2. Quality assessment of the four syntheses included in the umbrella review study.

A. PubMed

("Insulin Resistance"[Mesh] OR "Adipokines"[Mesh] OR "Insulin sensitivity"[tiab] OR "Adipose tissue"[tiab] OR "Visceral fat"[tiab] OR "Plasma leptin"[tiab] OR "Lipid profile"[tiab]) AND ("Lipectomy"[Mesh] OR Liposuction[tiab] OR Lipectomy[tiab] OR Abdominoplasty[tiab] OR Megalipoplasty[tiab] OR "Mega Lipoplasty"[tiab]) AND ("Metabolism"[Mesh] OR "Body Mass Index"[Mesh] OR Metabolic[tiab] OR Metabolism[tiab] OR "Adipokine secretion"[tiab]) AND ("Postoperative Period"[Mesh] OR Surgery[sh] OR Surgery[tiab] OR Surgical[tiab] OR Surgically[tiab] OR Postoperative[tiab]).

B. Embase

("Insulin Resistance"/exp/mj OR adipocytokine/exp/mj OR "Insulin sensitivity":ti,ab OR "Adipose tissue":ti,ab OR "Visceral fat":ti,ab OR "Plasma leptin":ti,ab OR "Lipid profile":ti,ab) AND (Lipectomy/exp/mj OR Liposuction:ti,ab OR Lipectomy:ti,ab OR Abdominoplasty:ti,ab OR Megalipoplasty:ti,ab OR "Mega Lipoplasty":ti,ab) AND (Metabolism/exp/mj OR "body mass"/exp OR Metabolic:ti,ab OR Metabolism:ti,ab OR "Adipokine secretion":ti,ab) AND ("Postoperative Period"/exp/mj OR Surgery:ti,ab OR Surgical:ti,ab OR Surgically:ti,ab OR Postoperative:ti,ab).

C. Scopus

(INDEXTERMS("Insulin Resistance") OR INDEXTERMS(Adipokines) OR TITLE-ABS("Insulin sensitivity") OR TITLE-ABS("Adipose tissue") OR TITLE-ABS("Visceral fat") OR TITLE-ABS("Plasma leptin") OR TITLE-ABS("Lipid profile")) AND (INDEXTERMS(Lipectomy) OR TITLE-ABS(Liposuction) OR TITLE-ABS(Lipectomy) OR TITLE-ABS(Abdominoplasty) OR TITLE-ABS(Megalipoplasty) OR TITLE-ABS("Mega Lipoplasty")) AND (INDEXTERMS(Metabolism) OR INDEXTERMS("Body Mass Index") OR TITLE-ABS(Metabolic) OR TITLE-ABS(Metabolism) OR TITLE-ABS("Adipokine secretion")) AND (INDEXTERMS("Postoperative Period") OR TITLE-ABS(Surgery) OR TITLE-ABS(Surgical) OR TITLE-ABS(Surgically) OR TITLE-ABS(Postoperative)).

Figure S3. Full search strings for all databases (SSFR-DRMA study).

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	P15
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	P3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	P5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	P6
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	P6-7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	P6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	P6
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	P6-7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	P8
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	P7-8
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	P7-8
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	P8
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	N/A
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	P6-7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	N/A
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	N/A
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	P9
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	P10-12

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	P9
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	N/A
Study characteristics	17	Cite each included study and present its characteristics.	P9
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	P12
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	P9
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	P12
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	P10-12
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	P17
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	P10-12
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	P12-17
	23b	Discuss any limitations of the evidence included in the review.	P17
	23c	Discuss any limitations of the review processes used.	N/A
	23d	Discuss implications of the results for practice, policy, and future research.	P17
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	N/A
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	P2
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	P2
Competing interests	26	Declare any competing interests of review authors.	P2
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	P6

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71
For more information, visit: http://www.prisma-statement.org/

Figure S4. PRISMA checklist (SSFR-DRMA study).

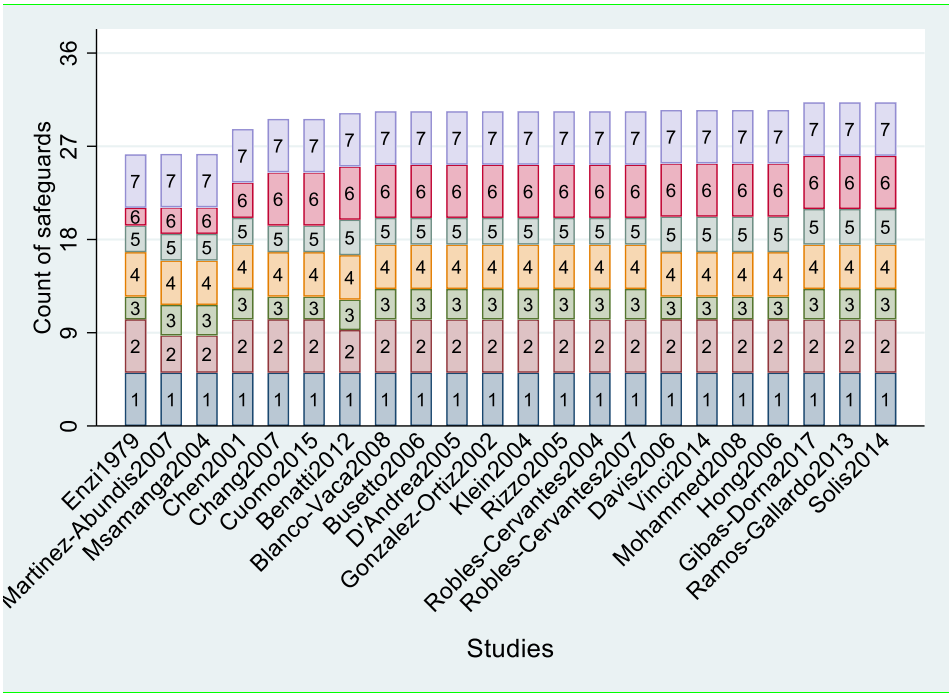


Figure S5. Quality assessment of the included studies using the MethodologicAl STandards for Epidemiological Research (MASTER) scale (SSFR-DRMA study).

1. **PubMed search**

("Ultrasonic Therapy"[Mesh] OR "High-Intensity Focused Ultrasound Ablation"[Mesh] OR "Fat removal"[tiab] OR "Fat freezing"[tiab] OR "High intensity focused ultrasound"[tiab] OR "Ultrasound cavitation"[tiab] OR "Focused ultrasound"[tiab] OR "Suction massage"[tiab] OR Vacuum[tiab] OR Radiofrequency[tiab] OR "High intensity electromagnetic"[tiab] OR "Infrared light energy"[tiab] OR "Electromagnetic Field"[tiab] OR HIFEM[tiab] OR "Ultrasonic Therapy"[tiab] OR "Ultrasound device"[tiab] OR "Fat destruction"[tiab])

AND

("Body Contouring"[Mesh] OR "Body contouring"[tiab] OR Body-contouring[tiab] OR "Body Lift"[tiab] OR "Body Contour"[tiab] OR Contour[tiab] OR Contouring[tiab] OR Noninvasive[tiab] OR Non-invasive[tiab] OR "Non invasive"[tiab] OR Nonsurgical[tiab] OR Non-surgical[tiab] OR "Non surgical"[tiab])

AND

("Adiposity"[Mesh] OR "Waist Circumference"[Mesh] OR Metabolic[tiab] OR Metabolism[tiab] OR "Abdominal circumference"[tiab] OR "Fat thickness"[tiab] OR BMI[tiab] OR "Waist

Figure S6. Search strategy (NSSFR DRMA study)

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	6
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	7-8
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	7
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplementary material 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	7-8
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	8-9
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	8-9
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	9
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	8
Effect	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation	8-9

Section and Topic	Item #	Checklist item	Location where item is reported
measures		of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	7-8
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	n/a
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Table 1
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	9-10
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	n/a
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	n/a
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	n/a
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	9-10
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	n/a
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	n/a
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Figure 2-3
Results of	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	n/a

Section and Topic	Item #	Checklist item	Location where item is reported
syntheses	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	11-12
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	n/a
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	n/a
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	n/a
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	11-12
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	13
	23b	Discuss any limitations of the evidence included in the review.	15
	23c	Discuss any limitations of the review processes used.	15
	23d	Discuss implications of the results for practice, policy, and future research.	13-15
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	n/a
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	n/a
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	n/a
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	2
Competing interests	26	Declare any competing interests of review authors.	2
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	n/a

Figure S7. PRISMA checklist (NSSFR DRMA study)

Table S8. Quality assessment of the included studies using the MethodologicAl STandards for Epidemiological Research (MASTER) scale (NSSFR DRMA study)

Standard Category

1-9: equal recruitment
10- 16: equal ascertainment
17- 22: equal implementation
23- 28: equal prognosis
29-31: Sufficient analysis
32- 36: Temporal precedence

Safeguards:

1	Data collected after the start of the study was not used to exclude participants or to select them into the analysis
2	Participants in all comparison groups met the same eligibility requirements and were from the same population
	and timeframe
3	Determination of eligibility and assignment to treatment group/ exposure strategy were synchronised

4	None of the eligibility criteria were common effects of exposure and outcome
5	Any attrition (or exclusions after entry) <20% (based on numbers)
6	Missing data was less than 20%
7	Analysis accounted for missing data
8	Exposure variations / treatment deviations were less than 20%
9	Variations in exposure or withdrawals after start of the study were addressed by the analysis
10	Procedures for data collection of covariates were reliable and the same for all participants
11	The outcome was objective and/ or reliably measured
12	Exposures/ interventions were objectively and/ or reliably measured
13	Outcome assessor(s) were blinded
14	Participants were blinded
15	Caregivers were blinded
16	Analyst(s) were blinded
17	Care was delivered equally to all participants

18	Cointerventions that could impact the outcome were comparable between groups or avoided
19	Control and active interventions/ exposures were sufficiently distinct
20	Exposure/intervention definition was consistently applied to all participants
21	Outcome definition was consistently applied to all participants
22	The time period between exposure and outcome was similar across patients and between groups or the analyses adjusted for different lengths of follow-up of patients
23	Design and/or analysis strategies were in place that addressed potential confounding
24	Key confounders addressed through design or analysis were not common effects of exposure and outcome
25	Key baseline characteristics / prognostic indicators for the study were comparable across groups
26	Participants were randomly allocated to groups with an adequate randomisation process
27	Allocation procedure was adequate and concealed
28	Conflict of interests were declared and absent
29	Analytic method was justified by study design (e.g., effect size not appropriate for the study design or cross-over designs properly handled etc)

30	Computation errors or contradictions were absent (calculation)
31	There was no discernible data dredging or selective reporting of the outcomes
32	All subjects were selected prior to intervention/ exposure and evaluated prospectively
33	Carry-over or refractory effects were avoided or considered in the design of the study or were not relevant- in medication
34	The intervention/ exposure period was long enough to have influenced the study outcome
35	Dose of intervention/ exposure was sufficient to influence the outcome
36	Length of follow-up was not too long or too short in relation to the outcome assessment

Study ID	SG1	SG2	SG3	SG4	SG5	SG6	SG7	SG8	SG9	SG10	SG11	SG12	SG13	SG14	SG15	SG16	SG17	SG18	SG19
1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

4	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
4	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1
4	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
4	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
4	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
4	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
5	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
5	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
5	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	1	0	1	0	1	0	0	1	1	0	1	0
6	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1

6	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1
6	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1
7	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
7	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
7	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
7	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
7	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

SG: Safeguard number.

Table S9. Trend Statement Checklist (quasi experiment pilot study)

TREND Statement Checklist

Paper Section/ Topic	Item No	Descriptor	Reported? ✓	Reported? Pg #
Title and Abstract				
Title and Abstract	1	• Information on how unit were allocated to interventions		
		• Structured abstract recommended		
		• Information on target population or study sample		
Introduction				
Background	2	• Scientific background and explanation of rationale		
		• Theories used in designing behavioral interventions		
Methods				
Participants	3	• Eligibility criteria for participants, including criteria at different levels in recruitment/sampling plan (e.g., cities, clinics, subjects)		
		• Method of recruitment (e.g., referral, self-selection), including the sampling method if a systematic sampling plan was implemented		
		• Recruitment setting		
		• Settings and locations where the data were collected		
Interventions	4	• Details of the interventions intended for each study condition and how and when they were actually administered, specifically including:		
		○ Content: what was given?		
		○ Delivery method: how was the content given?		
		○ Unit of delivery: how were the subjects grouped during delivery?		
		○ Deliverer: who delivered the intervention?		
		○ Setting: where was the intervention delivered?		
		○ Exposure quantity and duration: how many sessions or episodes or events were intended to be delivered? How long were they intended to last?		
		○ Time span: how long was it intended to take to deliver the intervention to each unit?		
		○ Activities to increase compliance or adherence (e.g., incentives)		
Objectives	5	• Specific objectives and hypotheses		
Outcomes	6	• Clearly defined primary and secondary outcome measures		
		• Methods used to collect data and any methods used to enhance the quality of measurements		
		• Information on validated instruments such as psychometric and biometric properties		
Sample Size	7	• How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules		
Assignment Method	8	• Unit of assignment (the unit being assigned to study condition, e.g., individual, group, community)		
		• Method used to assign units to study conditions, including details of any restriction (e.g., blocking, stratification, minimization)		
		• Inclusion of aspects employed to help minimize potential bias induced due to non-randomization (e.g., matching)		

TREND Statement Checklist

Blinding (masking)	9	• Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to study condition assignment; if so, statement regarding how the blinding was accomplished and how it was assessed.		
Unit of Analysis	10	• Description of the smallest unit that is being analyzed to assess intervention effects (e.g., individual, group, or community)		
		• If the unit of analysis differs from the unit of assignment, the analytical method used to account for this (e.g., adjusting the standard error estimates by the design effect or using multilevel analysis)		
Statistical Methods	11	• Statistical methods used to compare study groups for primary methods outcome(s), including complex methods of correlated data		
		• Statistical methods used for additional analyses, such as a subgroup analyses and adjusted analysis		
		• Methods for imputing missing data, if used		
		• Statistical software or programs used		
Results				
Participant flow	12	• Flow of participants through each stage of the study: enrollment, assignment, allocation, and intervention exposure, follow-up, analysis (a diagram is strongly recommended)		
		○ Enrollment: the numbers of participants screened for eligibility, found to be eligible or not eligible, declined to be enrolled, and enrolled in the study		
		○ Assignment: the numbers of participants assigned to a study condition		
		○ Allocation and intervention exposure: the number of participants assigned to each study condition and the number of participants who received each intervention		
		○ Follow-up: the number of participants who completed the follow-up or did not complete the follow-up (i.e., lost to follow-up), by study condition		
		○ Analysis: the number of participants included in or excluded from the main analysis, by study condition		
		• Description of protocol deviations from study as planned, along with reasons		
Recruitment	13	• Dates defining the periods of recruitment and follow-up		
Baseline Data	14	• Baseline demographic and clinical characteristics of participants in each study condition		
		• Baseline characteristics for each study condition relevant to specific disease prevention research		
		• Baseline comparisons of those lost to follow-up and those retained, overall and by study condition		
		• Comparison between study population at baseline and target population of interest		
Baseline equivalence	15	• Data on study group equivalence at baseline and statistical methods used to control for baseline differences		

TREND Statement Checklist

Numbers analyzed	16	• Number of participants (denominator) included in each analysis for each study condition, particularly when the denominators change for different outcomes; statement of the results in absolute numbers when feasible		
		• Indication of whether the analysis strategy was "intention to treat" or, if not, description of how non-compliers were treated in the analyses		
Outcomes and estimation	17	• For each primary and secondary outcome, a summary of results for each estimation study condition, and the estimated effect size and a confidence interval to indicate the precision		
		• Inclusion of null and negative findings		
		• Inclusion of results from testing pre-specified causal pathways through which the intervention was intended to operate, if any		
Ancillary analyses	18	• Summary of other analyses performed, including subgroup or restricted analyses, indicating which are pre-specified or exploratory		
Adverse events	19	• Summary of all important adverse events or unintended effects in each study condition (including summary measures, effect size estimates, and confidence intervals)		
DISCUSSION				
Interpretation	20	• Interpretation of the results, taking into account study hypotheses, sources of potential bias, imprecision of measures, multiplicative analyses, and other limitations or weaknesses of the study		
		• Discussion of results taking into account the mechanism by which the intervention was intended to work (causal pathways) or alternative mechanisms or explanations		
		• Discussion of the success of and barriers to implementing the intervention, fidelity of implementation		
		• Discussion of research, programmatic, or policy implications		
Generalizability	21	• Generalizability (external validity) of the trial findings, taking into account the study population, the characteristics of the intervention, length of follow-up, incentives, compliance rates, specific sites/settings involved in the study, and other contextual issues		
Overall Evidence	22	• General interpretation of the results in the context of current evidence and current theory		

From: Des Jarlais, D. C., Lyles, C., Crepaz, N., & the Trend Group (2004). Improving the reporting quality of nonrandomized evaluations of behavioral and public health interventions: The TREND statement. *American Journal of Public Health*, 94, 361-366. For more information, visit: http://www.cdc.gov/trendstatement/

REFERENCES

1 Kitzinger HB, Abayev S, Pittermann A, Karle B, Bohdjalian A, Langer FB *et al.* After massive weight loss: patients' expectations of body contouring surgery. *Obes Surg* 2012; 22: 544–548.

2 Almutairi K, Gusenoff JA, Rubin JP, K A, JA G, JP R. Body Contouring. Plast Reconstr Surg, 2016.

3 Sailon AM, Wasserburg JR, Kling RR, Pasick CM, Taub PJ, AM S *et al.* Influence of Large-Volume Liposuction on Metabolic and Cardiovascular Health: A Systematic Review. *Ann Plast Surg* 2017; 79: 623–630.

4 Seretis K, Goulis DG, Koliakos G, Demiri E, K S, DG G *et al.* The effects of abdominal lipectomy in metabolic syndrome components and insulin sensitivity in females: A systematic review and meta-analysis. *Metabolism* 2015; 64: 1640–1649.

5 Pinkhasov BB, Selyatitskaya VG, Karapetyan AR, Astrakhantseva EL, Pinkhasov BB, Selyatitskaya VG *et al.* Metabolic syndrome in men and women with upper or lower types of body fat distribution. *Health N Hav* 2012; 4: 1381–1389.

6 Després JP, Lemieux I. Abdominal obesity and metabolic syndrome. *Nature* 2006; 444: 881–887.

7 Fu J, Hofker M, Wijmenga C. No Title. 2015; 21: 507–508.

8 Kwon H, Kim D, Kim JS. Body Fat Distribution and the Risk of Incident Metabolic Syndrome: A Longitudinal Cohort Study. 2017; 7: 1–8.

9 Klein S. Is visceral fat responsible for the metabolic abnormalities associated with obesity?: implications of omentectomy. *Diabetes Care* 2010; 33: 1693–1694.

10 Klein S. The case of visceral fat: argument for the defense. *J Clin Invest* 2004; 113: 1530–1532.

11 Fabbrini E, Magkos F, Mohammed BS, Pietka T, Abumrad NA, Patterson BW *et al.* Intrahepatic fat, not visceral fat, is linked with metabolic complications of obesity. *Proc Natl Acad Sci U S A* 2009; 106: 15430–15435.

12 Obesity and overweight. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight (accessed 14 Mar2021).

13 Cao H. Adipocytokines in obesity and metabolic disease. Bioscientifica Ltd, 2014.

14 Bergé JP, Barnathan G. Fatty acids from lipids of marine organisms: molecular biodiversity, roles as biomarkers, biologically active compounds, and economical aspects. *Adv Biochem Eng Biotechnol* 2005; 96: 49–125.

15 Achari AE, Jain SK. Adiponectin, a Therapeutic Target for Obesity, Diabetes, and Endothelial Dysfunction. *Int J Mol Sci* 2017; 18. doi:10.3390/IJMS18061321.

16 Frayn KN. Adipose tissue and the insulin resistance syndrome. *Proc Nutr Soc* 2001; 60: 375–380.

17 Kusminski CM, Holland WL, Sun K, Park J, Spurgin SB, Lin Y *et al.* MitoNEET-driven alterations in adipocyte mitochondrial activity reveal a crucial adaptive process that preserves insulin sensitivity in obesity. *Nat Med* 2012; 18: 1539–1551.

18 Finucane MM, Stevens GA, Cowan MJ, Danaei G, Lin JK, Paciorek CJ *et al.* No Title. 2011; 377: 557–567.

19 Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K *et al.* Bariatric surgery: a systematic review and meta-analysis. *JAMA* 2004; 292: 1724–1737.

20 LJ B, AG W. Body contouring in the postbariatric surgery patient. *J Am Coll Surg* 2006; 203: 82–93.

21 Almutairi K, Gusenoff JA, Rubin JP. Body Contouring. *Plast Reconstr Surg* 2016; 137: 586e–602e.

22 Enzi G, Gasparo M, Raimondo Biondetti P, Fiore D, Semisa M, Zurlo F. Subcutaneous and visceral fat distribution according to sex, age, and overweight, evaluated by computed tomography. *Am J Clin Nutr* 1986; 44: 739–746.

23 Coelho M, Oliveira T, Fernandes R. Biochemistry of adipose tissue: an endocrine organ. *Arch Med Sci* 2013; 9: 191.

24 Nguyen NT, Varela JE. Bariatric surgery for obesity and metabolic disorders: state of the art. *Nature Reviews Gastroenterology & Hepatology 2017 14:3* 2016; 14: 160–169.

25 Seretis K, Goulis DG, Koliakos G, Demiri E. The effects of abdominal lipectomy in metabolic syndrome components and insulin sensitivity in females: A systematic review and meta-analysis. *Metabolism* 2015; 64: 1640–1649.

26 Sailon AM, Wasserburg JR, Kling RR, Pasick CM, Taub PJ. Influence of Large-Volume Liposuction on Metabolic and Cardiovascular Health: A Systematic Review. *Ann Plast Surg* 2017; 79: 623–630.

27 Boriani F, Villani R, Morselli PG. Metabolic effects of large-volume liposuction for obese healthy women: a meta-analysis of fasting insulin levels. *Aesthetic Plast Surg* 2014; 38: 1050–1056.

28 Danilla S, Longton C, Valenzuela K, Cavada G, Norambuena H, Tabilo C *et al.* Suction-assisted lipectomy fails to improve cardiovascular metabolic markers of disease: a meta-analysis. *J Plast Reconstr Aesthet Surg* 2013; 66: 1557–1563.

29 Seretis K, Goulis DG, Koliakos G, Demiri E. Short- and Long-Term Effects of Abdominal Lipectomy on Weight and Fat Mass in Females: a Systematic Review. *Obes Surg* 2015; 25: 1950–1958.

30 Inzucchi SE. Clinical practice. Diagnosis of diabetes. *N Engl J Med* 2012; 367: 542–50.

31 Doi SAR, Bashir M, Sheehan MT, Onitilo AA, Chivese T, Ibrahim IM *et al.* Unifying the diagnosis of gestational diabetes mellitus: Introducing the NPRP criteria. *Prim Care Diabetes* 2022; 16: 96–101.

32 Perry RC, Baron AD. Impaired glucose tolerance. Why is it not a disease? *Diabetes Care* 1999; 22: 883–885.

33 Badran S, Doi SA, Hamdi M, Hammouda A, Alharami S, Clark J *et al.* Metabolic aspects of surgical subcutaneous fat removal: an umbrella review and implications for future research. *Bosn J Basic Med Sci* 2022. doi:10.17305/BJBMS.2022.8175.

34 Ziccardi P, Nappo F, Giugliano G, Esposito K, Marfella R, Cioffi M *et al.* Reduction of inflammatory cytokine concentrations and improvement of endothelial functions in obese women after weight loss over one year. *Circulation* 2002; 105: 804–809.

35 Stevens VJ, Obarzanek E, Cook NR, Lee IM, Appel LJ, West DS *et al.* Long-term weight loss and changes in blood pressure: results of the Trials of Hypertension Prevention, phase II. *Ann Intern Med* 2001; 134: 1–11.

36 Madsbad S, Dirksen C, Holst JJ. Mechanisms of changes in glucose metabolism and bodyweight after bariatric surgery. *Lancet Diabetes Endocrinol* 2014; 2: 152–164.

37 Cazes L, Deitel M, Levine RH. Effect of Abdominal Lipectomy on Lipid Profile, Glucose Handling and Blood Pressure in Patients with Truncal Obesity. *Obes Surg* 1996; 6: 159–166.

38 Rizzo MR, Paolisso G, Grella R, Barbieri M, Grella E, Ragno E *et al.* Is

dermolipectomy effective in improving insulin action and lowering inflammatory markers in obese women? *Clin Endocrinol (Oxf)* 2005; 63: 253–258.

39 Swanson E, E S. Prospective clinical study reveals significant reduction in triglyceride level and white blood cell count after liposuction and abdominoplasty and no change in cholesterol levels. *Plast Reconstr Surg* 2011; 128. doi:10.1097/PRS.0B013E31822213C6.

40 M G-O, JA R-C, L C-C, R B-S, E M-A, González-Ortiz M *et al.* The effects of surgically removing subcutaneous fat on the metabolic profile and insulin sensitivity in obese women after large-volume liposuction treatment. *Horm Metab Res* 2002; 34: 446–449.

41 J Y, F B-V, S F, A C, R B, X P *et al.* The effects of liposuction removal of subcutaneous abdominal fat on lipid metabolism are independent of insulin sensitivity in normal-overweight individuals. *Obes Surg* 2008; 18: 408–414.

42 L B, F B, M Z, F Z, ML N, S P *et al.* The effects of the surgical removal of subcutaneous adipose tissue on energy expenditure and adipocytokine concentrations in obese women. *Nutr Metab Cardiovasc Dis* 2008; 18: 112–120.

43 DA D, DM P, DA D, WT D, Davis DA, Pellowski DM *et al.* Acute and 1-month effect of small-volume suction lipectomy on insulin sensitivity and cardiovascular risk. *Int J Obes (Lond)* 2006; 30: 1217–1222.

44 D'Andrea F, Grella R, Rizzo MR, Grella E, Grella R, Nicoletti G *et al.* Changing the metabolic profile by large-volume liposuction: a clinical study conducted with 123 obese women. *Aesthetic Plast Surg* 2005; 29: 472–478.

45 Samdal F, Birkeland KI, Ose L, Amland PF, F S, KI B *et al.* Effect of large-volume liposuction on sex hormones and glucose- and lipid metabolism in females. *Aesthetic Plast Surg* 1995; 19: 131–135.

46 Giugliano G, Nicoletti G, Grella E, Giugliano F, Esposito K, Scuderi N *et al.* Effect of liposuction on insulin resistance and vascular inflammatory markers in obese women. *Br J Plast Surg* 2004; 57: 190–194.

47 Giese SY, Neborsky R, Bulan EJ, Spear SL, Yanovski JA. Improvements in cardiovascular risk profile after large-volume lipoplasty: a 1-year follow-up study. *Aesthet Surg J* 2001; 21: 527–531.

48 Giese SY, Bulan EJ, Commons GW, Spear SL, Yanovski JA. Improvements in cardiovascular risk profile with large-volume liposuction: a pilot study. *Plast Reconstr Surg* 2001; 108: 510–519.

49 Esposito K, Giugliano G, Giugliano D, Arner P, Busetto L, Bassetto F *et al.* Metabolic effects of liposuction - Yes or no? [2] (multiple letters). *N Engl J Med* 2004; 351: 1354–7; author reply 1354-7.

50 Clark JM, Sanders S, Carter M, Honeyman D, Cleo G, Auld Y *et al.* Improving the translation of search strategies using the Polyglot Search Translator: a randomized controlled trial. *J Med Libr Assoc* 2020; 108: 195–207.

51 AMSTAR - Assessing the Methodological Quality of Systematic Reviews. https://amstar.ca/Amstar-2.php (accessed 29 Dec2021).

52 Clark JM, Sanders S, Carter M, Honeyman D, Cleo G, Auld Y *et al.* Improving the translation of search strategies using the Polyglot Search Translator: a randomized controlled trial. *J Med Libr Assoc* 2020; 108: 195–207.

53 Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP *et al.* Cochrane Database of Systematic Reviews Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. 2019. doi:10.1002/14651858.ED000142.

54 JC S, K G, J C, M R-H, Z M, P T *et al.* The MethodologicAl STandards for

Epidemiological Research (MASTER) scale demonstrated a unified framework for bias assessment. *J Clin Epidemiol* 2021; 134: 52–64.

55 C X, SAR D. The robust error meta-regression method for dose-response meta-analysis. *Int J Evid Based Healthc* 2018; 16: 138–144.

56 Tai MM. A mathematical model for the determination of total area under glucose tolerance and other metabolic curves. *Diabetes Care* 1994; 17: 152–154.

57 Doi SAR, Bashir M, Sheehan MT, Onitilo AA, Chivese T, Ibrahim IM *et al.* Unifying the diagnosis of gestational diabetes mellitus: Introducing the NPRP criteria. *Prim Care Diabetes* 2021. doi:10.1016/J.PCD.2021.08.006.

58 HOMA2 Calculator : Overview. https://www.dtu.ox.ac.uk/homacalculator/ (accessed 16 Dec2022).

59 Chung ST, Ha J, Onuzuruike AU, Kasturi K, Galvan-De La Cruz M, Bingham BA *et al.* Time to glucose peak during an oral glucose tolerance test identifies prediabetes risk. *Clin Endocrinol (Oxf)* 2017; 87: 484–491.

60 Manco M, Nolfe G, Pataky Z, Monti L, Porcellati F, Gabriel R *et al.* Shape of the OGTT glucose curve and risk of impaired glucose metabolism in the EGIR-RISC cohort. *Metabolism* 2017; 70: 42–50.

61 H P, None B. A new biometrical procedure for testing the equality of measurements from two different analytical methods. Application of linear regression procedures for method comparison studies in clinical chemistry, Part I. *J Clin Chem Clin Biochem* 1983; 21: 709–720.

62 Haynes AB, Haukoos JS, Dimick JB. TREND Reporting Guidelines for Nonrandomized/Quasi-Experimental Study Designs. *JAMA Surg* 2021; 156: 879–880.

63 Diabetes Trials Unit : Home page. https://www.dtu.ox.ac.uk/ (accessed 6

May2022).

64 Badran S, Doi SA, Hammouda A, Musa OAH, Habib AM, Biomolecules B. Validation of Doi's weighted average glucose as a measure of post-load glucose excursion for clinical use. *Biomolecules and Biomedicine* 2023. doi:10.17305/bb.2022.8807.

65 FX C, JL N, Crahay FX, Nizet JL. [Metabolic and cardiovascular consequences of suction-assisted lipectomy: Systematic review]. *Ann Chir Plast Esthet* 2016; 61: 270–286.

66 Seretis K, Goulis DG, Koliakos G, Demiri E, K S, DG G *et al.* Short- and Long-Term Effects of Abdominal Lipectomy on Weight and Fat Mass in Females: a Systematic Review. Obes Surg, 2015.

67 Danilla S, Longton C, Valenzuela K, Cavada G, Norambuena H, Tabilo C *et al.* Suction-assisted lipectomy fails to improve cardiovascular metabolic markers of disease: a meta-analysis. *J Plast Reconstr Aesthet Surg* 2013; 66: 1557–1563.

68 Boriani F, Villani R, Morselli PG. Metabolic effects of large-volume liposuction for obese healthy women: a meta-analysis of fasting insulin levels. *Aesthetic Plast Surg* 2014; 38: 1050–1056.

69 Robles-Cervantes JA, Yánez-Diaz S, Cárdenas-Camarena L. Modification of insulin, glucose and cholesterol levels in nonobese women undergoing liposuction: is liposuction metabolically safe? *Ann Plast Surg* 2004; 52: 64–67.

70 Martínez-Abundis E, Molina-Villa CA, González-Ortiz M, Robles-Cervantes JA, Saucedo-Ortiz JA, E M-A *et al.* Effect of surgically removing subcutaneous fat by abdominoplasty on leptin concentrations and insulin sensitivity. *Ann Plast Surg* 2007; 58: 416–419.

71 Mohammed BS, Cohen S, Reeds D, Young VL, Klein S. Long-term effects of

large-volume liposuction on metabolic risk factors for coronary heart disease. *Obesity (Silver Spring)* 2008; 16: 2648–2651.

72 Klein S, Fontana L, Young VL, Coggan AR, Kilo C, Patterson BW *et al.* Absence of an effect of liposuction on insulin action and risk factors for coronary heart disease. *N Engl J Med* 2004; 350: 2549–2557.

73 Pratt-Phillips SE, Geor RJ, McCutcheon LJ. Comparison among the euglycemic-hyperinsulinemic clamp, insulin-modified frequently sampled intravenous glucose tolerance test, and oral glucose tolerance test for assessment of insulin sensitivity in healthy Standardbreds. 2015; 76: 84–91.

74 Lin Y, Lee H, Berg AH, Lisanti MP, Shapiro L, Scherer PE. No Title. 2000; 275: 24255–24263.

75 Badran S, Doi SA, Hamdi M, Hammouda A, Alharami S, Clark J *et al.* Metabolic aspects of surgical subcutaneous fat removal: an umbrella review and implications for future research. *Bosn J Basic Med Sci* 2022; : 1.

76 Seretis K, Goulis DG, Koliakos G, Demiri E. Short- and Long-Term Effects of Abdominal Lipectomy on Weight and Fat Mass in Females: a Systematic Review. *Obes Surg* 2015; 25: 1950–1958.

77 Seretis K, Demiri E. Metabolic effects of large-volume liposuction for obese healthy women: a meta-analysis of fasting insulin levels. *Aesthetic Plast Surg* 2015; 39: 278–279.

78 Boriani F, Villani R, Morselli PG. Metabolic effects of large-volume liposuction for obese healthy women: a meta-analysis of fasting insulin levels. *Aesthetic Plast Surg* 2014; 38: 1050–1056.

79 Danilla S, Longton C, Valenzuela K, Cavada G, Norambuena H, Tabilo C *et al.* Suction-assisted lipectomy fails to improve cardiovascular metabolic markers of

disease: a meta-analysis. *J Plast Reconstr Aesthet Surg* 2013; 66: 1557–1563.

80 Sailon AM, Wasserburg JR, Kling RR, Pasick CM, Taub PJ. Influence of Large-Volume Liposuction on Metabolic and Cardiovascular Health: A Systematic Review. *Ann Plast Surg* 2017; 79: 623–630.

81 Seretis K, Goulis DG, Koliakos G, Demiri E. The effects of abdominal lipectomy in metabolic syndrome components and insulin sensitivity in females: A systematic review and meta-analysis. *Metabolism* 2015; 64: 1640–1649.

82 Badran S, Habib AM, Aljassem G, Musa OAH, Clark J, Hamd M *et al.* Metabolic changes after surgical fat removal: A dose–response meta-analysis. *Journal of Plastic, Reconstructive & Aesthetic Surgery* 2023; 76: 238–250.

83 Ziccardi P, Nappo F, Giugliano G, Esposito K, Marfella R, Cioffi M *et al.* Reduction of inflammatory cytokine concentrations and improvement of endothelial functions in obese women after weight loss over one year. *Circulation* 2002; 105: 804–809.

84 Stevens VJ, Obarzanek E, Cook NR, Lee IM, Appel LJ, West DS *et al.* Long-term weight loss and changes in blood pressure: results of the Trials of Hypertension Prevention, phase II. *Ann Intern Med* 2001; 134: 1–11.

85 Badran S, Doi SA, Iskeirjeh S, Aljassem G, Jafarian N, Clark J *et al.* Metabolic Changes after Non-Surgical Fat Removal: A Dose Response Meta-analysis. *Journal of Plastic, Reconstructive & Aesthetic Surgery* 2022. doi:10.1016/J.BJPS.2022.10.054.

86 Fontana L, Eagon JC, Trujillo ME, Scherer PE, Klein S. Visceral fat adipokine secretion is associated with systemic inflammation in obese humans. *Diabetes* 2007; 56: 1010–1013.

87 Ross R, Shaw KD, Martel Y, de Guise J, Avruch L. Adipose tissue distribution

measured by magnetic resonance imaging in obese women. *Am J Clin Nutr* 1993; 57: 470–475.

88 Patel P, Abate N. Body fat distribution and insulin resistance. *Nutrients* 2013; 5: 2019–2027.

89 Abate N, Garg A, Peshock RM, Stray-Gundersen J, Grundy SM. Relationships of generalized and regional adiposity to insulin sensitivity in men. *J Clin Invest* 1995; 96: 88–98.

90 Abate N, Garg A, Peshock RM, Stray-Gundersen J, Adams-Huet B, Grundy SM. Relationship of generalized and regional adiposity to insulin sensitivity in men with NIDDM. *Diabetes* 1996; 45: 1684–1693.

91 Goodpaster BH, Thaete FL, Simoneau JA, Kelley DE. Subcutaneous abdominal fat and thigh muscle composition predict insulin sensitivity independently of visceral fat. *Diabetes* 1997; 46: 1579–1585.

92 Dillard TH, Purnell JQ, Smith MD, Raum W, Hong D, Laut J *et al.* No Title. *Surg Obes Relat Dis* 2013; 9.https://pubmed.ncbi.nlm.nih.gov/22169758/ (accessed 29 Dec2021).

93 Lima MMO, Pareja JC, Alegre SM, Geloneze SR, Kahn SE, Astiarraga BD *et al.* Visceral fat resection in humans: effect on insulin sensitivity, beta-cell function, adipokines, and inflammatory markers. *Obesity (Silver Spring)* 2013; 21. doi:10.1002/OBY.20030.

94 Fabbrini E, Tamboli RA, Magkos F, Marks-Shulman PA, Eckhauser AW, Richards WO *et al.* Surgical removal of omental fat does not improve insulin sensitivity and cardiovascular risk factors in obese adults. *Gastroenterology* 2010; 139: 448–455.

95 Dunn JP, Abumrad NN, Breitman I, Marks-Shulman PA, Flynn CR, Jabbour

K *et al.* Hepatic and peripheral insulin sensitivity and diabetes remission at 1 month after Roux-en-Y gastric bypass surgery in patients randomized to omentectomy. *Diabetes Care* 2012; 35: 137–142.

96 Herrera MF, Pantoja JP, Velázquez-Fernández D, Cabiedes J, Aguilar-Salinas C, García-GarcíA E *et al.* Potential additional effect of omentectomy on metabolic syndrome, acute-phase reactants, and inflammatory mediators in grade III obese patients undergoing laparoscopic Roux-en-Y gastric bypass: a randomized trial. *Diabetes Care* 2010; 33: 1413–1418.

97 Shi J, Bao G, Hong J, Wang S, Chen YY, Zhao S *et al.* Deciphering CT texture features of human visceral fat to evaluate metabolic disorders and surgery-induced weight loss effects. *EBioMedicine* 2021; 69. doi:10.1016/J.EBIOM.2021.103471.

98 Lenz M, Arts ICW, Peeters RLM, de Kok TM, Ertaylan G. Adipose tissue in health and disease through the lens of its building blocks. *Sci Rep* 2020; 10. doi:10.1038/S41598-020-67177-1.

99 Ferrero R, Rainer P, Deplancke B. Toward a Consensus View of Mammalian Adipocyte Stem and Progenitor Cell Heterogeneity. *Trends Cell Biol* 2020; 30: 937–950.

100 Merlotti C, Ceriani V, Morabito A, Pontiroli AE. Subcutaneous fat loss is greater than visceral fat loss with diet and exercise, weight-loss promoting drugs and bariatric surgery: a critical review and meta-analysis. *Int J Obes (Lond)* 2017; 41: 672–682.

101 Karlsson T, Rask-Andersen M, Pan G, Höglund J, Wadelius C, Ek WE *et al.* Contribution of genetics to visceral adiposity and its relation to cardiovascular and metabolic disease. *Nat Med* 2019; 25: 1390–1395.

102 Zhang Y, Scarpace PJ, Y Z, PJ S, Zhang Y, Scarpace PJ. The role of leptin in

leptin resistance and obesity. *Physiol Behav* 2006; 88: 249–256.

103 Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM *et al.* The hormone resistin links obesity to diabetes. 2001; 409: 307–312.

104 Maeda K, Uysal KT, Makowski L, Görgün CZ, Atsumi G, Parker RA *et al.* Role of the fatty acid binding protein mal1 in obesity and insulin resistance. *Diabetes* 2003; 52: 300–307.

105 Yang Q, Graham TE, Mody N, Preitner F, Peroni OD, Zabolotny JM *et al.* Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes. *Nature 2005 436:7049* 2005; 436: 356–362.

106 Cianflone K, Xia Z, Chen LY. Critical review of acylation-stimulating protein physiology in humans and rodents. Elsevier, 2003.

107 Yan QW, Yang Q, Mody N, Graham TE, Hsu CH, Xu Z *et al.* The Adipokine Lipocalin 2 Is Regulated by Obesity and Promotes Insulin Resistance. *Diabetes* 2007; 56: 2533–2540.

108 Ernst MC, Sinal CJ. Chemerin: at the crossroads of inflammation and obesity. *Trends in Endocrinology & Metabolism* 2010; 21: 660–667.

109 Chang YH, Chang DM, Lin KC, Shin SJ, Lee YJ. Visfatin in overweight/obesity, type 2 diabetes mellitus, insulin resistance, metabolic syndrome and cardiovascular diseases: a meta-analysis and systemic review. *Diabetes Metab Res Rev* 2011; 27: 515–527.

110 Feng R, Li Y, Wang C, Luo C, Liu L, Chuo F *et al.* Higher vaspin levels in subjects with obesity and type 2 diabetes mellitus: A meta-analysis. *Diabetes Res Clin Pract* 2014; 106: 88–94.

111 Castan-Laurell I, Dray C, Attané C, Duparc T, Knauf C, Valet P. Apelin, diabetes, and obesity. Springer, 2011.

112 Hedjazifar S, Shahidi RK, Hammarstedt A, Bonnet L, Church C, Boucher J *et al.* No Title. *Diabetes* 2020; 69: 331–341.

113 Kadowaki T, Yamauchi T. Adiponectin and Adiponectin Receptors. *Endocr Rev* 2005; 26: 439–451.

114 de Souza Batista CM, Yang RZ, Lee MJ, Glynn NM, Yu DZ, Pray J *et al.* No Title. *Diabetes* 2007; 56: 1655–1661.

115 Ouchi N, Higuchi A, Ohashi K, Oshima Y, Gokce N, Shibata R *et al.* Sfrp5 is an anti-inflammatory adipokine that modulates metabolic dysfunction in obesity. *Science (1979)* 2010; 329: 454–457.

116 Moreno-Aliaga MJ, Pérez-Echarri N, Marcos-Gómez B, Larequi E, Gil-Bea FJ, Viollet B *et al.* No Title. *Cell Metab* 2011; 14: 242–253.

117 Seth M, Biswas R, Ganguly S, Chakrabarti N, Chaudhuri AG. Leptin and obesity. *Physiol Int* 2020; 107: 455–468.

118 Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. *Nature* 1994; 372: 425–432.

119 Yadav A, Jyoti P, Jain SK, Bhattacharjee J. Correlation of Adiponectin and Leptin with Insulin Resistance: A Pilot Study in Healthy North Indian Population. *Indian Journal of Clinical Biochemistry 2011 26:2* 2011; 26: 193–196.

120 Considine R v., Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR *et al.* Serum Immunoreactive-Leptin Concentrations in Normal-Weight and Obese Humans. *N Engl J Med* 1996; 334: 292–295.

121 Segal KR, Landt M, Klein S. Relationship between insulin sensitivity and plasma leptin concentration in lean and obese men. *Diabetes* 1996; 45: 988–991.

122 Berglund ED, Vianna CR, Donato J, Kim MH, Chuang JC, Lee CE *et al.* Direct

leptin action on POMC neurons regulates glucose homeostasis and hepatic insulin sensitivity in mice. *J Clin Invest* 2012; 122: 1000–1009.

123 Schwartz MW, Baskin DG, Bukowski TR, Kuijper JL, Foster D, Lasser G *et al.* Specificity of leptin action on elevated blood glucose levels and hypothalamic neuropeptide Y gene expression in ob/ob mice. *Diabetes* 1996; 45: 531–535.

124 Structure and expression of cDNA and genes for human interferon-beta-2, a distinct species inducible by growth-stimulatory cytokines - PubMed. https://pubmed.ncbi.nlm.nih.gov/3023045/ (accessed 21 Jan2022).

125 T H, K Y, H H, T T, Y W, T M *et al.* Complementary DNA for a novel human interleukin (BSF-2) that induces B lymphocytes to produce immunoglobulin. *Nature* 1986; 324: 73–76.

126 S K, T T, M N, T K, Kang S, Tanaka T *et al.* Targeting Interleukin-6 Signaling in Clinic. *Immunity* 2019; 50: 1007–1023.

127 Mohamed-Ali V, Goodrick S, Rawesh A, Katz DR, Miles JM, Yudkin JS *et al.* Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alpha, in vivo. *J Clin Endocrinol Metab* 1997; 82: 4196–4200.

128 Heinrich PC, Castell J v., Andus T. Interleukin-6 and the acute phase response. *Biochem J* 1990; 265: 621–636.

129 Hirano T. IL-6 in inflammation, autoimmunity and cancer. *Int Immunol* 2021; 33: 127–148.

130 Jonas MI, Kurylowicz A, Bartoszewicz Z, Lisik W, Jonas M, Wierzbicki Z *et al.* Interleukins 6 and 15 Levels Are Higher in Subcutaneous Adipose Tissue, but Obesity Is Associated with Their Increased Content in Visceral Fat Depots. *Int J Mol Sci* 2015; 16: 25817–25830.

131 Wisse BE. The inflammatory syndrome: the role of adipose tissue cytokines in

metabolic disorders linked to obesity. *J Am Soc Nephrol* 2004; 15: 2792–2800.

132 Laferrère B. Diabetes remission after bariatric surgery: is it just the incretins? 2011; : S22–S25.

133 Klein S, Allison DB, Heymsfield SB, Kelley DE, Leibel RL, Nonas C *et al.* Waist circumference and cardiometabolic risk: a consensus statement from Shaping America's Health: Association for Weight Management and Obesity Prevention; NAASO, The Obesity Society; the American Society for Nutrition; and the American Diabetes Association. *Am J Clin Nutr* 2007; 85: 1197–1202.

134 Hernandez TL, Kittelson JM, Law CK, Ketch LL, Stob NR, Lindstrom RC *et al.* Fat redistribution following suction lipectomy: defense of body fat and patterns of restoration. *Obesity (Silver Spring)* 2011; 19: 1388–1395.

135 van der Lei B, Halbesma GJ, van Nieuwenhoven CA, van Wingerden JJ. Spontaneous breast enlargement following liposuction of the abdominal wall: does a link exist? *Plast Reconstr Surg* 2007; 119: 1584–1589.

136 Gurunluoglu R. Discussion: photographic measurements in 301 cases of liposuction and abdominoplasty reveal fat reduction without redistribution. *Plast Reconstr Surg* 2012; 130. doi:10.1097/PRS.0B013E31825904D8.

137 Okamura T, Hashimoto Y, Hamaguchi M, Obora A, Kojima T, Fukui M. Ectopic fat obesity presents the greatest risk for incident type 2 diabetes: a population-based longitudinal study. *Int J Obes (Lond)* 2019; 43: 139–148.

138 Bosy-Westphal A, Braun W, Albrecht V, Müller MJ. Determinants of ectopic liver fat in metabolic disease. *Eur J Clin Nutr* 2019; 73: 209–214.

139 de Munck TJI, Soeters PB, Koek GH. The role of ectopic adipose tissue: benefit or deleterious overflow? *Eur J Clin Nutr* 2021; 75: 38–48.

140 Flaherty SE, Grijalva A, Xu X, Ables E, Nomani A, Ferrante AW. A lipase-

independent pathway of lipid release and immune modulation by adipocytes. *Science* 2019; 363: 989–993.

141 Andrew MS, Huffman DM, Rodriguez-Ayala E, Williams NN, Peterson RM, Bastarrachea RA. Mesenteric visceral lipectomy using tissue liquefaction technology reverses insulin resistance and causes weight loss in baboons. *Surg Obes Relat Dis* 2018; 14: 833–841.

142 Murillo AL, Kaiser KA, Smith DL, Peterson CM, Affuso O, Tiwari HK *et al.* A Systematic Scoping Review of Surgically Manipulated Adipose Tissue and the Regulation of Energetics and Body Fat in Animals. *Obesity (Silver Spring)* 2019; 27: 1404–1417.

143 Busetto L, Bassetto F, Zocchi M, Zuliani F, Nolli ML, Pigozzo S *et al.* The effects of the surgical removal of subcutaneous adipose tissue on energy expenditure and adipocytokine concentrations in obese women. *Nutr Metab Cardiovasc Dis* 2008; 18: 112–120.

144 D'Andrea F, Grella R, Rizzo MR, Grella E, Grella R, Nicoletti G *et al.* Changing the metabolic profile by large-volume liposuction: a clinical study conducted with 123 obese women. *Aesthetic Plast Surg* 2005; 29: 472–478.

145 Klein S, Fontana L, Young VL, Coggan AR, Kilo C, Patterson BW *et al.* Absence of an effect of liposuction on insulin action and risk factors for coronary heart disease. *N Engl J Med* 2004; 350: 2549–2557.

146 Ramos-Gallardo G, Pérez Verdin A, Fuentes M, Godínez Gutiérrez S, Ambriz-Plascencia AR, González-García I *et al.* Effect of abdominoplasty in the lipid profile of patients with dyslipidemia. *Plast Surg Int* 2013; 2013: 1–5.

147 Yazigi Solis M, Artioli GG, Montag E, de Salles Painelli V, Saito FL, Lima FR *et al.* The liposuction-induced effects on adiponectin and selected cytokines are

not affected by exercise training in women. *Int J Endocrinol* 2014; 2014. doi:10.1155/2014/315382.

148 González-Ortiz M, Robles-Cervantes JA, Cárdenas-Camarena L, Bustos-Saldaña R, Martínez-Abundis E. The effects of surgically removing subcutaneous fat on the metabolic profile and insulin sensitivity in obese women after large-volume liposuction treatment. *Horm Metab Res* 2002; 34: 446–449.

149 Rizzo MR, Paolisso G, Grella R, Barbieri M, Grella E, Ragno E *et al.* Is dermolipectomy effective in improving insulin action and lowering inflammatory markers in obese women? *Clin Endocrinol (Oxf)* 2005; 63: 253–258.

150 Gibas-Dorna M, Szulińska M, Turkowski P, Kupsz J, Sowińska A, Mikrut K *et al.* The Effect of VASER Abdominal Liposuction on Metabolic Profile in Overweight Males. *Am J Mens Health* 2017; 11: 284–293.

151 Benatti F, Solis M, Artioli G, Montag E, Painelli V, Saito F *et al.* Liposuction induces a compensatory increase of visceral fat which is effectively counteracted by physical activity: a randomized trial. *J Clin Endocrinol Metab* 2012; 97: 2388–2395.

152 Martínez-Abundis E, Molina-Villa CA, González-Ortiz M, Robles-Cervantes JA, Saucedo-Ortiz JA. Effect of surgically removing subcutaneous fat by abdominoplasty on leptin concentrations and insulin sensitivity. *Ann Plast Surg* 2007; 58: 416–419.

153 Robles-Cervantes JA, Yánez-Diaz S, Cárdenas-Camarena L. Modification of insulin, glucose and cholesterol levels in nonobese women undergoing liposuction: is liposuction metabolically safe? *Ann Plast Surg* 2004; 52: 64–67.

154 Esposito K, Giugliano G, Giugliano D, Arner P, Busetto L, Bassetto F *et al.* Metabolic effects of liposuction - Yes or no? [2] (multiple letters). *N Engl J Med* 2004; 351: 1354–7; author reply 1354-7.

155 Chen MD, Ou LF, Song YM. Postoperative plasma leptin levels in women undergoing suction lipectomy. *Mayo Clin Proc* 2001; 76: 1177–1178.

156 Robles-Cervantes JA, Martínez-Abundis E, González-Ortiz M, Cárdenas-Camarena L, Hernández-Salazar E, Olvera-Ozuna R. Behavior of insulin sensitivity and its relation to leptin and tumor necrosis factor-alpha in obese women undergoing liposuction: 6-month follow-up. *Obes Surg* 2007; 17: 1242–1247.

157 Enzi G, Cagnoni G, Baritussio A, de Biasi F, Favaretto L, Inelmen EM *et al.* Effects of fat mass reduction by dieting and by lipectomy on carbohydrate metabolism in obese patients. *Acta Diabetol Lat* 1979; 16: 147–156.

158 Chang PY, Wu TL, Tsao KC, Sun CF, Wu LL, Wu JT. Cosmetic liposuction causes only transient elevation of acute inflammatory response and does not advance to oxidative and nitrosative stress. *J Clin Lab Anal* 2007; 21: 418–425.

159 Davis DA, Pellowski DM, Davis DA, Donahoo WT. Acute and 1-month effect of small-volume suction lipectomy on insulin sensitivity and cardiovascular risk. *Int J Obes (Lond)* 2006; 30: 1217–1222.

160 Vinci V, Valaperta S, Klinger M, Montanelli A, Specchia C, Forcellini D *et al.* Metabolic Implications of Surgical Fat Removal: Increase of Adiponectin Plasma Levels After Reduction Mammaplasty and Abdominoplasty. *Ann Plast Surg* 2016; 76: 700–704.

161 Mohammed BS, Cohen S, Reeds D, Young VL, Klein S. Long-term effects of large-volume liposuction on metabolic risk factors for coronary heart disease. *Obesity (Silver Spring)* 2008; 16: 2648–2651.

162 Hong YG, Kim HT, Seo SW, Chang CH, Rhee EJ, Lee WY. Impact of large-volume liposuction on serum lipids in orientals: a pilot study. *Aesthetic Plast Surg* 2006; 30: 327–332.

163 Abdominoplasty in Mildly Obese Patients (BMI 30-35 kg/m2): Metabolic, Biochemical and Complication Analysis at One Year | Request PDF. https://www.researchgate.net/publication/283576110_Abdominoplasty_in_Mildly_Obese_Patients_BMI_30-35_kgm2_Metabolic_Biochemical_and_Complication_Analysis_at_One_Year (accessed 27 Nov2021).

164 Ybarra J, Blanco-Vaca F, Fernández S, Castellví A, Bonet R, Palomer X *et al.* The effects of liposuction removal of subcutaneous abdominal fat on lipid metabolism are independent of insulin sensitivity in normal-overweight individuals. *Obes Surg* 2008; 18: 408–414.

165 PL Y, M B, L F, BE K. Breast enlargement observed after power liposuction: a retrospective review. *Dermatol Surg* 2003; 29: 165–167.

166 B van der L, GJ H, CA van N, JJ van W. Spontaneous breast enlargement following liposuction of the abdominal wall: does a link exist? *Plast Reconstr Surg* 2007; 119: 1584–1589.

167 KE F, A R, MC B, BE K, RS N. Breast enlargement after liposuction: comparison of incidence between power liposuction versus traditional liposuction. *Dermatol Surg* 2005; 31: 292–296.

168 Hausman DB, Lu J, Ryan DH, Flatt WP, Harris RBS. Compensatory Growth of Adipose Tissue After Partial Lipectomy: Involvement of Serum Factors: *https://doi.org/101177/153537020422900609* 2016; 229: 512–520.

169 MM M, RB H, TJ B. The regulation of total body fat: lessons learned from lipectomy studies. *Neurosci Biobehav Rev* 2001; 25: 15–28.

170 TL H, JM K, CK L, LL K, NR S, RC L *et al.* Fat redistribution following suction lipectomy: defense of body fat and patterns of restoration. *Obesity (Silver*

Spring) 2011; 19: 1388–1395.

171 Y Z, PJ S. The role of leptin in leptin resistance and obesity. *Physiol Behav* 2006; 88: 249–256.

172 Crahay FX, Nizet JL. [Metabolic and cardiovascular consequences of suction-assisted lipectomy: Systematic review]. *Ann Chir Plast Esthet* 2016; 61: 270–286.

173 Parameswaran N, Patial S. Tumor necrosis factor-α signaling in macrophages. *Crit Rev Eukaryot Gene Expr* 2010; 20: 87–103.

174 Fantuzzi G. Adipose tissue, adipokines, and inflammation. *J Allergy Clin Immunol* 2005; 115: 911–919.

175 Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. *Nat Rev Immunol* 2006; 6: 772–783.

176 Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest* 2003; 112: 1796–1808.

177 Mohamed-Ali V, Goodrick S, Rawesh A, Katz DR, Miles JM, Yudkin JS *et al.* Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alpha, in vivo. *J Clin Endocrinol Metab* 1997; 82: 4196–4200.

178 Han MS, White A, Perry RJ, Camporez JP, Hidalgo J, Shulman GI *et al.* Regulation of adipose tissue inflammation by interleukin 6. *Proc Natl Acad Sci U S A* 2020; 117: 2751–2760.

179 Lucas T, Waisman A, Ranjan R, Roes J, Krieg T, Müller W *et al.* Differential roles of macrophages in diverse phases of skin repair. *J Immunol* 2010; 184: 3964–3977.

180 Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. *Cold Spring Harb Perspect Biol* 2014; 6.

doi:10.1101/CSHPERSPECT.A016295.

181 Castell J v., Gómez-Lechón MJ, David M, Andus T, Geiger T, Trullenque R *et al.* Interleukin-6 is the major regulator of acute phase protein synthesis in adult human hepatocytes. *FEBS Lett* 1989; 242: 237–239.

182 Mari A, Pacini G, Brazzale AR, Ahrén B. Comparative evaluation of simple insulin sensitivity methods based on the oral glucose tolerance test. *Diabetologia* 2005; 48: 748–751.

183 Amati F, Pennant M, Azuma K, Dubé JJ, Toledo FGS, Rossi AP *et al.* Lower Thigh Subcutaneous and Higher Visceral Abdominal Adipose Tissue Content Both Contribute to Insulin Resistance. *Obesity* 2012; 20: 1115–1117.

184 Mertens IL, Gaal LF van. Overweight, Obesity, and Blood Pressure: The Effects of Modest Weight Reduction. *Obes Res* 2000; 8: 270–278.

185 J S, R F, A A. The relationship between body weight and blood pressure. *J Hum Hypertens* 1988; 2: 207–217.

186 Bełtowski J. Role of leptin in blood pressure regulation and arterial hypertension. *J Hypertens* 2006; 24: 789–801.

187 Simonds SE, Pryor JT, Ravussin E, Greenway FL, Dileone R, Allen AM *et al.* Leptin Mediates the Increase in Blood Pressure Associated with Obesity. *Cell* 2014; 159: 1404.

188 Rydén M, Arner P. Subcutaneous Adipocyte Lipolysis Contributes to Circulating Lipid Levels. *Arterioscler Thromb Vasc Biol* 2017; 37: 1782–1787.

189 Swanson E. The clinical relevance of lower triglyceride and leukocyte levels after liposuction. *Plast Reconstr Surg* 2012; 129. doi:10.1097/PRS.0B013E31824A62F8.

190 Huang GJ, Bajaj AK, Gupta S, Petersen F, Miles DAG. Increased

intraabdominal pressure in abdominoplasty: delineation of risk factors. *Plast Reconstr Surg* 2007; 119: 1319–1325.

191 Brightman L, Weiss E, Chapas AM, Karen J, Hale E, Bernstein L *et al.* Improvement in arm and post-partum abdominal and flank subcutaneous fat deposits and skin laxity using a bipolar radiofrequency, infrared, vacuum and mechanical massage device. *Lasers Surg Med* 2009; 41: 791–798.

192 Shek S, Yu C, Yeung CK, Kono T, Chan HH. The use of focused ultrasound for non-invasive body contouring in Asians. *Lasers Surg Med* 2009; 41: 751–759.

193 Choi SY, Kim YJ, Kim SY, Lee WJ, Chang SE, Lee MW *et al.* Improvement in abdominal and flank contouring by a novel adipocyte-selective non-contact radiofrequency device. *Lasers Surg Med* 2018; 50: 738–744.

194 Boisnic S, Divaris M, Nelson AA, Gharavi NM, Lask GP. A clinical and biological evaluation of a novel, noninvasive radiofrequency device for the long-term reduction of adipose tissue. *Lasers Surg Med* 2014; 46: 94–103.

195 Shek SYN, Yeung CK, Chan JCY, Chan HHL. Efficacy of high-intensity focused ultrasonography for noninvasive body sculpting in Chinese patients. *Lasers Surg Med* 2014; 46: 263–269.

196 Tonucci LB, Mourão DM, Ribeiro AQ, Bressan J. Noninvasive body contouring: biological and aesthetic effects of low-frequency, low-intensity ultrasound device. *Aesthetic Plast Surg* 2014; 38: 959–967.

197 Katz B, Bard R, Goldfarb R, Shiloh A, Kenolova D. Ultrasound Assessment of Subcutaneous Abdominal Fat Thickness After Treatments With a High-Intensity Focused Electromagnetic Field Device: A Multicenter Study. *Dermatol Surg* 2019; 45: 1542–1548.

198 Hong JY, Ko EJ, Choi SY, Kwon TR, Kim JH, Kim SY *et al.* Efficacy and

Safety of High-Intensity Focused Ultrasound for Noninvasive Abdominal Subcutaneous Fat Reduction. *Dermatol Surg* 2020; 46: 213–219.

199 Fonseca VM, Campos PS, Certo TF, de-Faria LT, Juliano PB, Cintra DE *et al.* Efficacy and safety of noninvasive focused ultrasound for treatment of subcutaneous adiposity in healthy women. *J Cosmet Laser Ther* 2018; 20: 341–350.

200 Arabpour-Dahoue M, Mohammadzadeh E, Avan A, Nezafati P, Nasrfard S, Ghazizadeh H *et al.* Leptin level decreases after treatment with the combination of Radiofrequency and Ultrasound cavitation in response to the reduction in adiposity. *Diabetes Metab Syndr* 2019; 13: 1137–1140.

201 Moreno-Moraga J, Valero-Altés T, Martínez Riquelme A, Isarria-Marcosy MI, Royo De La Torre J. Body contouring by non-invasive transdermal focused ultrasound. *Lasers Surg Med* 2007; 39: 315–323.

202 Mahmoud ELdesoky MT, Mohamed Abutaleb EEl, Mohamed Mousa GS. Ultrasound cavitation versus cryolipolysis for non-invasive body contouring. *Australas J Dermatol* 2016; 57: 288–293.

203 Robinson DM, Kaminer MS, Baumann L, Burns AJ, Brauer JA, Jewell M *et al.* High-intensity focused ultrasound for the reduction of subcutaneous adipose tissue using multiple treatment techniques. *Dermatol Surg* 2014; 40: 641–651.

204 Solish N, Lin X, Axford-Gatley RA, Strangman NM, Kane M. A randomized, single-blind, postmarketing study of multiple energy levels of high-intensity focused ultrasound for noninvasive body sculpting. *Dermatol Surg* 2012; 38: 58–67.

205 Verner I. A novel nonfocused pulsed ultrasound technology for noninvasive circumference reduction. *Dermatol Ther* 2021; 34. doi:10.1111/DTH.15101.

206 Khedmatgozar H, Yadegari M, Khodadadegan MA, Khodabandeh AK, Ghazavi H, Esmaily H *et al.* The effect of ultrasound cavitation in combination with

cryolipolysis as a non-invasive selective procedure for abdominal fat reduction. *Diabetes Metab Syndr* 2020; 14: 2185–2189.

207 An Open-label, Single-center, Prospective Evaluation of a Novel Noninvasive Ultrasound Body Sculpting Device - PubMed. https://pubmed.ncbi.nlm.nih.gov/29942424/ (accessed 2 Jul2022).

208 Fritz K, Salavastru C. Long-term follow-up on patients treated for abdominal fat using a selective contactless radiofrequency device. *J Cosmet Dermatol* 2017; 16: 471–475.

209 Guth F, Bitencourt S, Bedinot C, Sinigaglia G, Tassinary JAF. Immediate effect and safety of HIFU single treatment for male subcutaneous fat reduction. *J Cosmet Dermatol* 2018; 17: 385–389.

210 Kwon TR, Yoo KH, Oh CT, Shin DH, Choi EJ, Jung SJ *et al.* Improved methods for selective cryolipolysis results in subcutaneous fat layer reduction in a porcine model. *Skin Research and Technology* 2015; 21: 192–200.

211 Abdel-Aal NM, Mostafa MSEM, Saweres JW, Ghait RS. Cavitation and radiofrequency versus cryolipolysis on leptin regulation in central obese subjects: A randomized controlled study. *Lasers Surg Med* 2022. doi:10.1002/LSM.23555.

212 [PDF] CRYO LIPOLYSIS VERSUS COLD LASER ON LIPID PROFILE AND BODY COMPOSITION IN WOMEN WITH CENTRAL OBESITY | Semantic Scholar. https://www.semanticscholar.org/paper/CRYO-LIPOLYSIS-VERSUS-COLD-LASER-ON-LIPID-PROFILE-Al-Agamy-Al-Nahas/dfb47a03dec92b095772b8f36d3c4ee50cb5f5ad (accessed 2 Jul2022).

213 Klein KB, Zelickson B, Riopelle JG, Okamoto E, Bachelor EP, Harry RS *et al.* Non-invasive cryolipolysis for subcutaneous fat reduction does not affect serum lipid levels or liver function tests. *Lasers Surg Med* 2009; 41: 785–790.

214 Klein KB, Bachelor EP, Becker E v., Bowes LE. Multiple same day cryolipolysis treatments for the reduction of subcutaneous fat are safe and do not affect serum lipid levels or liver function tests. *Lasers Surg Med* 2017; 49: 640–644.

215 Ferraro GA, de Francesco F, Cataldo C, Rossano F, Nicoletti G, D'Andrea F. Synergistic effects of cryolipolysis and shock waves for noninvasive body contouring. *Aesthetic Plast Surg* 2012; 36: 666–679.

216 Jewell ML, Solish NJ, Desilets CS. Noninvasive body sculpting technologies with an emphasis on high-intensity focused ultrasound. *Aesthetic Plast Surg* 2011; 35: 901–912.

217 Guth F, Bitencourt S, Bedinot C, Sinigaglia G, Tassinary JAF. Immediate effect and safety of HIFU single treatment for male subcutaneous fat reduction. *J Cosmet Dermatol* 2018; 17: 385–389.

218 Kwon TR, Kim JH, Jang YN, Lee SE, Hong JY, Yoo KH *et al.* Comparison of different energy response for lipolysis using a 1,060-nm laser: An animal study of three pigs. *Skin Research and Technology* 2021; 27: 5–14.

219 de Luca C, Olefsky JM. Inflammation and insulin resistance. *FEBS Lett* 2008; 582: 97–105.

220 Kanneganti TD, Dixit VD. Immunological complications of obesity. *Nature Immunology 2012 13:8* 2012; 13: 707–712.

221 Ybarra J, Blanco-Vaca F, Fernández S, Castellví A, Bonet R, Palomer X *et al.* The effects of liposuction removal of subcutaneous abdominal fat on lipid metabolism are independent of insulin sensitivity in normal-overweight individuals. *Obes Surg* 2008; 18: 408–414.

222 Swanson E. The clinical relevance of lower triglyceride and leukocyte levels after liposuction. *Plast Reconstr Surg* 2012; 129.

doi:10.1097/PRS.0B013E31824A62F8.

223 Bartoli E, Fra GP, Schianca GPC. The oral glucose tolerance test (OGTT) revisited. *Eur J Intern Med* 2011; 22: 8–12.

224 Genuth S, Alberti KGMM, Bennett P, Buse J, DeFronzo R, Kahn R *et al.* Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care* 2003; 26: 3160–3167.

225 Kanauchi M, Kimura K, Kanauchi K, Saito Y. Beta-cell function and insulin sensitivity contribute to the shape of plasma glucose curve during an oral glucose tolerance test in non-diabetic individuals. *Int J Clin Pract* 2005; 59: 427–432.

226 Carnevale Schianca GP, Mella R, Scaglia E, Bigliocca M, Colli E, Fra GP *et al.* Expanding the clinical use of standard OGTT: the percentage increment of 2 h with respect to fasting glucose as an index of β-cell dysfunction. *Diabetes Metab Res Rev* 2011; 27: 262–268.

227 Chung ST, Ha J, Onuzuruike AU, Kasturi K, Galvan-De La Cruz M, Bingham BA *et al.* Time to glucose peak during an oral glucose tolerance test identifies prediabetes risk. *Clin Endocrinol (Oxf)* 2017; 87: 484–491.

228 Nolfe G, Spreghini MR, Sforza RW, Morino G, Manco M. Beyond the morphology of the glucose curve following an oral glucose tolerance test in obese youth. *Eur J Endocrinol* 2012; 166: 107–114.

229 Wang X, Zhao X, Zhou R, Gu Y, Zhu X, Tang Z *et al.* Delay in glucose peak time during the oral glucose tolerance test as an indicator of insulin resistance and insulin secretion in type 2 diabetes patients. *J Diabetes Investig* 2018; 9: 1288–1295.

230 Manco M, Nolfe G, Pataky Z, Monti L, Porcellati F, Gabriel R *et al.* Shape of the OGTT glucose curve and risk of impaired glucose metabolism in the EGIR-RISC cohort. *Metabolism* 2017; 70: 42–50.

231 Smith EP, Polanco G, Yaqub A, Salehi M. Altered glucose metabolism after bariatric surgery: What's GLP-1 got to do with it? *Metabolism* 2018; 83: 159–166.

232 Markovic TP, Jenkins AB, Campbell L v., Furier SM, Kraegen EW, Chisholm DJ. The determinants of glycemic responses to diet restriction and weight loss in obesity and NIDDM. *Diabetes Care* 1998; 21: 687–694.

233 Lin E, Liang Z, Frediani J, Davis SS, Sweeney JF, Ziegler TR *et al.* Improvement in ß-cell function in patients with normal and hyperglycemia following Roux-en-Y gastric bypass surgery. *Am J Physiol Endocrinol Metab* 2010; 299. doi:10.1152/AJPENDO.00405.2010.

234 Lima MMO, Pareja JC, Alegre SM, Geloneze SR, Kahn SE, Astiarraga BD *et al.* Acute effect of roux-en-y gastric bypass on whole-body insulin sensitivity: a study with the euglycemic-hyperinsulinemic clamp. *J Clin Endocrinol Metab* 2010; 95: 3871–3875.

235 Abdul-Ghani MA, Jenkinson CP, Richardson DK, Tripathy D, DeFronzo RA. Insulin secretion and action in subjects with impaired fasting glucose and impaired glucose tolerance: results from the Veterans Administration Genetic Epidemiology Study. *Diabetes* 2006; 55: 1430–1435.

236 Tabák AG, Herder C, Rathmann W, Brunner EJ, Kivimäki M. Prediabetes: A high-risk state for developing diabetes. *Lancet* 2012; 379: 2279.

237 Unwin N, Shaw J, Zimmet P, Alberti KGMM. Impaired glucose tolerance and impaired fasting glycaemia: the current status on definition and intervention. *Diabet Med* 2002; 19: 708–723.

238 Mechanisms Underlying Postoperative Insulin Resistance and Inflammation - Full Text View - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT01470534 (accessed 1 Jan2023).

239 Klöting N, Fasshauer M, Dietrich A, Kovacs P, Schön MR, Kern M *et al.* Insulin-sensitive obesity. *Am J Physiol Endocrinol Metab* 2010; 299. doi:10.1152/AJPENDO.00586.2009.

240 Sjöström L. Review of the key results from the Swedish Obese Subjects (SOS) trial - a prospective controlled intervention study of bariatric surgery. *J Intern Med* 2013; 273: 219–234.

241 Badran S, Doi SA, Hamdi M, Hammouda A, Alharami S, Clark J *et al.* Metabolic aspects of surgical subcutaneous fat removal: an umbrella review and implications for future research. *Bosn J Basic Med Sci* 2022. doi:10.17305/BJBMS.2022.8175.

242 de Andrade Mesquita L, Pavan Antoniolli L, Cittolin-Santos GF, Gerchman F. Distinct metabolic profile according to the shape of the oral glucose tolerance test curve is related to whole glucose excursion: a cross-sectional study. *BMC Endocr Disord* 2018; 18. doi:10.1186/S12902-018-0286-7.

243 Badran S, Doi SA, Hamdi M, Hammouda A, Alharami S, Clark J *et al.* Metabolic aspects of surgical subcutaneous fat removal: an umbrella review and implications for future research. *Bosn J Basic Med Sci* 2022; : 1.

244 Badran S, Habib AM, Aljassem G, Musa OAH, Clark J, Hamd M *et al.* Metabolic Changes after Surgical Fat Removal: A Dose Response Meta-analysis. *Journal of Plastic, Reconstructive & Aesthetic Surgery* 2022. doi:10.1016/J.BJPS.2022.10.055.

245 Badran S, Doi SA, Iskeirjeh S, Aljassem G, Jafarian N, Clark J *et al.* Metabolic Changes after Non-Surgical Fat Removal: A Dose Response Meta-analysis. *Journal of Plastic, Reconstructive & Aesthetic Surgery* 2022. doi:10.1016/J.BJPS.2022.10.054.

246 Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature 2006 444:7121* 2006; 444: 840–846.

247 Van Harmelen V, Reynisdottir S, Eriksson P, Thörne A, Hoffstedt J, Lönnqvist F *et al.* Leptin secretion from subcutaneous and visceral adipose tissue in women. *Diabetes* 1998; 47: 913–917.

248 Margetic S, Gazzola C, Pegg GG, Hill RA. Leptin: a review of its peripheral actions and interactions. *International Journal of Obesity 2002 26:11* 2002; 26: 1407–1433.

249 Paz-Filho G, Mastronardi C, Wong M-L, Licinio J. Leptin therapy, insulin sensitivity, and glucose homeostasis. *Indian J Endocrinol Metab* 2012; 16: S549.

250 German JP, Wisse BE, Thaler JP, Oh-I S, Sarruf DA, Ogimoto K *et al.* Leptin Deficiency Causes Insulin Resistance Induced by Uncontrolled Diabetes. *Diabetes* 2010; 59: 1626–1634.

251 Bindlish S, Presswala LS, Schwartz F. Lipodystrophy: Syndrome of severe insulin resistance. *https://doi.org/101080/0032548120151015927* 2015; 127: 511–516.

252 German JP, Wisse BE, Thaler JP, Oh-I S, Sarruf DA, Ogimoto K *et al.* Leptin deficiency causes insulin resistance induced by uncontrolled diabetes. *Diabetes* 2010; 59: 1626–1634.

253 Mulligan K, Khatami H, Schwarz JM, Sakkas GK, Depaoli AM, Tai VW *et al.* The effects of recombinant human leptin on visceral fat, dyslipidemia, and insulin resistance in patients with human immunodeficiency virus-associated lipoatrophy and hypoleptinemia. *J Clin Endocrinol Metab* 2009; 94: 1137–1144.

254 Mulligan K, Khatami H, Schwarz JM, Sakkas GK, Depaoli AM, Tai VW *et al.* The effects of recombinant human leptin on visceral fat, dyslipidemia, and insulin

resistance in patients with human immunodeficiency virus-associated lipoatrophy and hypoleptinemia. *J Clin Endocrinol Metab* 2009; 94: 1137–1144.

255 Rodríguez AJ, Neeman T, Giles AG, Mastronardi CA, Paz-Filho G. Leptin replacement therapy for the treatment of non-HAART associated lipodystrophy syndromes: a meta-analysis into the effects of leptin on metabolic and hepatic endpoints. *Arq Bras Endocrinol Metabol* 2014; 58: 783–797.

256 Jørgensen NB, Bojsen-Møller KN, Dirksen C, Martinussen C, Svane MS, Kristiansen VB *et al.* Sustained Improvements in Glucose Metabolism Late After Roux-En-Y Gastric Bypass Surgery in Patients with and Without Preoperative Diabetes. *Scientific Reports 2019 9:1* 2019; 9: 1–10.

257 Douros JD, Niu J, Sdao S, Gregg T, Fisher-Wellman K, Bharadwaj M *et al.* Sleeve gastrectomy rapidly enhances islet function independently of body weight. *JCI Insight* 2019; 4. doi:10.1172/JCI.INSIGHT.126688.

258 Oppenländer L, Palit S, Stemmer K, Greisle T, Sterr M, Salinno C *et al.* Vertical sleeve gastrectomy triggers fast β-cell recovery upon overt diabetes. *Mol Metab* 2021; 54. doi:10.1016/J.MOLMET.2021.101330.

259 Sathananthan M, Shah M, Edens KL, Grothe KB, Piccinini F, Farrugia LP *et al.* Six and 12 Weeks of Caloric Restriction Increases β Cell Function and Lowers Fasting and Postprandial Glucose Concentrations in People with Type 2 Diabetes. *J Nutr* 2015; 145: 2046–2051.

260 Douros JD, Tong J, D'Alessio DA. The Effects of Bariatric Surgery on Islet Function, Insulin Secretion, and Glucose Control. *Endocr Rev* 2019; 40: 1394–1423.

261 Sridharan K, Kalayarasan R, Kamalanathan S, Sahoo J, Kar SS, Nandhini LP *et al.* Change in insulin resistance, beta cell function, glucagon-like peptide-1 and calcitonin levels two weeks after bariatric surgery. *Diabetes Metab Syndr* 2019; 13:

2142–2147.

262 Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature Publishing Group, 2006.

263 Khan M, Joseph F. Adipose Tissue and Adipokines: The Association with and Application of Adipokines in Obesity. *Scientifica (Cairo)* 2014; 2014: 1–7.

264 Bartoli E, Fra GP, Schianca GPC. The oral glucose tolerance test (OGTT) revisited. *Eur J Intern Med* 2011; 22: 8–12.

265 de Andrade Mesquita L, Pavan Antoniolli L, Cittolin-Santos GF, Gerchman F. Distinct metabolic profile according to the shape of the oral glucose tolerance test curve is related to whole glucose excursion: A cross-sectional study. *BMC Endocr Disord* 2018; 18: 1–8.

BJBMS
THE BOSNIAN JOURNAL OF BASIC MEDICAL SCIENCES

REVIEW

Metabolic aspects of surgical subcutaneous fat removal: an umbrella review and implications for future research

Saif Badran[1], Suhail A. Doi[1], Moustapha Hamdi[2], Atalla Hammouda[3], Sara Alharami[3], Justin Clark[4], Omran A. H. Musa[1], Abdul-Badi Abou-Samra[5,6], and Abdella M. Habib[7]

Although obesity is a preventable disease, maintaining a normal body weight can be very challenging and difficult, which has led to a significant increase in the demand for surgical subcutaneous fat removal (SSFR) to improve physical appearance. The need for SSFR is further exacerbated because of the global rise in the number of bariatric surgeries, which is currently the single most durable intervention for mitigating obesity. Fat tissue is now recognized as a vital endocrine organ that produces several bioactive proteins. Thus, SSFR-mediated weight (fat) loss can potentially have significant metabolic effects; however, currently, there is no consensus on this issue. This review focuses on the metabolic sequelae after SSFR interventions for dealing with cosmetic body appearance. Data was extracted from existing systematic reviews and the diversity of possible metabolic changes after SSFR are reported along with gaps in the knowledge and future directions for research and practice. We conclude that there is a potential for metabolic sequelae after SSFR interventions and their clinical implications for the safety of the procedures as well as for our understanding of subcutaneous adipose tissue biology and insulin resistance are discussed.

Keywords: Surgical subcutaneous fat removal (SSFR), body contouring surgery, metabolism, insulin resistance, inflammation, adipokines.

Introduction

Obesity has reached pandemic levels and currently affects all age groups and socioeconomic classes worldwide. Obesity prevalence has almost tripled in the last 50 years according to the World Health Organization and this, in turn, has led to more fatality than malnutrition and being underweight combined [1]. The rising obesity rate has led to a substantial rise in metabolic diseases, such as diabetes mellitus type 2 (T2D), hypertension, cardiovascular disease, non-alcoholic hepato-steatosis, and dyslipidemia [2].

Lipids comprise a wide range of molecules, such as phospholipids, fatty acids, and triglycerides [3]. These molecules represent a highly efficient energy resource. Recent studies have advanced our view of adipose tissue from being simply an energy store, into an active endocrine organ, which secretes several metabolically active adipokines, such as leptin, adiponectin, and resistin. The latter plays an essential role in glucose hemostasis and energy metabolism in our body [2]. These molecules have been ascribed to have a critical role in energy homeostasis through communication with organs that maintain system-wide metabolic homeostasis such as the liver. Of the adipocyte-derived factors, adiponectin and leptin are among the essential adipokines. Indeed, adiponectin analogs are now considered one of the promising new therapeutic targets for obesity-linked hyperglycemia, that mitigates obesity and improves insulin sensitivity [4].

Insulin resistance, as a consequence of such dysregulation associated with obesity, is what links the latter to T2D. Insulin resistance leads to dysregulation of glucose homeostasis via a combination of impaired glucose clearance and elevated glucose production in the liver. Adipose tissue is a major contributor to insulin sensitivity/resistance status. Too little fat mass, as seen in patients with lipodystrophy, results in a severe form of insulin resistance, and too much adipose mass can also result in a similar condition [5]. The primary reason for the latter form of insulin resistance may be hypoxia in adipose tissue that leads to inflammatory lipo-toxicity [6].

Currently, it is unknown if the removal of excess subcutaneous fat tissue through surgical subcutaneous fat removal (SSFR; also known as body contouring surgeries such as liposuction or abdominoplasty) ameliorates the mass of hypoxic fat thus reducing its consequences. Such surgeries have become very common because, although obesity can be prevented, maintaining a normal body weight can be very

[1]Department of Population Medicine, College of Medicine, QU Health, Qatar University, Doha, Qatar; [2]Department of Plastic and Reconstructive Surgery, Brussels University Hospital, Vrije Universiteit Brussel (VUB), Brussels, Belgium; [3]Department of Plastic Surgery, Hamad General Hospital, Doha, Qatar; [4]Institute for Evidence-Based Healthcare, Faculty of Health Sciences & Medicine, Bond University, Gold Coast, Queensland, Australia; [5]Department of Medicine, Weill Cornell Medicine Qatar, Qatar Foundation, Doha, Qatar; [6]Qatar Metabolic Institute, Hamad Medical Corporation, Doha, Qatar; [7]College of Medicine, QU Health, Qatar University, Doha, Qatar.

Correspondence to Abdella M. Habib: ahabib@qu.edu.qa

DOI: 10.17305/bjbms.2022.8175

challenging and difficult and the increase in demand for SSFR has been driven by patients seeking an improved physical appearance [7]. However, the precise effect of sudden removal of a patient's body fat on metabolism is still not fully understood.

Surgical subcutaneous fat removal

The current drift toward cosmetic plastic surgeries, especially the body contouring surgeries which aim to produce a more attractive body shape by removing the excess of skin and fat tissue from multiple body areas, is due to several reasons such as the increase in the safety of these procedures, the increase in the availability of these operations, and largely due to the recent increase in the number of bariatric surgeries. Bariatric surgery is performed for morbidly obese patients to facilitate loss of a significant amount of their body fat mass. Because of the rapid and massive weight loss following bariatric surgery such as sleeve gastrectomy, many patients tend to require body contouring plastic surgery to remove redundant skin and excess body fat [8]. The body-contouring surgery is also done for purely cosmetic purposes in patients not undergoing bariatric surgery.

A typical example of these body contouring surgeries is the abdominoplasty (as known as Tummy Tuck) surgery which suddenly removes around 2–3 kg of abdominal subcutaneous fat (ASF) tissue, and usually is followed by tightening of the abdominal wall muscles, to correct divarication of recti muscles [9]. The other commonly undertaken surgery is suction-assisted lipectomy and, together with abdominoplasty, these represent the commonest plastic surgery procedures that target subcutaneous fat from unwanted areas such as the abdominal wall and flanks. The accelerating demand for these surgical procedures has gradually moved the practice from removing a small amount of intractable fat tissue to the removal of a large volume (more than five liters) of subcutaneous fat tissue, which eventually can result in a significant metabolic effect [10]. However, whether the metabolic effects of these two surgeries are the same or different is not known. In fact, previous reviews and meta-analyses (MAs) have combined these two procedures together which might not be accurate. For example, the repair of the abdominal wall in abdominoplasty might result in an increased intra-abdominal pressure with reduced space for the future expansion of intra-abdominal fat tissue, which might result in different metabolic effects than liposuction [10, 11].

Finally, a distinction needs to be made between SSFR and other modalities of fat loss (such as diet, exercise, or bariatric surgeries) in that non-SSFR modalities result in a gradual decrease in both the subcutaneous and intra-abdominal fat tissue. This gradual reduction occurs through a decrease in the size of the adipocytes while with SSFR there is actual loss of subcutaneous adipocyte numbers, but without impact on intra-abdominal adipocytes.

Fat removal sites in SSFR

SSFR classically is from abdominal and thigh areas, although other sites may less commonly be targets for surgery. Abdominal (or upper-fat) distribution is correlated more strongly with obesity-associated metabolic risks and consequences than the gluteo-femoral (or lower-fat) distribution in the gluteal and thigh regions [12]. Fat in the abdomen may be subcutaneous (ASF) or as abdominal visceral fat (AVF) tissue and it should be noted that only ASF is the target for abdominal SSFR [9]. AVF is intraperitoneal fat that represents both the mesenteric as well as the omental fat cells [13]. AVF is typically formed of large adipocytes and contains necrotic and inflammatory tissues. There is also retroperitoneal fat in humans of unclear significance.

Central obesity in the abdominal area represents one of the essential components of metabolic syndrome, along with insulin resistance, elevated serum triglyceride, blood pressure, and low high-density lipoproteins. The distribution of fat deposits in the abdomen (ASF vs AVF) has thus been thought to determine metabolic outcomes and that AVF tissue is more "pathogenic" [14] and is what has been linked to metabolic syndrome and T2D [15]. Other studies have also proposed that both ASF and AVF play a role in metabolic risk [10] but largely the metabolic risk of obesity has been linked mainly to AVF because it is directly involved in the delivery of free fatty acids as well as inflammatory proteins such as interleukin-6 (IL-6), to the liver via the portal circulation [16]. It is nevertheless probable that ASF may also play a role given that more than 80% of the free fatty acids and other inflammatory proteins reach the liver via the systemic circulation [17]. This is supported by studies that report the intrahepatic triglyceride rather than AVF is a better marker for obesity-associated metabolic risk [18]. Therefore, it has recently been suggested that the metabolic risk in obesity is a shared effect of molecules secreted by both these compartments. Thus, there is an expectation that SSFR may alter glucose homeostasis and insulin resistance as a direct consequence of surgical ASF removal.

Potential for metabolic sequelae after SSFR

Research has found that even a small weight loss of ten percent can result in a significant improvement of obesity-linked metabolic abnormalities, such as insulin resistance, high blood pressure, and abnormal inflammatory marker levels [19, 20]. Additionally, increased knowledge of the metabolic consequences of excess body fat and observations after bariatric surgeries [21] have suggested that there could possibly be a similar effect after SSFR. This has been examined in several studies, which measure hormonal changes before and after SSFR at different time points. These studies have been small and heterogeneous and have reported inconsistent effects on metabolic parameters, such as insulin resistance, adipokine levels, and inflammation [22–34] To improve power and resolve the inconsistency, these studies have been combined in several syntheses, both systematic reviews (SRs) and MAs. The aim of this umbrella review therefore is to now examine these syntheses and summarize their findings as well as define current knowledge gaps in the metabolic impact of SSFR, particularly, changes in insulin resistance, inflammatory markers, and adipokines levels.

Materials and methods

Study inclusion and exclusion criteria

A search was conducted for evidence syntheses that synthesized data on the metabolic changes after SSFR. PubMed, Embase, and Scopus databases were searched without any date, language, or publication restriction but exclusion of non-English and animal studies, as well as non-surgical body fat removal and bariatric surgeries.

Search strategy

Search was conducted on 8 November 2021 by two independent authors using the polyglot Search Translator [35]. The search strings used are given in the supplementary material (Figure S1) for the syntheses that report changes in insulin sensitivity, inflammatory markers, and adipokines levels after SSFR. Data were extracted regarding synthesis type (SR or MA), title and author, year of publication, type of SSFR, a summary of included studies, follow-up duration after SSFR, and possible evidence gaps. Main findings were summarized regarding metabolic changes in terms of potential inflammatory and anti-inflammatory adipokines and other metabolic markers.

Quality assessment

A MeaSurement Tool to Assess systematic Reviews-2 (AMSTAR-2) was used to assess the quality of the included reviews and each included synthesis was examined against 16 quality safeguards to assess their methodological quality [36].

Data synthesis

A structured summary of findings was done for the eligible and included SRs and MAs. Metabolic change findings were assessed in three categories: insulin resistance, inflammatory markers, and adipokines. For each of the categories, a separate table of findings was formulated.

Results

Study selection

A search in the three databases: PubMed, Embase, and Scopus on (08/11/2021) resulted in 444 studies. A total of 186 duplicate studies were excluded. The remaining 258 articles were screened by title and manuscript for eligibility of which six met inclusion criteria. One synthesis was in French and was excluded from this umbrella review [37], while another was excluded as it reported changes in weight and fat mass only [38]. There were thus three MAs and one SR included, and Figure 1 depicts the PRISMA flow diagram for the selection of studies.

The first synthesis was conducted in 2013 [39], and since then, another three syntheses have been published [10, 11, 40]. None of the four included syntheses (15, 14, 12, and 11 studies included) examined the time trend after SSFR, and thus they looked at metabolic changes through quantitative analyses (if any) did not consider the heterogeneity in follow-up duration across studies. This umbrella review summarizes the changes reported in three categories: insulin resistance, inflammatory markers, and adipokines levels. Quality assessment of the included syntheses demonstrated that most of them included PICO components in the review, explanation of inclusion criteria, justification for the excluded studies, use of a satisfactory quality assessment tool in studies included in the review, and adequate description of the included studies. See supplementary material Figure S2.

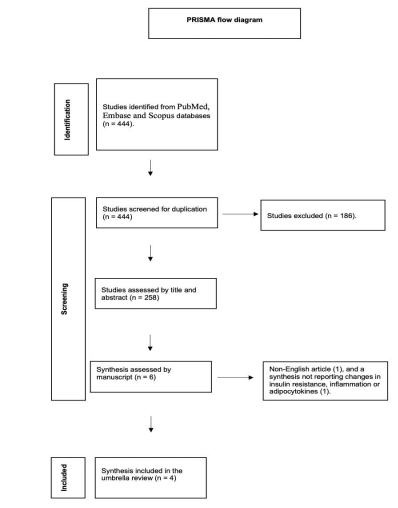


Figure 1. PRISMA flow diagram of the study selection process.

Impact of SSFR on insulin resistance

Several studies have measured changes in insulin resistance status after SSFR using different tests, such as measuring fasting glucose, fasting insulin, and the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) [31, 34, 41], insulin tolerance test (ITT) [42], oral glucose tolerance test [30, 43], and the gold standard glucose clamp test [29, 44]. Apart from the glucose clamp test, most of these tests are not accurate in assessing the change in insulin sensitivity, and the studies that used the glucose clamp test had a small sample size and a lot of variability among participants in terms of diabetic status, and degree of obesity. The challenge behind using accurate tests such as the hyper insulinemic glucose clamp and the intravenous glucose tolerance test is the fact that they are very demanding [45].

Across three MAs and one SR examining the effect of SSFR on insulin sensitivity, most of the evidence suggests a possible improvement in obesity-associated insulin resistance, however, there was a lack of clarity regarding the extent of the effect and clinical significance. This was because there were major problems in the design and analysis of the MAs and therefore results couldn't be thus interpreted. In terms of the SRs, there was no clarity on the extent of the changes across the

loss in baboons. Surg Obes Relat Dis 2018 Jun 1;14(6):833–41. https://doi.org/10.1016/j.soard.2018.03.004.
[88] Murillo AL, Kaiser KA, Smith Jr.,DL,Peterson CM, Affuso O, Tiwari HK, et al. A systematic scoping review of surgically manipulated adipose tissue and the regulation of energetics and body fat in animals. Obesity (Silver Spring) 2019;27(9):1404–17. https://doi.org/10.1002/oby.22511.
[89] Zhang Y, Scarpace PJ. The role of leptin in leptin resistance and obesity. Physiol Behav 2006 Jun 30;88(3):249–56. https://doi.org/10.1016/j.physbeh.2006.05.038.
[90] Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, et al. The hormone resistin links obesity to diabetes. Nature 2001 Jan 18;409(6818):307–12. https://doi.org/10.1038/35053000.
[91] Maeda K, Uysal KT, Makowski L, Gorgun CZ, Atsumi G, Parker RA, et al. Role of the fatty acid binding protein mal1 in obesity and insulin resistance. Diabetes 2003 Feb 1;52(2):300–7. https://doi.org/10.2337/diabetes.52.2.300.
[92] Yang Q, Graham TE, Mody N, Preitner F, Peroni OD, Zabolotny JM, et al. Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes. Nature 2005 Jul 21;436(7049):356–62. https://doi.org/10.1038/nature03711.
[93] Cianflone K, Xia Z, Chen LY. Critical review of acylation-stimulating protein physiology in humans and rodents. Biochim Biophys Acta Biomembr 2003 Jan 31;1609(2):127–43. https://doi.org/10.1016/s0005-2736(02)00686-7.
[94] Yan QW, Yang Q, Mody N, Graham TE, Hsu CH, Xu Z, et al. The adipokine lipocalin 2 is regulated by obesity and promotes insulin resistance. Diabetes 2007 Oct 1;56(10):2533–40. https://doi.org/10.2337/db07-0007.
[95] Ernst MC, Sinal CJ. Chemerin: at the crossroads of inflammation and obesity. Trends Endocrinol Metab 2010 Nov 1;21(11):660–7. https://doi.org/10.1016/j.tem.2010.08.001.
[96] Chang YH, Chang DM, Lin KC, Shin SJ, Lee YJ. Visfatin in overweight/obesity, type 2 diabetes mellitus, insulin resistance, metabolic syndrome and cardiovascular diseases: a meta-analysis and systemic review. Diabetes Metab Res Rev 2011 Sep 1;27(6):515–27. https://doi.org/10.1002/dmrr.1201.
[97] Feng R, Li Y, Wang C, Luo C, Liu L, Chuo F, et al. Higher vaspin levels in subjects with obesity and type 2 diabetes mellitus: a meta-analysis. Diabetes Res Clin Pract 2014 Oct 1;106(1):88–94. https://doi.org/10.1016/j.diabres.2014.07.026.
[98] Castan-Laurell I, Dray C, Attané C, Duparc T, Knauf C, Valet P. Apelin, diabetes, and obesity. Endocrine 2011;40:1–9. https://doi.org/10.1007/s12020-011-9507-9.
[99] Hedjazifar S, Khatib Shahidi R, Hammarstedt A, Bonnet L, Church C, Boucher J, et al. The novel adipokine Gremlin 1 antagonizes insulin action and is increased in type 2 diabetes and NAFLD/NASH. Diabetes 2020 Mar 1;69(3):331–41. https://doi.org/10.2337/db19-0701.
[100] Kadowaki T, Yamauchi T. Adiponectin and adiponectin receptors. Endocr Rev 2005 May 1;26(3):439–51. https://doi.org/10.1210/er.2005-0005.
[101] Pan X, Kaminga AC, Wen SW, Acheampong K, Liu A. Omentin-1 in diabetes mellitus: a systematic review and meta-analysis. PLoS One 2019 Dec 10;14(12):e0226292. https://doi.org/10.1371/journal.pone.0226292.
[102] Ouchi N, Higuchi A, Ohashi K, Oshima Y, Gokce N, Shibata R, et al. Sfrp5 is an anti-inflammatory adipokine that modulates metabolic dysfunction in obesity. Science 2010 Jul 23;329(5990):454–7. https://doi.org/10.1126/science.1188280.
[103] Moreno-Aliaga MJ, Pérez-Echarri N, Marcos-Gómez B, Larequi E, Gil-Bea FJ, Viollet B, et al. Cardiotrophin-1 is a key regulator of glucose and lipid metabolism. Cell Metab 2011 Aug 3;14(2):242–53. https://doi.org/10.1016/j.cmet.2011.05.013.

Related articles published in BJBMS

1. Skeletal muscle and fiber type-specific intramyocellular lipid accumulation in obese mice

Nejc Umek et al., BJBMS, 2021

[51] Abate N, Garg A, Peshock RM, Stray-Gundersen J, Adams-Huet B, Grundy SM. Relationship of generalized and regional adiposity to insulin sensitivity in men with NIDDM. Diabetes 1996;45(12):1684–93. https://doi.org/10.2337/diab.45.12.1684.

[52] Goodpaster BH, Thaete FL, Simoneau JA, Kelley DE. Subcutaneous abdominal fat and thigh muscle composition predict insulin sensitivity independently of visceral fat. Diabetes 1997;46(10):1579–85. https://doi.org/10.2337/diacare.46.10.1579.

[53] Wolfe BM, Kvach E, Eckel RH. Treatment of obesity: weight loss and bariatric surgery. Circ Res 2016 May 27;118(11):1844–55. https://doi.org/10.1161/CIRCRESAHA.116.307591.

[54] Lima MM, Pareja JC, Alegre SM, Geloneze SR, Kahn SE, Astiarraga BD, et al. Visceral fat resection in humans: effect on insulin sensitivity, beta-cell function, adipokines, and inflammatory markers. Obesity (Silver Spring) 2013 Mar;21(3):E182–9. https://doi.org/10.1002/oby.20030.

[55] Fabbrini E, Tamboli RA, Magkos F, Marks-Shulman PA, Eckhauser AW, Richards WO, et al. Surgical removal of omental fat does not improve insulin sensitivity and cardiovascular risk factors in obese adults. Gastroenterology 2010;139(2):448–55. https://doi.org/10.1053/j.gastro.2010.04.056.

[56] Dunn JP, Abumrad NN, Breitman I, Marks-Shulman PA, Flynn CR, Jabbour K, et al. Hepatic and peripheral insulin sensitivity and diabetes remission at 1 month after Roux-en-Y gastric bypass surgery in patients randomized to omentectomy. Diabetes Care 2012 Jan;35(1):137–42. https://doi.org/10.2337/dc11-1383.

[57] Herrera MF, Pantoja JP, Velázquez-Fernández D, Cabiedes J, Aguilar-Salinas C, García-García E, et al. Potential additional effect of omentectomy on metabolic syndrome, acute-phase reactants, and inflammatory mediators in grade III obese patients undergoing laparoscopic Roux-en-Y gastric bypass: a randomized trial. Diabetes Care 2010 Jul;33(7):1413–8. https://doi.org/10.2337/dc09-1833.

[58] Shi J, Bao G, Hong J, Wang S, Chen Y, Zhao S, et al. Deciphering CT texture features of human visceral fat to evaluate metabolic disorders and surgery-induced weight loss effects. EBioMedicine 2021 Jul 1;69:103471. https://doi.org/10.1016/j.ebiom.2021.103471.

[59] Lenz M, Arts ICW, Peeters RLM, de Kok TM, Ertaylan G. Adipose tissue in health and disease through the lens of its building blocks. Sci Rep 2020 Dec;10(1):10433. https://doi.org/10.1038/s41598-020-67177-1.

[60] Ferrero R, Rainer P, Deplancke B. Toward a consensus view of mammalian adipocyte stem and progenitor cell heterogeneity. Trends Cell Biol 2020 Dec 1;30(12):937–50. https://doi.org/10.1016/j.tcb.2020.09.007.

[61] Merlotti C, Ceriani V, Morabito A, Pontiroli AE. Subcutaneous fat loss is greater than visceral fat loss with diet and exercise, weight-loss promoting drugs and bariatric surgery: a critical review and meta-analysis. Int J Obes (Lond) 2017 May 1;41(5):672–82. https://doi.org/10.1038/ijo.2017.31.

[62] Karlsson T, Rask-Andersen M, Pan G, Höglund J, Wadelius C, Ek WE, et al. Contribution of genetics to visceral adiposity and its relation to cardiovascular and metabolic disease. Nat Med 2019 Sep 1;25(9):1390–5. https://doi.org/10.1038/s41591-019-0563-7.

[63] Seth M, Biswas R, Ganguly S, Chakrabarti N, Chaudhuri AG. Leptin and obesity. Physiol Int 2020 Dec 1;107(4):455–68. https://doi.org/10.1556/2060.2020.00038.

[64] Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. Nature 1994 Dec 1;372(6505):425–32. https://doi.org/10.1038/372425a0.

[65] Yadav A, Jyoti P, Jain SK, Bhattacharjee J. Correlation of adiponectin and leptin with insulin resistance: a pilot study in healthy North Indian population. Indian Clin Biochem 2011 Feb 18;26(2):193–6. https://doi.org/10.1007/s12291-011-0119-1.

[66] Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. N Engl J Med 1996 Feb 20;334(5):292–5. https://doi.org/10.1056/NEJM199602013340503.

[67] Segal KR, Landt M, Klein S. Relationship between insulin sensitivity and plasma leptin concentration in lean and obese men. Diabetes 1996 Jul 1;45(7):988–91. https://doi.org/10.2337/diab.45.7.988.

[68] Berglund ED, Vianna CR, Donato J, Kim MH, Chuang JC, Lee CE, et al. Direct leptin action on POMC neurons regulates glucose homeostasis and hepatic insulin sensitivity in mice. J Clin Invest 2012 Mar 1;122(3):1000–9. https://doi.org/10.1172/JCI59816.

[69] Schwartz MW, Baskin DG, Bukowski TR, Kuijper JL, Foster D, Lasser G, et al. Specificity of leptin action on elevated blood glucose levels and hypothalamic neuropeptide Y gene expression in ob/ob mice. Diabetes 1996;45(4):531–5. https://doi.org/10.2337/diab.45.4.531.

[70] Zilberstein A, Ruggieri R, Korn JH, Revel M. Structure and expression of cDNA and genes for human interferon-beta-2, a distinct species inducible by growth-stimulatory cytokines. EMBO J 1986 Oct;5(10):2529–37. https://doi.org/10.1002/j.1460-2075.1986.tb04531.x.

[71] Hirano T, Yasukawa K, Harada H, Taga T, Watanabe Y, Matsuda T, et al. Complementary DNA for a novel human interleukin (BSF-2) that induces B lymphocytes to produce immunoglobulin. Nature 1986 Nov;324(6092):73–6. https://doi.org/10.1038/324073a0.

[72] Kang S, Tanaka T, Narazaki M, Kishimoto T. Targeting interleukin-6 signaling in clinic. Immunity 2019 Apr 16;50(4):1007–23. https://doi.org/10.1016/j.immuni.2019.03.026.

[73] Mohamed-Ali V, Goodrick S, Rawesh A, Katz DR, Miles JM, Yudkin JS, et al. Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-α, in vivo. J Clin Endocrinol Metab 1997;82(12):4196–200. https://doi.org/10.1210/jcem.82.12.4450.

[74] Heinrich PC, Castell JV, Andus T. Interleukin-6 and the acute phase response. Biochem J 1990;265(3):621–36. https://doi.org/10.1042/bj2650621.

[75] Hirano T. IL-6 in inflammation, autoimmunity and cancer. Int Immunol 2021 Mar 1;33(3):127–48. https://doi.org/10.1093/intimm/dxaa078.

[76] Jonas MI, Kurylowicz A, Bartoszewicz Z, Lisik W, Jonas M, Wierzbicki Z, et al. Interleukins 6 and 15 levels are higher in subcutaneous adipose tissue, but obesity is associated with their increased content in visceral fat depots. Int J Mol Sci 2015 Oct 1;16(10):25817–30. https://doi.org/10.3390/ijms161025817.

[77] Wisse BE. The inflammatory syndrome: the role of adipose tissue cytokines in metabolic disorders linked to obesity. J Am Soc Nephrol 2004 Nov;15(11):2792–800. https://doi.org/10.1097/01.ASN.0000141966.69934.21.

[78] Laferrère B. Diabetes remission after bariatric surgery: is it just the incretins? Int J Obes (Lond) 2011 Sep;35:S22–5. https://doi.org/10.1038/ijo.2011.143.

[79] Klein S, Allison DB, Heymsfield SB, Kelley DE, Leibel RL, Nonas C, et al. Waist circumference and cardiometabolic risk: a consensus statement from shaping America's health: association for weight management and obesity prevention; NAASO, the obesity society; the American society for nutrition; and the American diabetes association. Am J Clin Nutr 2007 May 1;85(5):1197–202. https://doi.org/10.1093/ajcn/85.5.1197.

[80] Hernandez TL, Kittelson JM, Law CK, Ketch LL, Stob NR, Lindstrom RC, et al. Fat redistribution following suction lipectomy: defense of body fat and patterns of restoration. Obesity (Silver Spring) 2011 Jul;19(7):1388–95. https://doi.org/10.1038/oby.2011.64.

[81] Van der Lei B, Halbesma GJ, van Nieuwenhoven CA, van Wingerden JJ. Spontaneous breast enlargement following liposuction of the abdominal wall: does a link exist? Plast Reconstr Surg 2007 Apr;119(5):1584–9. https://doi.org/10.1097/01.prs.0000256069.54596.0b.

[82] Gurunluoglu R. Discussion: photographic measurements in 301 cases of liposuction and abdominoplasty reveal fat reduction without redistribution. Plast Reconstr Surg 2012 Aug;130(2):323e–4e. https://doi.org/10.1097/PRS.0b013e31825904d8.

[83] Okamura T, Hashimoto Y, Hamaguchi M, Obora A, Kojima T, Fukui M. Ectopic fat obesity presents the greatest risk for incident type 2 diabetes: a population-based longitudinal study. Int J Obes (Lond) 2019 Jan 1;43(1):139–48. https://doi.org/10.1038/s41366-018-0076-3.

[84] Bosy-Westphal A, Braun W, Albrecht V, Müller MJ. Determinants of ectopic liver fat in metabolic disease. Eur J Clin Nutr 2019 Feb 1;73(2):209–14. https://doi.org/10.1038/s41430-018-0323-7.

[85] De Munck TJI, Soeters PB, Koek GH. The role of ectopic adipose tissue: benefit or deleterious overflow? Eur J Clin Nutr 2021 Jan 1;75(1):38–48. https://doi.org/10.1038/s41430-020-00713-4.

[86] Flaherty SE, Grijalva A, Xu X, Ables E, Nomani A, Ferrante AW. A lipase-independent pathway of lipid release and immune modulation by adipocytes. Science 2019;363(6430):989–93. https://doi.org/10.1126/science.aaw2586.

[87] Andrew MS, Huffman DM, Rodriguez-Ayala E, Williams NN, Peterson RM, Bastarrachea RA. Mesenteric visceral lipectomy using tissue liquefaction technology reverses insulin resistance and causes weight

[17] Klein S. The case of visceral fat: argument for the defense. J Clin Invest 2004 Jun 1;113(11):1530–2. https://doi.org/10.1172/JCI22028.

[18] Fabbrini E, Magkos F, Mohammed BS, Pietka T, Abumrad NA, Patterson BW, et al. Intrahepatic fat, not visceral fat, is linked with metabolic complications of obesity. Proc Natl Acad Sci USA 2009 Sep 8;106(36):15430–5. https://doi.org/10.1073/pnas.0904944106.

[19] Ziccardi P, Nappo F, Giugliano G, Esposito K, Marfella R, Cioffi M, et al. Reduction of inflammatory cytokine concentrations and improvement of endothelial functions in obese women after weight loss over one year. Circulation 2002 Feb 19;105(7):804–9. https://doi.org/10.1161/hc0702.104279.

[20] Stevens VJ, Obarzanek E, Cook NR, Lee IM, Appel LJ, Smith West D, et al. Long-term weight loss and changes in blood pressure: results of the trials of hypertension prevention, phase II. Ann Intern Med 2001 Jan 2;134(1):1–11. https://doi.org/10.7326/0003-4819-134-1-200101020-00007.

[21] Madsbad S, Dirksen C, Holst JJ. Mechanisms of changes in glucose metabolism and bodyweight after bariatric surgery. Lancet Diabetes Endocrinol 2014 Feb 1;2(2):152–64. https://doi.org/10.1016/S2213-8587(13)70218-3.

[22] Cazes L, Deitel M, Levine RH. Effect of abdominal lipectomy on lipid profile, glucose handling and blood pressure in patients with truncal obesity. Obes Surg 1996;6(2):159–66. https://doi.org/10.1381/096089296765557123.

[23] Rizzo MR, Paolisso G, Grella R, Barbieri M, Grella E, Ragno E, et al. Is dermolipectomy effective in improving insulin action and lowering inflammatory markers in obese women? Clin Endocrinol (Oxf) 2005 Sep;63(3):253–8. https://doi.org/10.1111/j.1365-2265.2005.02337.x.

[24] Swanson E. Prospective clinical study reveals significant reduction in triglyceride level and white blood cell count after liposuction and abdominoplasty and no change in cholesterol levels. Plast Reconstr Surg 2011 Sep;128(3):182e–197e. https://doi.org/10.1097/PRS.0b013e31822213c6.

[25] Gonzalez-Ortiz M, Robles-Cervantes JA, Cardenas-Camarena L, Bustos-Saldana R, Martinez-Abundis E. The effects of surgically removing subcutaneous fat on the metabolic profile and insulin sensitivity in obese women after large-volume liposuction treatment. Horm Metab Res 2002 Aug;34(08):446–9. https://doi.org/10.1055/s-2002-33603.

[26] Ybarra J, Blanco-Vaca F, Fernández S, Castellví A, Bonet R, Palomer X, et al. The effects of liposuction removal of subcutaneous abdominal fat on lipid metabolism are independent of insulin sensitivity in normal-overweight individuals. Obes Surg 2008 Apr;18(4):408–14. https://doi.org/10.1007/s11695-007-9261-5.

[27] Busetto L, Bassetto F, Zocchi M, Zuliani F, Nolli ML, Pigozzo S, et al. The effects of the surgical removal of subcutaneous adipose tissue on energy expenditure and adipocytokine concentrations in obese women. Nutr Metab Cardiovasc Dis 2008 Feb 1;18(2):112–20. https://doi.org/10.1016/j.numecd.2006.09.009.

[28] Davis DA, Pellowski DM, Donahoo WT. Acute and 1-month effect of small-volume suction lipectomy on insulin sensitivity and cardiovascular risk. Int J Obes (Lond) 2006 Aug;30(8):1217–22. https://doi.org/10.1038/sj.ijo.0803120.

[29] D'Andrea F, Grella R, Rizzo MR, Grella E, Grella R, Nicoletti G, et al. Changing the metabolic profile by large-volume liposuction: a clinical study conducted with 123 obese women. Aesthetic Plast Surg 2005 Nov-Dec;29(6):472–8. https://doi.org/10.1007/s00266-005-0089-x.

[30] Samdal F, Birkeland KI, Ose L, Amland PF. Effect of large-volume liposuction on sex hormones and glucose-and lipid metabolism in females. Aesthetic Plast Surg 1995 Mar;19(2):131–5. https://doi.org/10.1007/BF00450248.

[31] Giugliano G, Nicoletti G, Grella E, Giugliano F, Esposito K, Scuderi N, et al. Effect of liposuction on insulin resistance and vascular inflammatory markers in obese women. Br J Plast Surg 2004;57(3):190–4. https://doi.org/10.1016/j.bjps.2003.12.010.

[32] Giese SY, Neborsky R, Bulan EJ, Spear SL, Yanovski JA. Improvements in cardiovascular risk profile after large-volume lipoplasty: a 1-year follow-up study. Aesthet Surg J 2001;21(6):527–31. https://doi.org/10.1067/maj.2001.120434.

[33] Giese SY, Bulan EJ, Commons GW, Spear SL, Yanovski JA. Improvements in cardiovascular risk profile with large-volume liposuction: a pilot study. Plast Reconstr Surg 2001;108(2):510–9. https://doi.org/10.1097/00006534-200108000-00036.

[34] Esposito K, Giugliano G, Giugliano D, Arner P, Busetto L, Bassetto F, et al. Metabolic effects of liposuction–yes or no?. N Engl J Med 2004 Sep 23;351(13):1354–7. https://doi.org/10.1056/NEJM200409233511320.

[35] Clark JM, Sanders S, Carter M, Honeyman D, Cleo G, Auld Y, et al. Improving the translation of search strategies using the polyglot search translator: a randomized controlled trial. J Med Libr Assoc 2020 Apr 1;108(2):195–207. https://doi.org/10.5195/jmla.2020.834.

[36] Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol 2007 Dec;7(1):1–7. https://doi.org/10.1186/1471-2288-7-10.

[37] Crahay FX, Nizet JL. Metabolic and cardiovascular consequences of suction-assisted lipectomy: systematic review. Ann Chir Plast Esthet 2016 Aug 1;61(4):270–86. https://doi.org/10.1016/j.anplas.2016.03.005.

[38] Seretis K, Goulis DG, Koliakos G, Demiri E. Short- and long-term effects of abdominal lipectomy on weight and fat mass in females: a systematic review. Obes Surg 2015 Oct;25(10):1950–8. https://doi.org/10.1007/s11695-015-1797-1.

[39] Danilla S, Longton C, Valenzuela K, Cavada G, Norambuena H, Tabilo C, et al. Suction-assisted lipectomy fails to improve cardiovascular metabolic markers of disease: a meta-analysis. J Plast Reconstr Aesthet Surg 2013 Nov;66(11):1557–63. https://doi.org/10.1016/j.bjps.2013.07.001.

[40] Boriani F, Villani R, Morselli PG. Metabolic effects of large-volume liposuction for obese healthy women: a meta-analysis of fasting insulin levels. Aesthetic Plast Surg 2014 Sep 25;38(5):1050–6. https://doi.org/10.1007/s00266-014-0386-3.

[41] Robles-Cervantes JA, Yánez-Diaz S, Cárdenas-Camarena L. Modification of insulin, glucose and cholesterol levels in nonobese women undergoing liposuction: is liposuction metabolically safe? Ann Plast Surg 2004 Jan;52(1):64–7. https://doi.org/10.1097/01.sap.0000096448.59407.43.

[42] Martínez-Abundis E, Molina-Villa CA, González-Ortiz M, Robles-Cervantes JA, Saucedo-Ortiz JA. Effect of surgically removing subcutaneous fat by abdominoplasty on leptin concentrations and insulin sensitivity. Ann Plast Surg 2007 Apr;58(4):416–9. https://doi.org/10.1097/01.sap.0000240033.00047.cc.

[43] Mohammed BS, Cohen S, Reeds D, Young VL, Klein S. Long-term effects of large-volume liposuction on metabolic risk factors for coronary heart disease. Obesity (Silver Spring) 2008 Dec;16(12):2648–51. https://doi.org/10.1038/oby.2008.418.

[44] Klein S, Fontana L, Young VL, Coggan AR, Kilo C, Patterson BW, et al. Absence of an effect of liposuction on insulin action and risk factors for coronary heart disease. N Engl J Med 2004 Jun 17;350(25):2549–57. https://doi.org/10.1056/NEJMoa033179.

[45] Pratt-Phillips SE, Geor RJ, McCutcheon LJ. Comparison among the euglycemic-hyperinsulinemic clamp, insulin-modified frequently sampled intravenous glucose tolerance test, and oral glucose tolerance test for assessment of insulin sensitivity in healthy standardbreds. Am J Vet Res 2015;76(1):84–91. https://doi.org/10.2460/ajvr.76.1.84.

[46] Rehman K, Akash MSH. Mechanisms of inflammatory responses and development of insulin resistance: how are they interlinked?. J Biomed Sci 2016 Dec;23(1):1–8. https://doi.org/10.1186/s12929-016-0303-y.

[47] Fontana L, Eagon JC, Trujillo ME, Scherer PE, Klein S. Visceral fat adipokine secretion is associated with systemic inflammation in obese humans. Diabetes 2007 Apr;56(4):1010–3. https://doi.org/10.2337/db06-1656.

[48] Ross R, Shaw KD, Martel Y, de Guise J, Avruch L. Adipose tissue distribution measured by magnetic resonance imaging in obese women. Am J Clin Nutr 1993;57(4):470–5. https://doi.org/10.1093/ajcn/57.4.470.

[49] Patel P, Abate N. Body fat distribution and insulin resistance. Nutrients 2013 Jun 5;5(6):2019–27. https://doi.org/10.3390/nu5062019.

[50] Abate N, Garg A, Peshock RM, Stray-Gundersen J, Grundy SM. Relationships of generalized and regional adiposity to insulin sensitivity in men. J Clin Invest 1995;96(1):88–98. https://doi.org/10.1172/JCI118083.

context of SSFR, it is unclear to what extent the redistributed fat contributes to the ectopic fat accumulation in tissues, such as intramuscular, intrahepatic, and myocardial fat and if it has a protective or detrimental effect. Furthermore, it is unclear if and how or which specific factors drive the fat redistribution to ectopic regions in preference to the rest of the body spatiotemporally. Identifying such factors can be helpful surrogate biomarkers for predicting potential risk factors in epidemiological studies. However, it should be noted that rodent models of fat biology do not adequately represent what happens in humans, and higher mammals such as baboons may be a better model that closely resembles human adipocyte function [87].

Thus far, results from studies designed to identify the factors that address the regulation of energetics and body fat redistribution/ regeneration post-SSFR in rats, mice, or hamsters have limited contribution in closing the knowledge gap because of insufficient mechanistic data, inadequate sample size, or lack of proper statistical tests reported [88]. Therefore, future studies in appropriate animal models or human clinical trials should account for the biological consequences of ectopic fat redistribution following weight gain post-SSFR. However, there is a need to ascertain the beneficial or detrimental nature of fat redistribution at specific anatomical sites, in relation to its quantity, rate, and time of accumulation following weight gain post-SSFR.

Conclusion

We conclude that there is a gap in terms of the probability of weight gain or accumulation of fat post-SSFR, but there is data that in the short term there might be a metabolic benefit of excess ASF removal. Longer-term data are needed to determine if this benefit is sustained in the longer term. Patients going for SSFR represent a unique population with a sudden removal of their ASF. However, the metabolic changes after these procedures are still unclear, and existing studies suggest a trend toward benefit rather than harm. There is thus no immediate harm from these procedures but there is a need for properly designed dose-response MAs as well as well-conducted prospective clinical studies to unravel these putative changes. In turn, this will help us not only to confirm the safety of these procedures but also to define if these procedures can be used for metabolic benefit and to broaden our knowledge about the mechanisms underpinning excess ASF and associated metabolic consequences.

Acknowledgments

The authors thank the Department of Plastic Surgery at Hamad General Hospital and the Department of Population Medicine at the College of Medicine at Qatar University for their contribution to this paper.

Conflict of interest: The authors declare no conflicts of interest.

Funding: This project was supported by the Medical Research Office at Hamad Medical Corporation (#01-20-466) and the Qatar National Research Fund (Projects #NPRP13S-0209-200315 and #NPRP14S-0406-210153). The responsibility for the paper lies with the authors and there was no influence of the funder.

Submitted: 1 August 2022
Accepted: 28 September 2022
Published online: 29 September 2022

References

[1] Obesity and overweight [Internet]. [cited 2021 Mar 14]. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
[2] Cao H. Adipocytokines in obesity and metabolic disease. J Endocrinol 2014 Feb 1;220(2):T47–59. https://doi.org/10.1530/JOE-13-0339.
[3] Bergé J-P,Barnathan G. Fatty acids from lipids of marine organisms: molecular biodiversity, roles as biomarkers, biologically active compounds, and economical aspects. Adv Biochem Eng Biotechnol 2005 Aug 24;96:49–125. https://doi.org/10.1007/b135782.
[4] Achari AE, Jain SK. Adiponectin, a therapeutic target for obesity, diabetes, and endothelial dysfunction. Int J Mol Sci 2017 Jun 21;18(6):1321. https://doi.org/10.3390/ijms18061321.
[5] Frayn KN. Adipose tissue and the insulin resistance syndrome. Proc Nutr Soc 2001 Aug;60(3):375–80. https://doi.org/10.1079/pns200195.
[6] Kusminski CM, Holland WL, Sun K, Park J, Spurgin SB, Lin Y, et al. MitoNEET-driven alterations in adipocyte mitochondrial activity reveal a crucial adaptive process that preserves insulin sensitivity in obesity. Nat Med 2012 Oct;18(10):1539–49. https://doi.org/10.1038/nm.2899.
[7] Finucane MM, Stevens GA, Cowan MJ, Danaei G, Lin JK, Paciorek CJ, et al. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9•1 million participants. Lancet 2011 Feb 12;377(9765):557–67. https://doi.org/10.1016/S0140-6736(10)62037-5.
[8] Kitzinger HB, Abayev S, Pittermann A, Karle B, Bohdjalian A, Langer FB, et al. After massive weight loss: patients' expectations of body contouring surgery. Obes Surg 2012 Apr;22(4):544–8. https://doi.org/10.1007/s11695-011-0551-6.
[9] Almutairi K, Gusenoff JA, Rubin JP. Body contouring. Plast Reconstr Surg 2016 Mar;137(3):586e–602e. https://doi.org/10.1097/PRS.0000000000002140.
[10] Sailon AM, Wasserburg JR, Kling RR, Pasick CM, Taub PJ. Influence of large-volume liposuction on metabolic and cardiovascular health: a systematic review. Ann Plast Surg 2017 Dec;79(6):623–30. https://doi.org/10.1097/SAP.0000000000001195.
[11] Seretis K, Goulis DG, Koliakos G, Demiri E. The effects of abdominal lipectomy in metabolic syndrome components and insulin sensitivity in females: a systematic review and meta-analysis. Metabolism 2015 Dec 1;64(12):1640–9. https://doi.org/10.1016/j.metabol.2015.09.015.
[12] Pinkhasov BB, Selyatitskaya VG, Karapetyan AR, Astrakhantseva EL. Metabolic syndrome in men and women with upper or lower types of body fat distribution. Health N Hav 2012 Dec 31;4(12):1381–9. https://doi.org/10.4236/health.2012.412A200.
[13] Després J-P,Lemieux I. Abdominal obesity and metabolic syndrome. Nature 2006 Dec 14;444(7121):881–7. https://doi.org/10.1038/nature05488.
[14] Fu J, Hofker M, Wijmenga C. Apple or pear: size and shape matter. Cell Metab 2015 Apr 7;21(4):507–8. https://doi.org/10.1016/j.cmet.2015.03.016.
[15] Kwon H, Kim D, Kim JS. Body fat distribution and the risk of incident metabolic syndrome: a longitudinal cohort study. Sci Rep 2017 Dec 1;7(1):1–8. https://doi.org/10.1038/s41598-017-09723-y.
[16] Klein S. Is visceral fat responsible for the metabolic abnormalities associated with obesity?. Diabetes Care 2010 Jul;33(7):1693–4. https://doi.org/10.2337/dc10-0744.

Table 5. Description of the potential anti-inflammatory adipokines

	Hormone	Source	Observed changes in obesity	Main function
1	Adiponectin [100]	Adipose tissue and skeletal muscles.	Lower levels in diabetic patients.	Anti-obesity, anti-atherogenic, anti-inflammatory, and anti-diabetic effects.
2	Omentin-1 [101]	Visceral adipose tissue.	Lower levels in obese and diabetic patients	Anti-inflammatory, anti-obesity, anti-diabetic properties, and insulin sensitizing effect.
3	Secreted frizzled related protein 5 (SSFRP5) [102, 103]	Adipose tissue.	Lower levels in obese and diabetic patients.	Anti-inflammatory and insulin sensitizing effect.
4	Cardiotrophin-1 (CT-1) [103]	Adipose tissue, liver, kidney, muscle, heart, and lung, brain and testis.	Controversi al results regarding the changes in serum levels of obese patients.	One of the IL-6 cytokine family, play a role in glucose and lipid metabolism, has an insulin sensitizing potential effect.

IL-6: Interleukin 6.

hold. It remains to be determined if this molecule does indeed exist and what it could be.

Interleukin-6 (IL-6), ASF and inflammation

IL-6 is a 212-residue protein cytokine encoded by the IL-6 gene [70]. Since its identification in 1986 by molecular cloning of B-cell stimulatory factor-2 [71], IL-6 has been recognized as a cytokine with various biological activities implicated with a detrimental role in a wide range of inflammation-associated disease states, including susceptibility to diabetes mellitus [72]. IL-6 is synthesized by various cell types of which white adipocytes are responsible for one-third of basal serum levels in humans [73].

The IL-6 level is probably the single most important factor associated with the hepatic acute-phase response and this is a response to tissue damage or infection that initiates host defense mechanisms and whose goal is to eliminate the threat and facilitate tissue repair [74]. Obesity however is associated with chronic low-grade inflammation possibly from hypoxia in adipocytes, resulting in the release of IL-6 and activation of other factors that positively feedback and amplify IL-6 release [75]. This leads to the metabolic syndrome and similar to leptin, *in vitro* studies have shown that ASF produces more IL-6 than VSF [76] making the link between ASF and metabolic syndrome stronger than that for VSF [77].

Leptin, IL6 and the SSFR- bariatric surgery interaction

It is important to note that some SSFR patients tend to have had bariatric surgery, which is associated with enhanced postprandial gut hormone release, particularly GLP-1, a hormone interlinked with factors released from adipose tissue, e.g., leptin and IL-6 highlighted above. However, what remains unclear is whether or to what extent this crosstalk gets perturbed in patients undergoing SSFR and/or bariatric surgery. Furthermore, what are the long-term metabolic sequelae? Thus, a robust examination of the changes of IL-6 after the sudden removal of fat surgically by body contouring procedures might widen our understanding of the mechanisms behind these metabolic changes.

Other considerations and future tasks

Apart from the potentially favorable effects of SSFR on metabolism and adipokines discussed above, many studies also support the effectiveness of bariatric surgery for treating obesity and weight-related disease [21, 78]. However, the question about the combined impacts of these surgical interventions has been relatively under-studied, and the results remain inconclusive. Future studies that can link the metabolic improvement after bariatric surgery and bariatric medications such as Semaglutide to the preferential loss of AVF or ASF will be of great benefit. Additionally, a dose response MAs is needed to examine the time trend of the metabolic changes after SSFR, which can answer important questions regarding the durability and extent of changes induced by these procedures over time.

When a negative energy balance is induced by interventions such as SSFR, resulting in a moderate initial reduction of 5% to 10% from baseline body weight, the physiological adaptations certainly favor weight regain; thus, most people recover weight post-SSFR or at the end of lifestyle interventions. With the common SSFR procedures, this loss is of abdominal fat that constitutes <15% of total adipose tissue [79], with the main component of the latter being ASF.

Given that fat distribution is one parameter that modifies the impact of obesity on health, knowledge about whether fat tissue removed through SSFR is replaced by new fat tissue and if this occurs in the same or at different anatomical sites is important since the latter may have worse effects. Previous studies reported that the fat could return to sites other than that from which fat has been removed, such as the breast, hip, and thigh regions [80, 81], but this is not always the case [82]. There is also the possibility that new fat may accumulate at sites where fat does not commonly accumulate (ectopic fat) and such ectopic adipose tissues may deposit in several organs/tissues (intramuscular/cardiac/hepatic) in the body with adverse consequences [83, 84]. However, recent studies of the heart [85, 86] have suggested that ectopic fat is protective against the risk of developing cardiovascular complications by increasing glycolysis, as a physiological healing response. In the

Table 4. Description of the potential inflammatory adpokines

	Hormone	Source	Observed changes in obesity	Main function
1	Leptin [89]	Mainly from adipocytes.	It is a well-known marker of obesity.	It is a satiety hormone that regulates body weight by suppressing the feeling of hunger, inhibit fat storage, and promote fatty acid oxidization. It also promotes inflammation.
2	Resistin [90]	Adipocytes, monocytes, and macrophages.	Increased in obesity, insulin resistance, and diabetic patients.	It is a pro-inflamm atory adipokine. It is thought to play a role in insulin resistance.
3	Fatty acid binding protein-4 (FABP-4) [91]	Adipocytes and macrophages.	Increased in obesity, insulin resistance, and diabetic patients.	Play a role insulin resistance and inflammation.
4	Retinol binding protein (RBP-4) [92]	Adipocytes (especially visceral fat), macrophages, and liver.	Increased in obesity, insulin resistance, and diabetic patients. Associated with hypertension, and dyslipidemia.	Act as a transporter for retinol and play a role in insulin resistance development.
5	Acylation stimulating protein (ASP) [93]	Adipocyte	Increased in obesity and dyslipidemia patients.	Autocrine function that leads to increasing triglyceride synthesis.
6	Lipocalin-2 (LCN2) [94]	Adipose tissue, liver, kidney, lung, macrophages, and neutrophils.	Increased in obesity (especially in severely obese females).	Play a role in inflammation and insulin resistance.
7	Chemerin [95]	Adipose tissue, liver, as well as innate immune cells.	Elevated with obesity and diabetic patients.	Play a role in insulin resistance, adipocyte metabolism, and diabetic induced cardiovascular disease.
8	Visfatin [96]	Adipose tissue and neutrophils.	Increased in obesity, and diabetic patients.	Act as a proinflammatory mediator.
9	Vaspin [97]	Adipose tissue, liver, pancreas, stomach, muscles and skin.	Increased in obesity, insulin resistance and diabetic patients.	Act as a member of the serine protease inhibitor family
10	Apelin [98]	Adipose tissue, hypothalamus, heart, and skeletal muscles.	Increased in obesity, insulin resistance and diabetic patients.	Play a role in regulating glucose metabolism, by inducing glucose uptake.
11	Gremlin-1 [99]	Preadipocytes.	Increased in obesity.	Act as an inhibitor of bone morphogenetic protein (BMP), which is one of the transforming growth factor-beta family.

from the gastric epithelium and other tissues [63]. Since its identification in 1994 by positional cloning [64], leptin has gained much recognition as a crucial peripheral and central signaling molecule associated with energy balance. This, in turn, has contributed to changing the perception of the adipose tissue from being a form of passive energy depot (primarily in the form of energy-rich triglycerides (9 kilocalories per gram) to that of an active endocrine organ that actively modulates food intake and systemic energy metabolism.

Leptin levels are positively associated with BMI, HOMA-IR, and serum triglycerides and negatively with serum HDL in mostly normal weight health individuals suggesting that leptin increases with BMI as well as in those with insulin resistance [65]. The latter study suggests that leptin was coming mainly from ASF given correlation with hip and waist circumference but not with waist–hip ratio [65]. Under normal physiological conditions, bloodstream levels of leptin are proportional to fat mass for a given individual [66] suggesting that the increase in leptin is driven by fat mass and that both leptin and insulin resistance are consequences of an increase in fat mass. Nevertheless, basal plasma leptin concentrations are significantly lower in insulin-sensitive than in insulin-resistant men (1.90 ± 0.4 vs. 4.35 ± 1.21 ng/ml, $P < 0.05$) of identical body fat composition [67] suggesting either that excess leptin may also lead to increases in insulin resistance independent of adiposity or that leptin production increases in insulin resistant men in response to unknown feedback mechanisms in an effort to ameliorate the insulin resistance. The latter seems more plausible given that a direct action of leptin on its hypothalamic neuronal target is required to maintain normal glucose homeostasis data and insulin sensitivity [68, 69] and therefore the rising leptin level and insulin resistance in obesity lends plausibility to the conclusion that another fat derived molecule required for the leptin effect on glucose homeostasis may be downregulated in obesity for this paradoxical observation to

Table 2. Syntheses that report changes in inflammatory markers after SSFR

	Synthesis author and year	Synthesis type	Type of SSFR	Included studies	Follow up	Main finding	Remaining evidence gaps
1	Sailon et al. 2017 [10]	SR	Liposuction	Four prospective studies (210 participants). The review examined the effect of large volume liposuction (more than 3.5 liters) on IL-6 and TNF-α.	10 weeks–6 months.	Two studies reported a statistically significant decrease in plasma IL-6 and TNF-α levels.	Neither a clear extent of change nor the clinical significance was reported.
2	Danilla et al. 2013 [39]	MA	Liposuction	Eight prospective studies (239 participants) examined the changes in CRP (4 studies), IL-6 (3 studies), and TNF-a (3 studies).	1–6 months.	No association between the amount of aspirated fat and serum levels of CRP, IL-6, and TNF-a.	No clear report on the results, rather than just a general conclusion of no association.

SR: Systemic review; MA: Meta-analysis; CI: Confidence interval; CRP: C-reactive protein; IL-6: Interleukin 6; TNF-a: Tumor necrosis factor-alpha; SSFR: Surgical subcutaneous fat removal.

Table 3. Syntheses that report changes in adipokines after SSFR

	Synthesis author and year	Synthesis Type	Type of SSFR	Included studies	Follow up	Main finding	Remaining evidence gaps
1	Sailon et al. 2017 [10]	SR	Liposuction	Five prospective studies (225 participants) examined the effect of large volume liposuction (>3.5 liters) on adipokines levels (namely leptin and adiponectin).	10 weeks–6 months.	Leptin was examined by 4 studies, which all reported a statistically significant reduction. Adiponectin was assessed in all studies, two of which reported a significant increase.	Neither a clear extent of change, nor the clinical significance was reported. Other adipokines were not assessed.
2	Danilla et al. 2013 [39]	MA	Liposuction	Six quasi experiment studies (191 participants) examined the effect of SSFR on leptin levels.	6 weeks–6 months.	The MA showed a statistically significant reduction in leptin levels (Coefficient: 0.18). This reduction was proportional to the amount of aspirated fat, and patient BMI.	The study didn't report the changes in other adipokines, nor the clinical significance of the reported changes.

SR: Systemic review; MA: Meta-analysis; SSFR: Surgical subcutaneous fat removal; BMI: Body mass index.

Table 1. Syntheses that report changes in insulin sensitivity after SSFR

	Synthesis author and year	Synthesis type	Type of SSFR	Included studies	Follow up	Main finding	Remaining evidence gaps
1	Sailon et al. 2017 [10]	SR	Liposuction	Ten prospective studies (346 participants), which examined large volume liposuction (> 3.5 liters).	3 weeks–6 months.	Author reported conflicting results but stated that surgical fat removal by large volume liposuction can improve insulin sensitivity. No clear extent of change was reported.	This SR focused examining the statistical significance of these changes post SSFR, without reporting the extent of change, or its clinical importance. The review had substantial heterogeneity in terms of participants baseline characteristics, included studies sample size, and different assessment tools for insulin resistance.
2	Seretis et al. 2015 [11]	MA	Liposuction + Abdominoplasty	Four studies (140 participants).	2 months–2 years.	Fasting glucose levels changes after SSFR were not statistically significant (1.42, 95% CI: −1.57, 4.40). Changes in insulin sensitivity were also assessed either by insulin tolerance test or HOMA index, however the result reported a lack of significant change after SSFR (0.14, 95% CI -0.69–0.96).	This MA included studies that were so contrived in terms of control group that no conclusion was possible. The small number of studies limited its validity and prevented subgroup analysis according to certain confounders such as age or BMI.
3	Boriani et al. 2014 [40]	MA	liposuction	Five prospective studies (190 participants).	3 months–1 year.	Fasting insulin levels were significantly higher before SSFR by a weighted mean difference of 3.49 mIU/ml (95% CI 1.12, 5.87).	There was a degree of heterogeneity among studies ($p = 0.02$, $I2 = 67\%$). Fasting insulin levels were used as a surrogate for insulin resistance, which is an indirect measure.
4	Danilla et al., 2013 [39]	MA	Liposuction	Five quasi experiment studies (111 participants).	3 weeks–1 year.	Analysis reported that SSFR result in decreased fasting insulin levels, and the amount of reduction was associated with the amount of aspirated fat, independent with the baseline BMI. No significant change was reported in HOMA-IR levels after SSFR.	Although this MA studied the effect of time on the SSFR induces changes in insulin resistance, the sample size of the included studies was small.

SSFR: Surgical subcutaneous fat removal; SR: Systemic review; MA: Meta-analysis; CI: Confidence interval; BMI: Body mass index; HOMA-IR: Homeostatic model assessment for insulin resistance.

studies since there was a focus on statistical significance only. In summary, syntheses were inconsistent, there was a trend toward improvement in insulin sensitivity, and the clinical extent or duration of any improvement remains unclear. The impact of SSFR on insulin resistance thus remains unknown given the data reported in (Table 1) and we recommend that a dose response MA be conducted to answer this question.

Impact of SSFR on inflammation

Obesity is associated with chronic low-grade inflammation. This is a result of the increased influx of immune cells to the fat tissue, as well as the increased secretion of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-a) [2]. Adipocytes have an equal proinflammatory effect on the macrophages [46]. This inflammatory status is thought to be the mechanism behind most of obesity-linked metabolic disorders [2].

One SR and one MA examined the effect of SSFR on multiple inflammatory markers such as TNF-a, C-reactive protein (CRP), and IL-6, and the findings are detailed in Table 2. In summary, the syntheses combined heterogeneous studies with different follow-up times. Conclusions varied between no change after SSFR or lower levels of IL-6 and TNF-a after surgery. However, the extent and time-trend were not reported, thus a dose response MA remains a needed future task.

Impact of SSFR on adipokine levels

Changes in the adipokines have been examined by only one SR and one MA, and both reported a reduction of leptin levels after SSFR. However, there was heterogeneity in the reported changes in other adipokines, such as adiponectin and resistin (Table 3).

Summary of findings

This umbrella review summarizes four attempts at evidence synthesis on the metabolic changes after surgical fat removal, with a total of 29 unique studies included and 759 total participants. There was a possible improvement in obesity-associated insulin resistance, however, there was a lack of clarity regarding the extent of the effect and clinical significance. Nevertheless, it seems likely that ASF removal is associated with improved insulin sensitivity. In terms of inflammation, one of the two syntheses reported that ASF removal results in a lower degree of IL-6 and TNF-a, and thus potentially a more favorable metabolic risk profile. These syntheses also reported a reduction of leptin levels after ASF removal through surgery. There was heterogeneity in the reported changes in other adipokines, such as adiponectin and resistin. Clearly, the data from the previous studies are not conclusive, nevertheless, it seems likely that SSFR is associated with improved insulin sensitivity and lower levels of inflammatory cytokines.

Implications for future research

The role of ASF vs AVF in human metabolism

The central obesity in the abdominal area represents one of the essential components of metabolic syndrome, along with insulin resistance, elevated serum triglyceride, blood pressure, and low high-density lipoproteins, and it is distributed between the ASF and AVF compartments [11] Although some studies have linked the metabolic risk of obesity mainly to the AVF tissue [16, 47], others have proposed that both AVF and ASF play a role in metabolic risk [10]. Generally, subcutaneous fat mass is more than twice the visceral fat mass, especially among females [48]. As a result, 85% of bloodstream free fatty acids are coming from the subcutaneous fat stores, which is a major contributor to systemic insulin resistance by inhibiting glucose uptake by skeletal muscles [49]. There is evidence from some studies among healthy men [50] and those with T2DM [51] that ASF may be more strongly correlated with insulin resistance than AVF. There has also been a report from a study of a healthy cohort of mixed genders that ASF correlates with insulin resistance independently of AVF, but not the other way around [52]. To sum this up, there is some evidence from the umbrella review as well as other studies suggesting that ASF may make an important contribution to obesity-related metabolic change, and this thus can be a mechanism through which SSFR can create a more favorable metabolic profile.

When studies have looked directly at the added impact of AVF on metabolism, by examining the effect of adding omentectomy to bariatric procedures, results were inconsistent. Some studies reported that it could result in better glucose homeostasis and lower inflammatory markers [53, 54]. Conversely, others reported a lack of clinical improvement in the metabolic profile [55–57]. Many open questions remain therefore about the role of AVF vs ASF and part of the problem lies in their study design, for example, the lack of clarity regarding patient selection, determining the type of surgery, the parameters that needed to be measured, and accounting for patient factors [58]. In addition, there were also technical limitations of older studies regarding advanced imaging technologies to measure visceral adipose tissue accurately. At a more fundamental level, improved knowledge of all aspects of adipose biology, including adipose tissue cellular heterogeneity [59, 60] as well as divergent responses to metabolic and endocrine stimuli that will be required to make significant advances and resolve the problem highlighted above [61]. In addition, a recent genome-wide association study also shows the contribution of genetics to visceral adiposity and its relation to ethnicities and gender in the context of metabolic disease. In particular, the study suggests that increased AVF is more harmful compared with ASF, but it is not clear why this should be the case [62].

Adipokines

To determine why SSFR impacts adipokines levels, one needs to understand the roles of adipocyte-derived factors, as well as their effects on intermediary metabolism. Adipocyte-derived factors need to be understood in terms of source, relation to obesity, and main function. Tables 4 and 5 summarize the inflammatory and anti-inflammatory adipokines, the most well-known candidates are leptin and IL-6.

Leptin, ASF and insulin sensitivity

Leptin is a 167-residue peptide hormone encoded by the Ob gene, and it is secreted mainly by the adipocytes but also

Journal of Plastic, Reconstructive & Aesthetic Surgery 76 (2023) 238–250

JPRAS
An International Journal of Surgical Reconstruction
www.JPRASurg.com

Review

Metabolic changes after surgical fat removal: A dose-response meta-analysis

Saif Badran[a,b], Abdella M. Habib[c], Ghanem Aljassem[d], Omran A.H. Musa[b], Justin Clark[e], Moustapha Hamdi[f], Abdul-Badi Abou-Samra[g,h], Graeme E. Glass[g,i], Suhail A. Doi[b,*]

[a] *Division of Plastic and Reconstructive Surgery, Washington University, St. Louis, MO, USA*
[b] *Department of Population Medicine, College of Medicine, QU Health, Qatar University, Doha, Qatar*
[c] *College of Medicine, QU Health, Qatar University, Doha, Qatar*
[d] *Department of Plastic Surgery, Hamad General Hospital, Doha, Qatar*
[e] *Institute for Evidence-Based Healthcare, Faculty of Health Sciences & Medicine, Bond University, Queensland, Australia*
[f] *Department of Plastic and Reconstructive Surgery, Brussels University Hospital, Vrije Universiteit Brussel (VUB), UZB- Laarbeeklaan 101, 1090 Brussels, Belgium*
[g] *Weill Cornell Medicine Qatar, Qatar Foundation, Doha, Qatar*
[h] *Qatar Metabolic Institute (QMI), Hamad Medical Corporation, Doha, Qatar*
[i] *Department of Surgery, Sidra Medicine, Doha, Qatar*

Received 21 July 2022; accepted 26 October 2022

KEYWORDS
Body contouring surgery;
Surgical fat removal;
Insulin resistance;
Inflammation;
Blood pressure;
Lipid profile

Abstract *Background:* Bariatric surgery averts obesity-induced insulin resistance and the metabolic syndrome. By contrast, surgical fat removal is considered merely an esthetic endeavor. The aim of this article was to establish whether surgical fat removal, similar to bariatric surgery, exerts measurable, lasting metabolic benefits.
Methods: PubMed, Embase, and Scopus were searched using the Polyglot Search Translator to find studies examining quantitative expression of metabolic markers. Quality assessment was done using the MethodologicAl STandard for Epidemiological Research scale. The robust-error meta-regression model was employed for this synthesis.
Results: Twenty-two studies with 493 participants were included. Insulin sensitivity improved gradually with a maximum reduction in fasting insulin and homeostatic model assessment for insulin resistance of 17 pmol/L and 1 point, respectively, at postoperative day 180. Peak metabolic benefits manifest as a reduction of 2 units in body mass index, 3 kg of fat mass, 5 cm

* Corresponding author at: Head, Department of Population Medicine & Clinical Endocrinologist, College of Medicine, Qatar University, Doha, Qatar.
E-mail addresses: badran@wustl.edu (S. Badran), Sdoi@qu.edu.qa (S.A. Doi).

https://doi.org/10.1016/j.bjps.2022.10.055

of waist circumference, 15 μg/L of serum leptin, 0.75 pg/ml of tumor necrosis factor-alpha, 0.25 mmol/L of total cholesterol, and 3.5 mmHg of systolic and diastolic blood pressure that were observed at day 50 but were followed by a return to preoperative levels by day 180. Serum high-density lipoproteins peaked at 50 days post-surgery before falling below the baseline. No significant changes were observed in lean body mass, serum adiponectin, resistin, interleukin-6, C-reactive protein, triglyceride, low-density lipoproteins, free fatty acids, and fasting blood glucose.

Conclusion: Surgical fat removal exerts several metabolic benefits in the short term, but only improvements in insulin sensitivity last beyond 6 months.

Contents

Introduction

Obesity is a global health crisis and, after smoking, the leading cause of avoidable death in the developed world. Comorbidities include diabetes mellitus, hypertension, obstructive sleep apnea, ischemic heart disease, cancer, osteoarthritis, and depression.[1] Lifestyle changes are largely ineffective in the long term, and there are no efficacious pharmacological interventions. Bariatric surgery aims to induce weight loss by altering intestinal absorption and/or inducing changes in perceived satiety. Categories include gastric bypass, gastric banding, and pancreatico-biliary diversion. The efficacy of bariatric surgery in the management of morbid obesity is well established.[2]

While bariatric surgery addresses the physiological root causes of obesity, surgical fat removal (SFR) tackles the physical manifestations.[3] Options for SFR include en-bloc excision of skin and fat to the level of the muscle fascia, known as body contouring surgery (e.g., abdominoplasty, belt lipectomy, brachioplasty, thigh lift, and breast reduction) and the percutaneous avulsion and aspiration of fat (e.g., liposuction).[4] Bariatric surgery-induced weight loss results in the depletion of fat stores from both subcutaneous deposits and the viscera (accounting for approximately 20% of fat stores),[5] while SFR selectively depletes the subcutaneous stores.

Fat is an endocrine organ.[6] The long-term metabolic impact of fat loss by bariatric surgery is well documented.[2,7] Attempts have been made to evaluate the comparable metabolic impact of selective loss of subcutaneous fat,[8–12] but uncertainties persist owing to the heterogeneity of variables and study parameters. It is important to seek clarity

here, for, while the metabolic benefits of bariatric surgery are well established, SFR continues to be considered cosmetic in nature and subject to health-care rationing. This article describes a systematic review and dose–response meta-analysis (DRMA) of observational studies pertaining to the metabolic impact of body contouring surgery with a view to establishing how these procedures impact patient physiology over time.

Methods

Search strategy

A search string was initially designed in PubMed, then translated and run in Embase and Scopus using the Polyglot Search Translator.[13] The search string was designed by an experienced information specialist and was run across all databases on 8 November 2021. The search string was comprised of both medical subject heading terms and free-text terms. Additionally, the online trials register ClinicalTrials.gov and the national research register were scrutinized for completed, discontinued, and ongoing trials relating to body contouring surgery and physiological and/or metabolic parameters. The search strategy was performed in accordance with the Cochrane Highly Sensitive Search Strategy guideline in the *Cochrane Handbook for Systematic Reviews of Interventions*.[14] The review is reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Full search strings for all databases and PRISMA checklist are available in Supplementary Figures 1 and 2.

Inclusion criteria

Papers were included if they provided quantitative data permitting analyses of the effect of SFR (abdominoplasty or suction lipectomy) on physiology and/or metabolism. Only human studies were considered. No date, language, or publication limits were applied to the search.

Exclusion criteria

Nonhuman (in vivo) studies were excluded from consideration as were studies that used non-SFR procedures.

Quality assessment

The quality assessment of the eligibly included articles was independently done by two reviewers using the MethodologicAl STandard for Epidemiological Research (MASTER) scale.[15] This scale evaluates each included study against 36 safeguards across seven domains that, if present, may mitigate systematic error in the trial. Then, a quality rank for each assessed article was computed and reported qualitatively. The MASTER scale provided a unified framework for the assessment of the methodological quality of quasi-experimental and randomized controlled trials included in this synthesis.

Outcome measures

The outcome measures sought encompassed six domains. These included anthropometrics/body composition, serum adipokines, inflammatory cytokines, glucose homeostasis, lipid profile, and blood pressure. Data units were unified to the Systeme International d'Unites (SI) units. Specifically, the quantitative data extracted (before and after SFR) included the following:

1. Anthropometrics/ body composition: body mass index (BMI), fat mass (FM), lean body mass (LBM), and waist circumference (WC).
2. Serum adipokines: leptin, adiponectin, and resistin.
3. Markers of glucose homeostasis: fasting blood glucose (FBG), fasting insulin, and homeostatic model assessment for insulin resistance (HOMA-IR).
4. Inflammatory cytokines: tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP).
5. Lipid profile: low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (TG), total cholesterol (TC), and free fatty acids (FFA).
6. Blood pressure: systolic blood pressure (SBP) and diastolic blood pressure (DBP).

Other metabolic variables that were reported in less than 5 studies were excluded, such as waist–hip ratio, body fat percentage, free FM, bone mineral content, IL-10, 2-hour postprandial glucose, very low-density lipoprotein-cholesterol, whole-body glucose disposal, glucose oxidative metabolism, nonoxidative glucose metabolism, lipid oxidative metabolism, and glycerol.

Data extraction

Data were retrieved from all full-text articles by two authors. Where necessary, clarification was sought with the senior author (SD).

Statistical methods

To establish an "average" dose–response relationship between the outcome parameters (metabolic changes) and time based on the data of all available studies, the robust-error meta-regression (REMR) model was employed in this study.[16] This is a one-stage approach that treats each study as a cluster and uses robust error variance to address the potential correlations among the within-study effects as these effects share the same reference within the study. A nonlinear curve was fitted using restricted cubic splines with three knots. The Wald test was used to test potential nonlinearity by assuming the coefficient of the nonlinear terms was zero. All analyses were performed using the *remr* module in Stata version 15, College Station, TX, USA.

Results

The literature review yielded a total of 444 studies. Duplicate studies were excluded, leaving 258 studies, of which

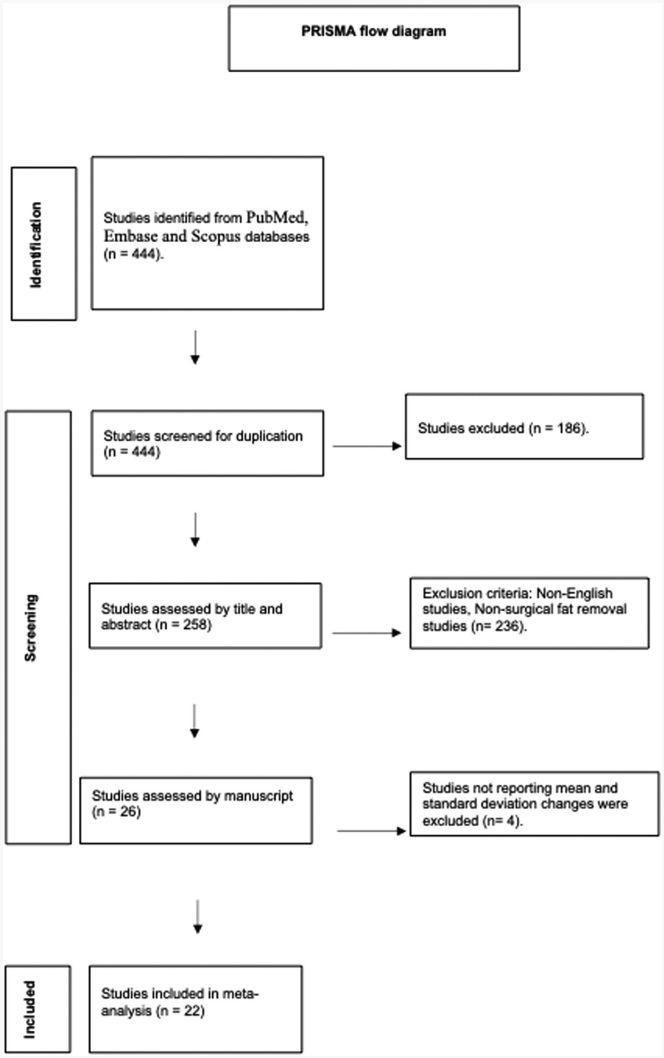


Figure 1 PRISMA flow diagram for selection of studies.

236 were excluded by abstract review. Eventually 22 studies with a total of 493 participants were selected as relevant to this synthesis.[17–38] The conduct of the literature review is summarized in Figure 1.

Characteristics of included studies

Characteristics of the selected studies are summarized in Table 1 and include study identifier, country, design, num-

Table 1 Characteristics of included studies.

Study	Country	Study design	No. of sub-jectss	Population (gender, age, comorbidities)	Baseline BMI (kg/m^2)	Type of SFR	Outcome measures	Follow-up time points (days)	Average fat mass (kg) or lipoaspirate (L) removed
Vinci et al., 2016	Italy	Case-control	13	-males - age (18-55) yrs	30.3 ± 3.06	abdomino-plasty	Adiponectin, IL6, CRP, TNF-a, FBG, LDL, HDL, TG, TC	0 40	NR
Gibas-dorna et al., 2016	Poland	Case-control	17	-males - age (37.15 ± 9.60) yrs —35% are diabetic type 2	29.16 ± 4.02	lipo-suction	BMI, WC, leptin, adiponectin, FBG, insulin, HOMA-IR	0 60 180	2.208 ± 0.562 L
Cuomo et al., 2015	Italy	Quasi-experiment	64	-females -age (32-48) yrs	33.44 ± 2.3	abdomino-plasty	Leptin, adiponectin, resistin, FBG, insulin, TG, TC	0 180 360	1.6 kg
Solis et al., 2014	Brazil	RCT	18	-females -age (20 —35) yrs	23.1 ± 1.6	lipo-suction	FM, LBM, leptin, adiponectin, IL6, TNF-a, FBG, insulin.	0 60 180	1.240 ± 0.363 L
Ramos-gallardo et al., 2013	Mexico	Quasi-experiment	26	-female -age (26 —56 yrs - all are dyslipidemic	27.4 ± 1.1	abdomino-plasty	BMI, FBG, insulin, HOMA-IR, LDL, HDL, TG, TC	0 90	1.7 kg
Benatti et al., 2012	Brazil	RCT	18	-females -ages (20-35) yrs	23.2 ± 1.3	lipo-suction	FM, LBM	0 60 180	1.240 ± 0.363 L
Yabarra et al., 2008	Spain	Quasi-experiment	20	—18 female —2 males -age (24 — 52 yrs	19.8 -36	lipo-suction	BMI, WC, adiponectin, CRP, FBG, insulin, HOMA-IR, LDL, HDL, TG, TC, FFA, SBP, DBP	0 120	5.494 ± 5.297 L
Mohammed et al., 2008	USA	Quasi-experiment	7	-females - 43% diabetic type 2	39± 2	lipo-suction	BMI, FM, FBG, HOMA-IR, LDL,HDL, TG, SBP, DBP	0 70 189	18 L
Robles-cervantes et al., 2007	Mexico	RCT	6	-females -age (30-40) yrs	31.9 ± 1.2	lipo-suction	Leptin, FBG, HDL, TG, TC	0 30	NR

(*continued on next page*)

Table 1 (*continued*)

Study	Country	Study design	No. of sub-jectss	Population (gender, age, comorbidities)	Baseline BMI (kg/m^2)	Type of SFR	Outcome measures	Follow-up time points (days)	Average fat mass (kg) or lipoaspirate (L) removed
Chang et al., 2007	USA	Quasi-experiment	15	-females -age (21 - 39) yrs	18- 25	lipo-suction	Leptin, adiponectin, IL6, CRP	0 1	NR
Martinez-abundis et al., 2007	Mexico	RCT	6	-females -age (20 - 50) yrs	30.7 ± 0.9	abdomino-plasty	Leptin, LDL, HDL, TG, TC	0 21	3.2 kg
Busetto et al., 2006	Italy	Quasi-experiment	15	- females -pre-menopausal	30.7 - 53.6	lipo-suction	FM,LBM, leptin, adiponectin, resistin, IL6, CRP, FBG, insulin, HOMA-IR, FFA	0 1 3 28 180	16.3 ± 4.3 L
Hong et al., 2006	Korea	Quasi-experiment	11	-age (19 —40) yrs	23.8 ± 4.4	lipo-suction	BMI, LDL, HDL, TC	0 60	6790 L
Andrea et al., 2005	Italy	Quasi-experiment	123	-females -age (32 - 40) yrs	32.8 ± 0.8	lipo-suction	BMI, leptin, adiponectin, resistin, IL6, TNF-a, FBG, insulin, HOMA-IR, TG, TC, FFA, SBP, DBP	0 21 90	4.984 ± 0.821 L
Rizzo et al., 2005	Italy	Quasi-experiment	20	-females -age (25-40) yrs	31·1 ± 0.7	abdomino-plasty	BMI, FM, leptin, adiponectin, resistin, IL6, TNF-a, FBG, insulin, TG, TC, FFA, SBP, DBP	0 40	2·3 ± 0·2 kg
Davis et al., 2005	USA	Quasi-experiment	15	-females -age (23-45) yrs	25-35	lipo-suction	BMI, leptin, adiponectin, IL6, TNF-a, FBG, insulin, HOMA-IR, TG, FFA	0 1 30	1.88 ± 0.213 L

(*continued on next page*)

Table 1 (*continued*)

Study	Country	Study design	No. of sub-jectss	Population (gender, age, comorbidities)	Baseline BMI (kg/m^2)	Type of SFR	Outcome measures	Follow-up time points (days)	Average fat mass (kg) or lipoaspirate (L) removed
Klein et al., 2004	USA	Quasi-experiment	15	-females —46% diabetic type 2	nonDM 35.1 ± 2.4, DM 39.9 ± 5.6	lipo-suction	BMI, WC, FM, leptin, adiponectin, IL6, CRP, TNF-a, FBS, insulin, LDL, HDL, TG, TC, SBP, DBP	0 84	17±2
Robles-cervantes et al., 2004	Mexico	Quasi-experiment	15	-females -age (28.8) yrs	26.35	lipo-suction	BMI, FBG, insulin, HOMA-IR, TC	0 21	3.570 ± 1.543 L
Esposito et al., 2004	Italy	Quasi-experiment	45	-females -pre-menopausal	35.1 ± 2.9	lipo-suction	BMI, WC, adiponectin, HOMA-IR, TG, TC	0 90 180	NR
Gonzalez-Ortiz et al., 2002	Mexico	RCT	6	-females -age (20 - 40) yrs	31.7 ± 1.7	lipo-suction	BMI, FBG, insulin, LDL, HDL, TG, TC	0 28	4.308 ± 1.126 L
Chen et al., 2001	China	Case series	4	-females - age (34.0 ± 3.7) yrs.	23.6 - 42.7	lipo-suction	leptin	0 1 2 14	range 1.25 - 12.78 L
Enzi 1979	Italy	Quasi-experiment	14	—12 females - 2 males -age (34—58) - all are diabetic type 2	34.5	abdomino-plasty	FM, FBG, TG	0 30	6.0 ± 0.5 kg

RCT; randomized controlled trial. *BMI*; body mass index. *FM*; fat mass. *LBM*; lean body mass. *WC*; waist circumference. *TNF-α*; tumor necrosis factor-alpha. *CRP*; C-reactive protein. *IL6*; interleukin 6. *FBG*; fasting blood glucose. *HOMA-IR*; homeostatic model assessment for insulin resistance. *SBP*; systolic blood pressure. *DBP*; diastolic blood pressure. *LDL*; low-density lipoprotein cholesterol. *HDL*; high-density lipoprotein cholesterol. *TC*; total cholesterol. *FFA*; free fatty acids. *L*; liters. *NR*; not reported.

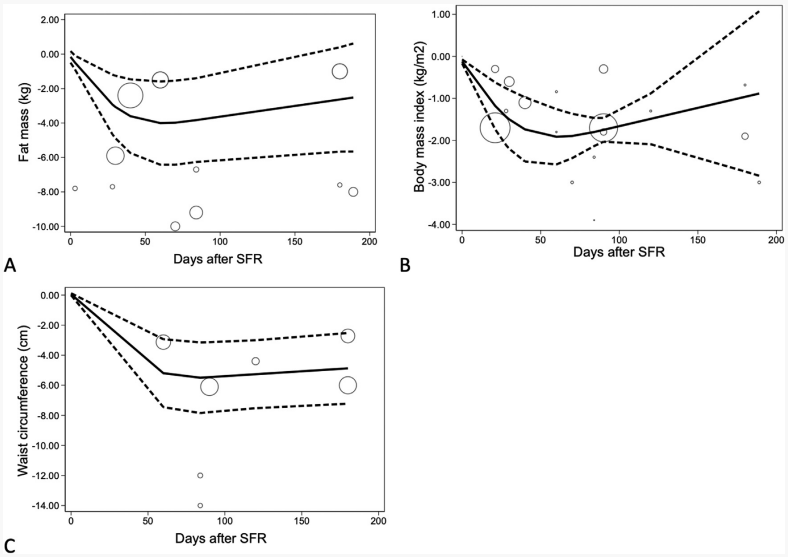


Figure 2 Changes in (A) body mass index, (B) fat mass, and (C) waist circumference over time since surgical fat removal (SFR). The "dose" is time in days after surgical fat removal (SFR). The circles represent the weighted mean difference in each individual study at this time point, with the marker size reflecting the weight of the corresponding study.

ber of participants (sample size), population demographics, preoperative (baseline) BMI, type of SFR (abdominoplasty versus liposuction), follow-up time points after surgery (in days), and FM (in kg) removed in abdominoplasty or lipoaspirate (in liters) (which consists of infiltrated solution plus removed FM) in liposuction procedures.

Metabolic changes after SFR

Anthropometrics/body composition

BMI (kg/m^2), FM (kg), WC (cm), and LBM (kg) were measured. There was significant heterogeneity in BMI and FM changes across studies; however, the DRMA suggested that postsurgical weight reduction was maximal at fifty days (2 BMI units and 3 kg of FM, respectively), after which there was a return toward the average presurgical weight (Figure 2). Because of the paucity of studies, confidence intervals were wide and the trend could not be confirmed more precisely as this was driven by the bigger studies. Nevertheless, the effect of SFR on BMI and related parameters persisted for at least 50 days. The WC showed a clear reduction of around 5 cm after surgery, which was maintained till the end of follow-up. LBM showed no significant change after SFR.

Serum adipokines

Serum leptin (μg/L), adiponectin (μg/ml), and resistin (μg/L) were measured before and after SFR. Leptin exhibited a significant postoperative reduction that peaked at

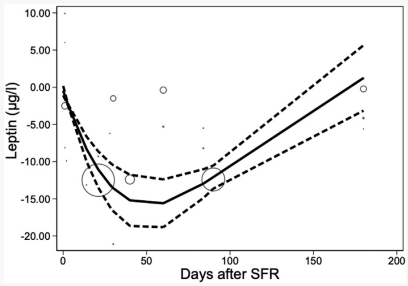


Figure 3 Changes in leptin over time since SFR. The "dose" is time in days after surgical fat removal (SFR). The circles represent the weighted mean difference in each individual study at this time point, with the marker size reflecting the weight of the corresponding study.

postoperative day 50 (average of 15 μg/L) and returned to preoperative levels by day 180 (Figure 3). The DRMA yielded no significant differences in serum adiponectin and resistin over time.

Markers of glucose homeostasis

FBG (mmol/L), fasting insulin (pmol/L), and HOMA-IR levels were measured. The DRMA suggested that postsurgical

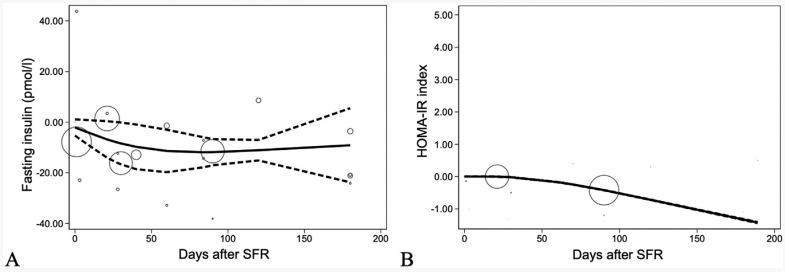


Figure 4 Changes in (A) fasting insulin and (B) homeostasis model assessment for insulin resistance (HOMA-IR) over time since SFR. The "dose" is time in days after surgical fat removal (SFR). The circles represent the weighted mean difference in each individual study at this time point, with the marker size reflecting the weight of the corresponding study.

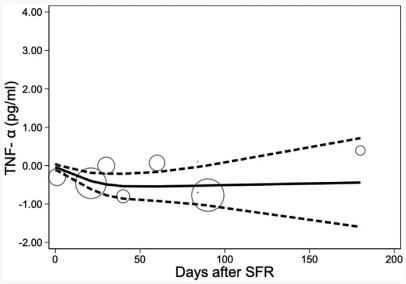


Figure 5 Changes in tumor necrosis factor-alpha (TNF-α) over time since SFR. The "dose" is time in days after surgical fat removal (SFR). The circles represent the weighted mean difference in each individual study at this time point, with the marker size reflecting the weight of the corresponding study.

insulin resistance reduction was a lasting feature of SFR for the duration of the study. Peak reductions were 17 pmol/L and 1 point for fasting insulin and HOMA-IR, respectively. There was no change seen with FBG (Figure 4).

Inflammatory markers
TNF-α (pg/ml), IL-6 (pg/ml), and CRP (mg/L) were measured. While there was substantial heterogeneity across studies, the DRMA suggested that postsurgical reduction in serum TNF-α peaked at day 50 (0.75 pg/ml) and thereafter exhibited a return to presurgical levels (Figure 5). No significant differences were observed in serum levels of IL-6 or CRP over the course of the study.

Lipid profile
LDL cholesterol (mmol/L), HDL cholesterol (mmol/L), serum fasting TGs (mmol/L), TC (mmol/L), and FFA (g/L) were measured. Serum HDL increased post-surgically, peaking at day 50. However, by day 100, expression had returned to the baseline and thereafter continued to fall to the end of the study period at day 180. TC reduced by 0.25 mmol/L post-surgically to day 50; however, the trend thereafter is obscured by wide confidence intervals owing to the paucity of data (Figure 6). No significant differences were observed in serum levels of TG, LDL, and FFA.

Blood pressure
Following SFR, there was a mean reduction in both SBP and DBP of 3.5 mmHg by day 50, which thereafter exhibited a return to presurgical levels at day 180 (Figure 7).

Quality assessment of included studies

Most of the studies were ranked in the 4th quartile of the count of safeguards. Moreover, the most deficient standards across articles were equal ascertainment and equal prognosis. In contrast, equal implementation, equal recruitment, equal retention, sufficient analysis, and temporal precedence were found to be the least deficient standards. See Supplementary Figure 3.

Discussion

We examined the influence of SFR on body anthropometrics/body composition measurements, serum adipokines and inflammatory cytokines, glucose homeostasis, lipid profile, and blood pressure by means of a systematic review of clinical data and subjected these data to DRMA. We observed that SFR resulted in a significant and lasting improvement in insulin resistance as evidenced by serum fasting insulin and HOMA-IR index and transient improvements in BMI, FM, SBP, and DBP and in serum leptin, TNF-α, HDL, and TC concentrations. There were no observable improvements in LBM, serum adiponectin, resistin, IL-6, CRP, LDL, FFA, or FBG.

Weight loss after SFR peaked at day 50 post-surgery, but thereafter weight gain was observed with BMI and FM, returning to near-preoperative levels after a period of 6 months. This might be because of the loss of the negative energy balance after surgery, or increased energy intake, particularly if it was not accompanied by physical exercise after SFR.[9,12] Another possibility is that this return toward baseline has an underlying hormonal basis such as residual

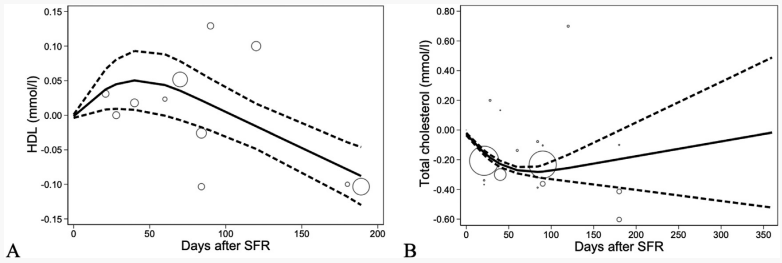


Figure 6 Changes in (A) high-density lipoprotein (HDL) cholesterol and (B) total cholesterol over time since SFR. The circles represent the weighted mean difference in each individual study at this time point, with the marker size reflecting the weight of the corresponding study.

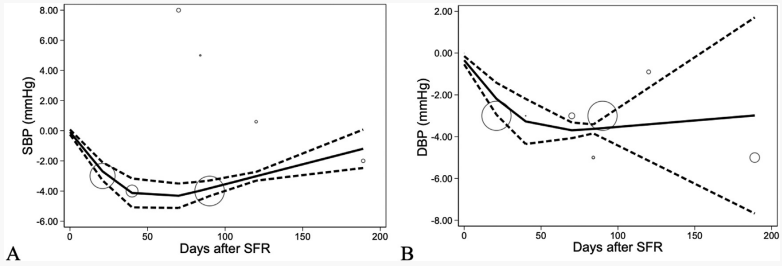


Figure 7 Changes in (A) systolic blood pressure (SBP) and (B) diastolic blood pressure (DBP) over time since SFR. The "dose" is time in days after surgical fat removal (SFR). The circles represent the weighted mean difference in each individual study at this time point, with the marker size reflecting the weight of the corresponding study.

fat cells hypertrophy.[39–41] This has also been noted in similar animal studies, where surgical fat reduction was followed after weeks to months by a compensatory increase in the FM elsewhere.[42,43] Using dual-energy x-ray absorptiometry scans and magnetic resonance imaging, a clinical trial observed compensatory abdominal FM deposition in a 12-month period after thigh liposuction.[44] Other retrospective human studies reported an increase in breast size after abdomen and thigh liposuction surgeries, which was postulated to be due to an altered ratio of androgen-to-estrogen levels,[39–41] but this may not be the only explanation.

Leptin was the only hormone derived from adipose tissue that exhibited an expression pattern altered by SFR. This was similar to the findings of a meta-analysis on the effect of large-volume liposuction on serum leptin and adiponectin levels. In this study, too, leptin, but not adiponectin, was reduced after SFR. Because leptin is secreted mainly from fat cells and correlates with FM,[45] the transient fall in serum leptin levels is understood in the context of the postsurgical reduction in FM. More interestingly, we may speculate that the rebound rise in serum leptin to presurgical levels may involve hypersecretion and/or hypertrophy by the residual FM.[39–41] The physiological adaptation underpinning this phenomenon remains obscure, but the fact that the postsurgical BMI mirrors the postsurgical temporal expression profile of leptin (which governs satiety) suggests a homeostatic mechanism.

There is no clear relationship in the literature between SFR and variations in the expression profiles of the inflammatory cytokines TNF-α and IL-6.[9,11,46] That said, the transient reduction in serum TNF-α identified in this study has been observed before.[46] Compared with leptin, the synthesis of TNF-α occurs mainly in the monocyte lineage.[47] The accumulation of resident macrophages in the adipose tissue correlates with the degree of obesity.[48,49] Animal models suggest that in morbid obesity, macrophages (responsible for most of the overall secretion of TNF-α) may account for up to 40% of the cellular mass of adipose tissue.[50] Our analysis suggests that SFR-mediated removal of the resident macrophages in the adipose tissue results in the initial reduction in TNF-α levels. The underlying mechanisms for the recovery in TNF-α level after the first two months of the SFR remain unclear. However, toll-like receptors-induced synthesis of TNF-α from existing resident macrophages and/or through recruitment of circulating myeloid-derived blood monocytes that give rise to adipose tissue-resident macrophages are potential pathways for TNF-α recovery.

Accumulation of adipose tissue-resident macrophages is facilitated by IL-6 secreted from adipocyte, and obesity is associated with elevated circulating IL-6 levels.[51,52] During the inflammatory phase, macrophages promote the return to homeostasis by removing apoptotic cells and cell debris and contributing to damage repair.[53] Circulating IL-6 plays an important role in mediating inflammation and is a central stimulus for the acute-phase inflammation response.[54] Our analysis found no significant changes in serum IL-6 and CRP (a known marker for acute inflammation), suggesting the absence of systemic inflammatory response after SFR. IL-6 stimulates CRP synthesis in the liver,[55] and, thus, the stable serum CRP level after SFR is consistent with a stable IL-6 level for the same period. Our analysis could not exclude the possibility of an increase in IL-6 levels at the surgery site.

Several syntheses have examined the changes in insulin sensitivity after SFR, and a trend toward improvement in insulin sensitivity has been described without elucidation of the magnitude of effect or clinical significance thereof.[8–11] Moreover, results were inconsistent because of the heterogeneity in the design and analysis of studies. The present synthesis demonstrates a gradual and steady decrease in the fasting insulin, which reaches an average decline of 17 pmol/L by 6 months. The HOMA-IR showed a similar trend with a 1-unit reduction by 6 months. There have so far been reports of more accurate measurements for insulin sensitivity, such as the oral glucose tolerance test.[56] Interestingly, the return of BMI toward baseline after 50 days, as shown above, was not coupled with a similar return in insulin sensitivity toward baseline values. This finding may reflect extra-abdominal postsurgical fat deposition, which might be less harmful.[57]

There is a strong positive relationship between body mass and blood pressure. A reduction in body mass of between 5 and 10% can reduce blood pressure in both hypertensive and normotensive cohorts.[58] Indeed, a reduction of 1 kg of body mass in obese patients results in a sustained decrease of 1.2 mmHg and 1 mmHg in SBP and DBP, respectively.[59] Additionally, chronic hyperleptinemia as seen among the obese population is also correlated with blood pressure.[60] Loss-of-function mutations in leptin and leptin receptors are associated with decreased blood pressure despite severe obesity.[61] The effect of leptin is mediated by the neurons in the dorsomedial hypothalamus. Inhibiting leptin receptor-expressing neuronal activity in the hypothalamus leads to a rapid decrease in blood pressure in obese mice, independent of changes in body mass.[61] In this study, the correlation between postsurgical blood pressure and serum leptin may be understood in these terms.

Subcutaneous FM plays a causative role in obesity-linked dyslipidemia.[62] Thus, SFR may have a positive effect on lipid profile,[38] particularly in the absence of morbid obesity.[63] However, the present study failed to demonstrate a clinically significant clear correlation between SFR and postsurgical lipid profile.

Several small and heterogeneous studies have measured changes in body composition, adipokines, and inflammatory marker,[17–38] and have been followed by systematic reviews and meta-analyses in an attempt to examine the effect of SFR on body metabolism. Only one synthesis looked at these changes in terms of time since surgery,[12] but even then, the latter study only reported the differences in physical biometrics such as body weight and FM. The remaining syntheses combined several heterogeneous studies with different follow-up durations,[8–11] resulting in contradicting and unclear conclusions regarding the metabolic benefit or harm of SFR. The ideal approach to the synthesis of the existing body of evidence required a DRMA because this is the only way to reduce the existing clinical heterogeneity.

A major limitation of this study is the small number of eligible studies, many of which had recruited a small number of patients. Thus, when the margin for error was taken into consideration, few obvious trends emerged. While we considered the inclusion of different types of SFR to be a strength of our meta-analysis, it is possible that the technical differences of each approach bequeathed unique and dissimilar physiological legacies on the patient that manifest as different changes in postsurgical metabolic parameters. For example, abdominoplasty surgery for obesity or weight loss often includes, as an operative step, correction of divarication of the rectus muscles. This, in turn, results in an increase in the abdominal pressure, myocardial preload, and compresses visceral fat.[64] It is clear from the synthesis that metabolic changes after SFR need further study in a well-designed prospective design, and this in turn will help us not only to identify the changes and the safety of these procedures but also broaden our knowledge about the metabolic effects of obesity.

Conclusion

This study shows that body contouring surgery correlates with enhanced insulin sensitivity for at least 6 months after surgery. Transient benefits were observed in BMI, blood pressure, serum leptin, and TNF-α. An evaluation of the metabolic benefits of body contouring surgery beyond 6 months is hampered by lack of data.

Conflict of interest

The authors declare no competing interests.

Funding

This project was supported by the Medical Research Office at Hamad Medical Corporation (#01-20-466) and the Qatar National Research Fund (projects #NPRP13S-0209-200315 and #NPRP14S-0406-210153). The responsibility for the article lies with the authors, and there was no influence of the funder.

Category

Meta-analysis.

Declaration

This article has not previously been presented at any national or international meeting.

Ethical Approval

Not required.

Acknowledgement

The authors thank Tawanda Chivese, Chang Xu, and the Department of Plastic Surgery at Hamad General Hospital for their contribution to this article. Data, analytic methods, and study materials could be available to other researchers by contacting the corresponding author.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.bjps.2022.10.055.

References

1. Hurt RT, Kulisek C, Buchanan LA, McClave SA. The obesity epidemic: challenges, health initiatives, and implications for gastroenterologists. *Gastroenterol Hepatol* 2010;**6**:780.
2. Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K, et al. Bariatric surgery: a systematic review and meta-analysis. *JAMA* 2004;**292**:1724–37.
3. Borud LJ, Warren AG. Body contouring in the postbariatric surgery patient. *J Am Coll Surg* 2006;**203**:82–93.
4. Almutairi K, Gusenoff JA, Rubin JP. Body contouring. *Plast Reconstr Surg* 2016;**137** 586e–602e.
5. Enzi G, Gasparo M, Raimondo Biondetti P, Fiore D, Semisa M, Zurlo F. Subcutaneous and visceral fat distribution according to sex, age, and overweight, evaluated by computed tomography. *Am J Clin Nutr* 1986;**44**:739–46.
6. Coelho M, Oliveira T, Fernandes R. Biochemistry of adipose tissue: an endocrine organ. Archives of Medical Science:. *Arch Med Sci* 2013;**9**:191.
7. Nguyen NT, Varela JE. Bariatric surgery for obesity and metabolic disorders: state of the art. *Nat Rev Gastroenterol Hepatol* 2016;**14**:160-9 2017 14:3.
8. Seretis K, Goulis DG, Koliakos G, Demiri E. The effects of abdominal lipectomy in metabolic syndrome components and insulin sensitivity in females: a systematic review and meta-analysis. *Metab Clin Exp* 2015;**64**:1640–9.
9. Sailon AM, Wasserburg JR, Kling RR, Pasick CM, Taub PJ. Influence of large-volume liposuction on metabolic and cardiovascular health: a systematic review. *Ann Plast Surg* 2017;**79**:623–30.
10. Boriani F, Villani R, Morselli PG. Metabolic effects of large-volume liposuction for obese healthy women: a meta-analysis of fasting insulin levels. *Aesthetic Plast Surg* 2014;**38**:1050–6.
11. Danilla S, Longton C, Valenzuela K, Cavada G, Norambuena H, Tabilo C, et al. Suction-assisted lipectomy fails to improve cardiovascular metabolic markers of disease: a meta-analysis. *J Plast Reconstr Aesthet Surg* 2013;**66**:1557–63.
12. Seretis K, Goulis DG, Koliakos G, Demiri E. Short- and long-term effects of abdominal lipectomy on weight and fat mass in females: a systematic review. *Obes Surg* 2015;**25**:1950–8.
13. Clark JM, Sanders S, Carter M, Honeyman D, Cleo G, Auld Y, et al. Improving the translation of search strategies using the Polyglot Search Translator: a randomized controlled trial. *J Med Libr Assoc* 2020;**108**:195–207.
14. Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, Thomas J. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane Database Syst Rev* 2019;**10**(ED000142).
15. Stone JC, Glass K, Clark J, Ritskes-Hoitinga M, Munn Z, Tugwell P, Doi SA. The MethodologicAl STandards for Epidemiological Research (MASTER) scale demonstrated a unified framework for bias assessment. *J Clin Epidemiol* 2021;**134**:52–64.
16. Xu C, Doi SA. The robust error meta-regression method for dose-response meta-analysis. *Int J Evid Based Healthc* 2018;**16**:138–44.
17. Busetto L, Bassetto F, Zocchi M, Zuliani F, Nolli ML, Pigozzo S, et al. The effects of the surgical removal of subcutaneous adipose tissue on energy expenditure and adipocytokine concentrations in obese women. Nutrition, metabolism, and cardiovascular diseases:. *Nutr Metab Cardiovasc Dis* 2008;**18**:112–20.
18. D'Andrea F, Grella R, Rizzo MR, Grella E, Grella R, Nicoletti G, et al. Changing the metabolic profile by large-volume liposuction: a clinical study conducted with 123 obese women. *Aesthetic Plast Surg* 2005;**29**:472–8.
19. Klein S, Fontana L, Young VL, Coggan AR, Kilo C, Patterson BW, et al. Absence of an effect of liposuction on insulin action and risk factors for coronary heart disease. *N Engl J Med* 2004;**350**:2549–57.
20. Ramos-Gallardo G, Pérez Verdin A, Fuentes M, Godínez Gutiérrez S, Ambriz-Plascencia AR, González-García I, et al. Effect of abdominoplasty in the lipid profile of patients with dyslipidemia. *Plast Surg Int* 2013;**2013**:1–5.
21. Yazigi Solis M, Artioli GG, Montag E, de Salles Painelli V, Saito FL, Lima FR, et al. The liposuction-induced effects on adiponectin and selected cytokines are not affected by exercise training in women. *Int J Endocrinol* 2014;**2014**.
22. González-Ortiz M, Robles-Cervantes JA, Cárdenas-Camarena L, Bustos-Saldaña R, Martínez-Abundis E. The effects of surgically removing subcutaneous fat on the metabolic profile and insulin sensitivity in obese women after large-volume liposuction treatment. *Horm Metab Res* 2002;**34**:446–9.
23. Rizzo MR, Paolisso G, Grella R, Barbieri M, Grella E, Ragno E, et al. Is dermolipectomy effective in improving insulin action and lowering inflammatory markers in obese women? *Clin Endocrinol* 2005;**63**:253–8.
24. Gibas-Dorna M, Szulińska M, Turkowski P, Kupsz J, Sowińska A, Mikrut K, et al. The effect of VASER abdominal liposuction on metabolic profile in overweight males. *Am J Mens Health* 2017;**11**:284–93.
25. Benatti F, Solis M, Artioli G, Montag E, Painelli V, Saito F, et al. Liposuction induces a compensatory increase of visceral fat which is effectively counteracted by physical activity: a randomized trial. *J Clin Endocrinol Metab* 2012;**97**:2388–95.
26. Martínez-Abundis E, Molina-Villa CA, González-Ortiz M, Robles-Cervantes JA, Saucedo-Ortiz JA. Effect of surgically removing subcutaneous fat by abdominoplasty on leptin concentrations and insulin sensitivity. *Ann Plast Surg* 2007;**58**:416–19.
27. Robles-Cervantes JA, Yánez-Diaz S, Cárdenas-Camarena L. Modification of insulin, glucose and cholesterol levels in nonobese women undergoing liposuction: is liposuction metabolically safe? *Ann Plast Surg* 2004;**52**:64–7.
28. Esposito K, Giugliano G, Giugliano D. Metabolic effects of liposuction—yes or no. *N Engl J Med* 2004;**351**(13):1354–7.
29. Chen MD, Ou LF, Song YM. Postoperative plasma leptin levels in women undergoing suction lipectomy. *Mayo Clin Proc* 2001;**76**:1177–8.
30. Robles-Cervantes JA, Martínez-Abundis E, González-Ortiz M, Cárdenas-Camarena L, Hernández-Salazar E, Olvera-Ozuna R. Behavior of insulin sensitivity and its relation to leptin and tumor necrosis factor-alpha in obese women undergoing liposuction: 6-month follow-up. *Obes Surg* 2007;**17**:1242–7.

31. Enzi G, Cagnoni G, Baritussio A, de Biasi F, Favaretto L, Inelmen EM, et al. Effects of fat mass reduction by dieting and by lipectomy on carbohydrate metabolism in obese patients. *Acta Diabetol Lat* 1979;**16**:147–56.
32. Chang PY, Wu TL, Tsao KC, Sun CF, Wu LL, Wu JT. Cosmetic liposuction causes only transient elevation of acute inflammatory response and does not advance to oxidative and nitrosative stress. *J Clin Lab Anal* 2007;**21**:418–25.
33. Davis DA, Pellowski DM, Davis DA, Donahoo WT. Acute and 1-month effect of small-volume suction lipectomy on insulin sensitivity and cardiovascular risk. *Int J Obes* 2006;**30**:1217–22.
34. Vinci V, Valaperta S, Klinger M, Montanelli A, Specchia C, Forcellini D, et al. Metabolic implications of surgical fat removal: increase of adiponectin plasma levels after reduction mammaplasty and abdominoplasty. *Ann Plast Surg* 2016;**76**:700–4.
35. Mohammed BS, Cohen S, Reeds D, Young VL, Klein S. Long-term effects of large-volume liposuction on metabolic risk factors for coronary heart disease. *Obesity* 2008;**16**:2648–51.
36. Hong YG, Kim HT, Seo SW, Chang CH, Rhee EJ, Lee WY. Impact of large-volume liposuction on serum lipids in orientals: a pilot study. *Aesthetic Plast Surg* 2006;**30**:327–32.
37. Cuomo R, Russo F, Sisti A, Nisi G, Grimaldi L, Brandi C, D'Aniello C. Abdominoplasty in mildly obese patients (BMI 30-35kg/m2): metabolic, biochemical and complication analysis at one year. *In Vivo* 2015;**29**(6):757–61.
38. Ybarra J, Blanco-Vaca F, Fernández S, Castellví A, Bonet R, Palomer X, et al. The effects of liposuction removal of subcutaneous abdominal fat on lipid metabolism are independent of insulin sensitivity in normal-overweight individuals. *Obes Surg* 2008;**18**:408–14.
39. Yun PL, Bruck M, Felsenfeld L, Katz BE. Breast enlargement observed after power liposuction: a retrospective review. *Dermatol Surg: Off Public Am Soc Dermatol Surg* 2003;**29**:165–7.
40. Lei BVD, Halbesma GJ, Nieuwenhoven CAV, Wingerden JJW. Spontaneous breast enlargement following liposuction of the abdominal wall: does a link exist? *Plast Reconst Surg* 2007;**119**:1584–9.
41. Frew KE, Rossi A, Bruck MC, Katz BE, Narins RS. Breast enlargement after liposuction: comparison of incidence between power liposuction versus traditional liposuction. *Dermatol Surg: Off Public Am Soc Dermatol Surg* 2005;**31**:292–6.
42. Hausman DB, Lu J, Ryan DH, Flatt WP, Harris RBS. Compensatory growth of adipose tissue after partial lipectomy: involvement of serum factors. *Exp Biol Med* 2004;**229**(6):512–20.
43. Mauer MM, Harris RB, Bartness TJ. The regulation of total body fat: lessons learned from lipectomy studies. *Neurosci Biobehav Rev* 2001;**25**:15–28.
44. Hernandez TL, Kittelson JM, Law CK, Ketch LL, Stob NR, Lindstrom RC, et al. Fat redistribution following suction lipectomy: defense of body fat and patterns of restoration. *Obesity* 2011;**19**:1388–95.
45. Zhng Y, Scarpace PJ. The role of leptin in leptin resistance and obesity. *Physiol Behav* 2006;**88**:249–56.
46. Crahay FX, Nizet JL. Metabolic and cardiovascular consequences of suction-assisted lipectomy: systematic review. *Ann Chir Plast Esthet* 2016;**61**:270–86.
47. Parameswaran N, Patial S. Tumor necrosis factor-α signaling in macrophages. *Crit Rev Eukaryot Gene Expr* 2010;**20**:87–103.
48. Fantuzzi G. Adipose tissue, adipokines, and inflammation. *J Allergy Clin Immunol* 2005;**115**:911–19.
49. Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. *Nat Rev Immunol* 2006;**6**:772–83.
50. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest* 2003;**112**:1796–808.
51. Mohamed-Ali V, Goodrick S, Rawesh A, Katz DR, Miles JM, Yudkin JS, et al. Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alpha, in vivo. *J Clin Endocrinol Metab* 1997;**82**:4196–200.
52. Han MS, White A, Perry RJ, Camporez JP, Hidalgo J, Shulman GI, et al. Regulation of adipose tissue inflammation by interleukin 6. *Proc Natl Acad Sci USA* 2020;**117**:2751–60.
53. Lucas T, Waisman A, Ranjan R, Roes J, Krieg T, Müller W, et al. Differential roles of macrophages in diverse phases of skin repair. *J Immunol* 2010;**184**:3964–77.
54. Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. *Cold Spring Harb Perspect Biol* 2014;**6**(10):a016295.
55. Castell JV, Gómez-Lechón MJ, David M, Andus T, Geiger T, Trullenque R, et al. Interleukin-6 is the major regulator of acute phase protein synthesis in adult human hepatocytes. *FEBS Lett* 1989;**242**:237–9.
56. Mari A, Pacini G, Brazzale AR, Ahrén B. Comparative evaluation of simple insulin sensitivity methods based on the oral glucose tolerance test. *Diabetologia* 2005;**48**:748–51.
57. Amati F, Pennant M, Azuma K, Dubé JJ, Toledo FGS, Rossi AP, et al. Lower thigh subcutaneous and higher visceral abdominal adipose tissue content both contribute to insulin resistance. *Obesity* 2012;**20**:1115–17.
58. Mertens IL, van Gaal LF. Overweight, obesity, and blood pressure: the effects of modest weight reduction. *Obes Res* 2000;**8**:270–8.
59. Stassen J, Fagard R, Amery A. The relationship between body weight and blood pressure. *J Hum Hypertens* 1988;**2**:207–17.
60. Bełtowski J. Role of leptin in blood pressure regulation and arterial hypertension. *J Hypertens* 2006;**24**:789–801.
61. Simonds SE, Pryor JT, Ravussin E, Greenway FL, Dileone R, Allen AM, et al. Leptin mediates the increase in blood pressure associated with obesity. *Cell* 2014;**159**:1404.
62. Rydén M, Arner P. Subcutaneous adipocyte lipolysis contributes to circulating lipid levels. *Arterioscler Thromb Vasc Biol* 2017;**37**:1782–7.
63. Swanson E. The clinical relevance of lower triglyceride and leukocyte levels after liposuction. *Plast Reconst Surg* 2012;**129**(5) 846e–847e.
64. Huang GJ, Bajaj AK, Gupta S, Petersen F, Miles DAG. Increased intraabdominal pressure in abdominoplasty: delineation of risk factors. *Plast Reconst Surg* 2007;**119**:1319–25.

Journal of Plastic, Reconstructive & Aesthetic Surgery 77 (2023) 68–77

JPRAS
An International Journal of Surgical Reconstruction
www.JPRASurg.com

Review

Metabolic changes after nonsurgical fat removal: A dose response meta-analysis

Saif Badran[a,b], **Suhail A. Doi**[b], **Sara Iskeirjeh**[c], **Ghanem Aljassem**[d], **Nasrin Jafarian**[d], **Justin Clark**[e], **Abdella M. Habib**[b], **Graeme E. Glass**[f,g,*]

[a] *Division of Plastic and Reconstructive Surgery, Washington University, St. Louis, MO, USA*
[b] *College of Medicine, QU Health, Qatar University, Doha, Qatar*
[c] *College of Medicine and Public Heath, Flinders University, Adelaide, SA*
[d] *Department of Plastic Surgery, Hamad General Hospital, Doha, Qatar*
[e] *Institute for Evidence-Based Healthcare, Faculty of Health Sciences & Medicine, Bond University, Queensland, SA, Australia*
[f] *Weill Cornell Medicine Qatar, Qatar Foundation, Doha, Qatar*
[g] *Department of Surgery, Sidra Medicine, Doha, Qatar*

Received 21 July 2022; accepted 26 October 2022

KEYWORDS
Cryolipolysis;
Laser lipolysis;
Radiofrequency ablation;
High intensity focused thermal ultrasound (HIFU);
BMI;
Lipid profile

Summary *Background:* Obesity-induced insulin resistance leads to the metabolic syndrome. Both bariatric surgery and surgical fat removal have been shown to improve metabolic health, but the metabolic benefits of nonsurgical fat removal remain uncertain. The aim of this paper is to establish whether nonsurgical fat removal exerts measurable, lasting metabolic benefits by way of changes to serum lipid profiles.
Methods: PubMed, Cochrane CENTRAL, Embase, and clinical trials registers were searched using the Polyglot Search Translator to find studies examining quantitative changes in metabolic markers after nonsurgical body contouring procedures. The MethodologicAl STandard for Epidemiological Research (MASTER) scale was adopted for the quality assessment of the included studies. The robust-error meta-regression (REMR) model was employed.
Results: Twenty-two studies and 676 participants were included. Peak body compositions measures manifest as a reduction of 2 units in body mass index (BMI), 1 kg of body weight (BW), 5 cm in waist circumference (WC) and 1.5 cm in abdominal fat thickness (FT), sustained up to 60 days postprocedure. Transient increases of 15 mg/dL in low-density lipoprotein (LDL), 10 mg/dl in triglycerides (TG), and 15 mg/dl in total cholesterol (TC) were observed at 2 weeks postprocedure.

* Corresponding author at: Department of Surgery, Sidra Medicine, Associate Professor of Clinical Surgery, Weill Cornell Medical College, New York, Qatar.
E-mail address: gglass@sidra.org (G.E. Glass).

https://doi.org/10.1016/j.bjps.2022.10.054

Conclusion: While nonsurgical fat removal exerts sustained effects on body anthropometrics, changes to serum lipid profiles were transient. There is no compelling evidence at present to support the conclusion that nonsurgical fat removal is metabolically beneficial.

Contents

Introduction

Obesity is a global health crisis and one of the principle causes of avoidable death in the developed world.[1] Chronic nutritional over sufficiency leads to adipocyte stress, upregulation of pro-inflammatory cytokines, recruitment of resident tissue macrophages, and, ultimately, local and systemic inflammatory dysregulation.[2] This pathophysiologic process exerts deleterious effects on insulin signal transduction[3] and is the crucial component of the metabolic syndrome.[4] Complications of the metabolic syndrome include atherosclerosis, hypertension, ischemic heart disease, liver disease, cancer, and susceptibility to respiratory infections, all of which have a basis in a common pathway of immune dysregulation.[5] There is some evidence to suggest that visceral fat is a key source of the cytokines (adipokines) that, collectively, induce insulin resistance.[6]

Reducing fat deposits through diet and exercise or by way of bariatric/metabolic surgery has observable, long-term immunologic and metabolic benefits.[7] More recently, it has been established that benefical effects can also be observed following surgical removal of subcutaneous fat by way of percutaneous avulsion and aspiration (liposuction) or by body contouring surgery such as abdominoplasty, belt lipectomy, brachioplasty, and bilateral breast reduction.[8,9] While these observations have not provided evidence of a magnitude or longevity of effect comparable with bariatric surgery, they have helped dispel the myth that body contouring surgery is merely an esthetic endeavor.

Nonsurgical fat removal is one of the fastest areas of growth and innovation within the aesthetics industry. Options include cryolipolysis, laser lipolysis, radiofrequency ablation, and high intensity focused thermal ultrasound (HIFU). While the mechanism of action of each method differs, the result is the focused elimination of subcutaneous fat in a noninvasive manner. The question of whether nonsurgical fat removal (NSFR) exerts measurable, beneficial metabolic benefits remains unclear. To answer this question, the current paper describes a systematic review and dose-response meta-analysis (DRMA) of observational studies pertaining to the metabolic impact of NSFR.

Methods

Search strategy

A search string was designed using relevant MeSH terms in PubMed, Cochrane CENTRAL, Embase databases, and online clinical trials registers using the Polyglot Search Translator.[10] The search strategy and used strings were designed and conducted by the first author (SB) and an experienced information specialist (JC) and were run across all databases on the 10th of March 2022. The search string included both

medical subject heading (MeSH) terms and free-text terms. The online trial registers were searched at *ClinicalTrials.gov* and the national research registers were examined as well for relevant trials relating to nonsurgical body contouring procedures targeting the abdominal area and body compositions, and physiological and/or metabolic changes.

The Cochrane Highly Sensitive Search Strategy guideline in the Cochrane Handbook for Systematic Reviews of Interventions was adopted during the search process.[11] The results were reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Full search strings for all databases and the PRISMA checklist are available in **Supplementary Figures 1 and 2**.

Inclusion criteria

Papers and trials were included if they provided quantitative data permitting analyses of the effect of nonsurgical body contouring procedures (Ultrasound, cryolipolysis, radiofrequency, and high intensity electromagnetic) on body compositions, physiology, and/or metabolism. Only human studies that target the abdominal areas were considered. No search restrictions for a date, language, or publication were applied.

Exclusion criteria

Nonhuman (*in vivo*) studies were excluded from consideration as were studies that targeted other anatomical areas (e.g., thighs and arms) and studies on surgical body contouring procedures (e.g., abdominoplasty).

Quality assessment

The quality assessment of the eligibly included articles was independently done by two reviewers (SB and NJ) utilizing the MethodologicAl STandard for Epidemiological Research (MASTER) scale.[12] This scale evaluates each included study against 36 safeguards across seven domains that, if present, may mitigate systematic error in the trial. The MASTER scale delivered a robust framework for assessing the methodological quality of the included quasi-experimental and randomized controlled trials in this paper.

Outcome measures

The outcome measures sought include two domains. These included body compositions/ anthropometrics and lipid profiles. Data units were unified to the Systeme International d'Unites (SI) units. The extracted quantitative data (before and after nonsurgical body contouring procedures) included the following markers:

1. Body compositions/ anthropometric: BMI, BW, WC, and abdominal FT.
2. Lipid profile: LDL, high-density lipoprotein (HDL), TG, and TC.

Other body measurements and physiological/metabolic variables that were reported in less than 5 studies were excluded such as other anthropometrics measurements (e.g., hip circumference), fasting glucose, fasting insulin, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), leptin, fatty acids, C-reactive protein, very-low density lipoprotein (VLDL), alanine aminotransferase (AST), and aspartate aminotransferase (ALT).

Data extraction

Studies screening and data collection were retrieved from all full-text articles by four authors (SB, SI, GA, and NJ). Where necessary, clarification was sought with the senior author (GG).

Statistical methods

An "average" dose-response relationship between the measured outcome parameters (body compositions and lipid profile) and time elapsed after the body contouring procedure was established using the robust-error meta-regression (REMR) model.[13] Which represents a one-stage approach that treats each study as a cluster. The robust error variance was used in order to address any possible correlations among the within-study effects because these effects share the same reference within the single study. A nonlinear curve was fitted using restricted cubic splines with three knots. The Wald test was used to test for potential nonlinearity by assuming the coefficient of the nonlinear terms was zero. All analyses were performed using the *remr* module in Stata version 15, College Station, TX, USA.

Results

The conducted literature review resulted in a total of 818 articles and 33 registered trials (a total of 851 studies). Duplicate studies (252 studies) were excluded leaving 599 studies, of which 534 were excluded by title and abstract. The remaining 65 studies were examined by manuscript, and 46 studies were excluded due to a lack of a clear statement of the metabolic changes magnitude and/or the precise time of assessment after surgery. Eventually, 19 studies with a total of 601 participants were selected as relevant to this synthesis.[14–32] The conduct of the literature review is summarized by the PRISMA flowchart in Figure 1.

Characteristics of included studies

Characteristics of the selected studies are summarized in Table 1 and include study identifier, country, design, number of participants (sample size), population demographics, preoperative (baseline) BMI, type of nonsurgical body contouring procedure (Ultrasound (HIFU), cryolipolysis, radiofrequency, and high intensity electromagnetic), outcome measures (BMI, BW, WC, FT, LDL, HDL, TG, and TC), and follow-up time points after surgery (in days).

Table 1 Characteristics of included studies.

Study number	Study identifier	Country/ Region	Study design	Number of subjects	Population demographics	Baseline BMI (kg/m2)	Procedure	Outcome measures	Follow up time points (days)
1	Brightman et al., 2009	USA	quasi-experiment	10	Age 28- 70 years, all females	NA	radiofrequency + laser	WC	0, 30, 90
2	Shek et al., 2009	China & Japan)	quasi-experiment	53	51 females and 2 males, age range 26 - 69 years	N/A	ultrasound	FT, WC	0, 30
3	Choi et al., 2018	Korea	quasi-experiment	24	21 females and 3 males, age 20 - 60 years	23.97 ± 2.64	radiofrequency	FT, WC	0, 28, 56
4	Shek et al., 2014	China	quasi-experiment	12	9 females and 3 males, age 27- 56 years	25.230 ± 2.0310	ultrasound (HIFU)	WC, WT	0, 28, 56, 84
5	Boisnic et al., 2014	France	quasi-experiment	21	all females, age 31- 59 years	N/A	radiofrequency	FT, WC, WT	0, 30, 90
6	Tonucci et al., 2014	Brazil	quasi-experiment	20	all females, ages 18-60 years	25.85 ± 4.07	ultrasound	BMI, TC, HDL, LDL, TG, WC, WT	0, 14
7	Katz et al., 2019	USA	quasi-experiment	33	age 21- 65 years	20.0 - 30.0	high intensity electromagnetic	FT	0, 30, 90
8	Hong et al., 2019	Korea	quasi-experiment	20	17 females, 3 males,	27.34 ± 6 1.82	ultrasound (HIFU)	FT	0, 28, 56
9	Fonsea et al., 2018	Brazil	quasi-experiment	31	Females, age 20-40 years	≥ 30.0	ultrasound	TC, HDL, LDL, TG	0, 10
10	Arabpour-Dahoue et al., 2019	Iran	RCT	25	50 females, age 35.32 ± 8.70 years, DM, hyperlipidemia	16.1 - 56.7	radiofrequency+ US	TC, HDL, LDL, TG	0, 1
11	Moreno-Moraga et al., 2007	Spain	quasi-experiment	10	22 females and 8male, age 18 - 62 years	N/A	ultrasound	WC	0, 1

(*continued on next page*)

Table 1 (*continued*)

Study number	Study identifier	Country/ Region	Study design	Number of subjects	Population demographics	Baseline BMI (kg/m2)	Procedure	Outcome measures	Follow up time points (days)
12	ELdesoky et al., 2015	Middle east	RCT	20	5 males and 15 females, age 34.1 ± 4.95 years	32.67± 0.91	ultrasound	BMI, FT, WC, WT	0, 60
13	ELdesoky et al., 2015	Middle east	RCT	20	6 males and 14 females, age 33.3 ± 5.33 years	32.4 ± 1.0	cryolipolysis	BMI, FT, WC, WT	0, 60
14	Katz et al., 2019	USA	quasi-experiment	33	mean age 40.8 years	20.0 to 30.0	high intensity electromagnetic	FT	0, 30, 90
15	Robinson et al., 2014	USA	quasi-experiment	118	males and females, median age: 45.2 years	24.7 ± 2.6	ultrasound	WT	0, 28, 56, 84
16	Solish et al., 2011	Canada	quasi-experiment	45	majority females, age 42 −44 years	25.0 - 27.0	ultrasound	WT	0, 28, 56, 84
17	Verner et al., 2021	Middle east	quasi-experiment	15	females, mean age 45.5 ± 5.0 years	≤26	ultrasound	WC	0, 7, 30, 84
18	Khedmatgozar et al., 2020	Iran	quasi-experiment	30	females, age 18-65	29.55 ± 3.08	cryolipolysis	BMI, WC, WT	0, 56
19	Khedmatgozar et al., 2020	Iran	quasi-experiment	30	females, age 18-65 years	30.43 ± 4.38	Ultrasound cavitation, cryolipolysis, and diet	BMI, WC, WT	0, 56
20	Dhillon et al., 2018	United Kingdom	quasi-experiment	20	17 females 3 males, mean age 37.6 ± 7.11 years	25.1 ± 3.80	ultrasound	WC	0, 90
21	Fritz et al., 2017	Germany	quasi-experiment	20	18 females, 2 males	25.78 ± 2.37	ultrasound	WT, WC	0, 30
22	Guth et al., 2017	Brazil	quasi-experiment	24	males, age 18- 59 years	≤ 30	ultrasound (HIFU)	TC, HDL, LDL, TG	0, 1
23	Fonseca et al., 2018	Brazil	quasi-experiment	31	Females, age 20-40 years	≥ 30.0	ultrasound	TC, HDL, LDL, TG	0, 10
24	Boisnic et al., 2014	France	quasi-experiment	21	age 31 −59 years	N/A	radiofrequency	FT, WC, WT	0, 30, 90

RCT; randomized controlled trial. *BMI*; body mass index. *FM*; fat mass. *LBM*; lean body mass. *WC*; waist circumference. *TNF- α*; tumor necrosis factor alpha. *CRP*; C - reactive protein. *IL6*; interteukin 6. *FBG*; fasting blood glucose. *HOMA-IR*; homeostatic model assessment for insulin resistance. *SBP*; systolic blood pressure. *DBP*; diastolic blood pressure. *LDL*; low-density lipoprotein cholesterol. *HDL*; high-density lipoprotein cholesterol. *TC*; total cholesterol. *FFA*; free fatty acids. *L*; liters. *NR*; not reported.

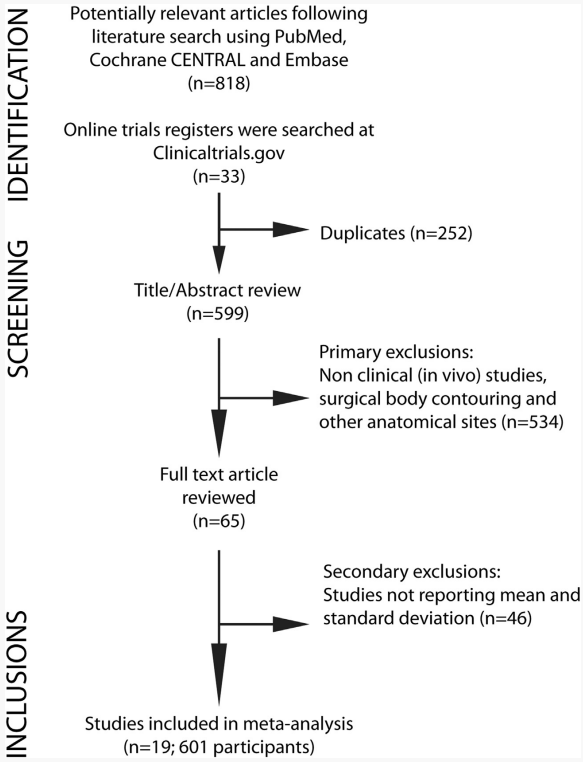


Figure 1 PRISMA flow diagram for selection of studies.

Metabolic changes after SFR

Anthropometrics / body compositions

Changes in (A) BMI, (B) BW, (C) WC, and (D) FT were measured over time in days since the body contouring procedure. A clear drop of 2 units in the BMI, 1 kg in the BW, 5 cm in WC, and 1.5 cm in abdominal FT was noted up to 60 days after the procedure. FT continued to decrease up to 90 days after the procedure. A moderate heterogeneity in the last three outcome variables was noted across studies, and the confidence intervals were wide due to the paucity of studies and the effect of bigger studies. However, the meta-analysis showed that the effect of body contouring procedures on BMI and related parameters persisted for at least 60 days. FT showed a clear continuous reduction up to 90 days after the procedure, see Figure 2**: A-D.**

Lipid profile

Changes in LDL, (B) HDL, (C) TG, and (D) TC were measured over time in days since the body contouring procedure. A serum increase of 15 mg/dL in LDL, 10 mg/dl in TG, and 15 mg/dl in TC was noted up to two weeks after the procedure. No significant change was noted in serum HDL. Due to the paucity of studies, confidence intervals were wide, and the trend could not be confirmed more precisely as this was driven by the bigger studies, see Figure 3**: A-D**.

Quality assessment of included studies

The majority of the included studies were ranked in the 4th quartile of the safeguards' count. Additionally, the most deficient safeguard standards were equal ascertainment and equal prognosis. On the other hand, the remaining standard safeguards were found to be less deficient. See **Supplementary Figure 3**.

Discussion

We examined the influence of nonsurgical body contouring procedures on body anthropometrics/ body composi-

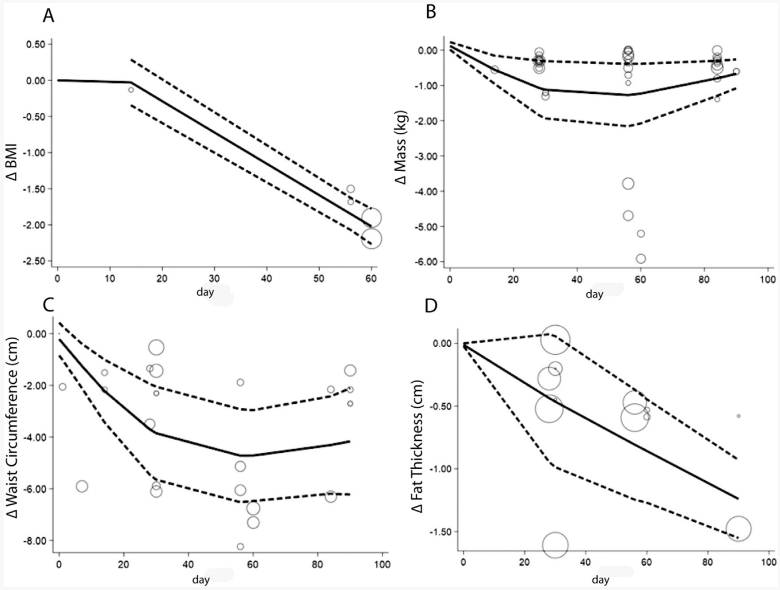


Figure 2 Change in (**A**) BMI, **(B**) BW, (**C**) WC, and **(D)** FT over time since body contouring procedure. The "dose" is time in days after the procedure. The circles represent the weighted mean difference in each individual study at this time point with the marker size reflecting the weight of corresponding study.

tion measurements and lipid profile using a systematic review of clinical data and subjected these data to a dose-response meta-analysis. Transient increases in serum LDLs, TG, and TC were observed up to two weeks following exposure to nonsurgical fat removal. In the longer term, no significant differences were observed. Anthropometric data confirmed a reduction in FT over the treated area, which persisted throughout the observation period (day 90). Taken as a whole, these data suggest that nonsurgical fat removal is efficacious, and that evidence of fat lysis may be inferred by transient rises in serum lipid profiles in the weeks following exposure to nonsurgical fat removal. However, no firm conclusions about the effect of nonsurgical fat removal on serum lipid profiles in the long term were permissible. This is in contrast to the results obtained when these analyses were performed for surgical fat removal. Here, the data confirmed that the surgical removal of fat by aspiration (liposuction) or excision (body contouring) resulted in favorable changes to the serum lipid profiles in the long term (Badran et al.- in press). Most likely, there were simply insufficient data to be able to conclude.

The preclinical and clinical evidence for favorable metabolic changes associated with cryolipolysis is variable. Using a porcine model, Kwon and colleagues[33] demonstrated that cryolipolysis was associated with a transient increase in serum TC, LDL and HDL cholesterol, and TG to day 30. By day 60, however, each had fallen below the baseline level. By day 90, serum LDL cholesterol was still below the baseline level. These observations were supported by a recently published study by Abdel-Aal et al.[34] involving 60 obese women randomized to receive a low-calorie diet for 3 months with or without 3 sessions of cryolipolysis. The group that received cryolipolysis demonstrated significant improvements in serum lipid profiles and liver enzymes relative to the control group. A study by Al Agamy et al.[35] comparing cryolipolysis with cold laser therapy observed a significant reduction in serum TG and a significant increase in serum HDL cholesterol following application of exposure to either device. This contrasts with the work of Klein and colleagues. In two separate studies of cryolipolysis of the flanks (40 patients)[36] and the abdomen and flanks (35 patients),[37] they reported no significant changes in serum lipid profiles over the timepoints studied. Similarly, a study of 50 patients by Ferraro et al.[38] exposed to cryolipolysis and extracorporeal shock wave therapy did not reveal any significant changes in serum lipid profile over 7 days. Clinical studies of lipolysis using high-intensity focused ultrasound (HIFU)[39,40] and radiofrequency failed to demonstrate significant changes in metabolic parameters after exposure. The transient nature of lipid profile variations observed in the current study was also observed in a preclinical study of laser lipolysis in pigs.[41]

The study raises several important questions about the role of nonsurgical fat removal as an endocrinological,

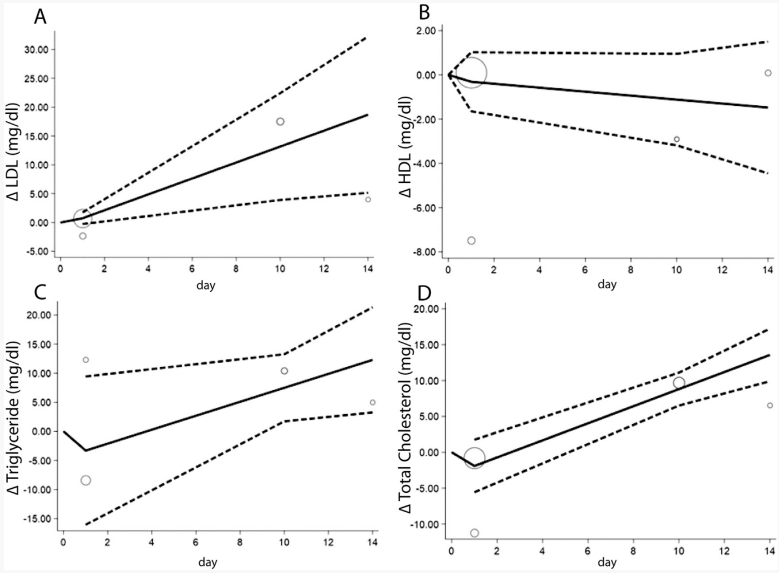


Figure 3 Change in (**A**) LDL, (**B**) HDL, (**C**) TG, and **(D)** TC over time since body contouring procedure The "dose" is time in days after the procedure. The circles represent the weighted mean difference in each individual study at this time point with the marker size reflecting the weight of corresponding study.

as opposed to purely esthetic, intervention. With a rising tide of obesity owing to calorie-rich diets and sedentary lifestyles, the desire for fat removal has fueled burgeoning surgical and nonsurgical aesthetics industries tailored to the pursuit of anthropometric ideals. Interestingly, however, these industries have neglected the potential health benefits of fat removal. Adipocytes regulate energy homeostasis by the synthesis and secretion of metabolic hormones known as adipokines.[3,5] It is hypothesized that circulating free fatty acids induce insulin-mediated triglyceride storage in adipose tissue, skeletal muscle, and liver. Chronic insulin overstimulation causes a stress response in each of these tissues with a synthesis of pro-inflammatory cytokines, recruitment of inflammatory cells, systemic inflammation, and insulin resistance via negative feedback controls. Many clinical studies have demonstrated that insulin sensitivity and lipid profiles may be improved merely by the removal of subcutaneous adipocytes.[42,43] It is interesting to speculate on whether evidence of metabolic benefits would influence the industry that has built up around nonsurgical fat removal. On the one hand, such evidence would be a powerful refutation of critics who espouse the view that there are no inherent health benefits to nonsurgical fat removal. On the other hand, more data are needed before authoritative conclusions can be reached.

A major limitation with this study is the small number of eligible studies, many of which had recruited a small number of patients. Thus, when the margin for error was taken into consideration, few obvious trends emerged. The lack of compelling source data reflects the fact that, on the whole, esthetic practitioners are less interested in the potential health benefits of nonsurgical fat removal than in the commercial potential of the pursuit of anthropometric ideals. If nothing else, this study highlights the pressing need for more metabolic data. Moreover, we included a number of different methods of nonsurgical fat removal. This inevitably leads to concerns that our data are heterogeneous and that, as such, our conclusions mean little for any one specific commercial device. The third limitation is the relatively limited number of metabolic parameters, and the narrow metabolic window studied. Again, we are limited by the data available from the source material.

Conclusion

This study shows that nonsurgical body contouring procedures correlates with a sustained improvement in anthropometrics and body compositions for at least two months after procedure. A transient deterioration in lipid profile is observed over the first two weeks, consistent with lipolysis. The long-term metabolic effects of nonsurgical fat removal remain uncertain.

Funding

This project was supported by the Medical Research Office at Hamad Medical Corporation (Project ID: 01-20-466)

and QNRF (Projects ID: NPRP14S-0406-210153 and NPRP13S-0203-200234). The responsibility for the paper lies with the authors and there was no influence of the funder. Authors have complete access to the study data that support this publication.

Category: Review.

Declaration: This paper has not previously been presented at any national or international meeting.

Ethical approval: Not required.

Declaration of Competing Interest

The authors declare no competing interests.

Acknowledgments

The authors thank the Department of Plastic Surgery at the Hamad General Hospital for their contribution to this paper and Ms Anushka Hardas, Librarian at Sidra Medicine for help in sourcing the papers used to complete this work.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.bjps.2022.10.054.

References

1. Hruby A, Hu FB. The epidemiology of obesity: a big picture. *Pharmacoeconomics* 2015;**33**:673.
2. Shoelson SE, Herrero L, Naaz A. Obesity, inflammation, and insulin resistance. *Gastroenterology* 2007;**132**:2169–80.
3. de Luca C, Olefsky JM. Inflammation and insulin resistance. *FEBS Lett* 2008;**582**:97–105.
4. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet* 2005;**365**:1415–28.
5. Kanneganti TD, Dixit VD. Immunological complications of obesity. *Nat Immunol* 2012;**13**:707–12 *2012 13:8*.
6. Hocking S, Samocha-Bonet D, Milner KL, Greenfield JR, Chisholm DJ. Adiposity and insulin resistance in humans: the role of the different tissue and cellular lipid depots. *Endocr Rev* 2013;**34**:463–500.
7. Pareek M, Schauer PR, Kaplan LM, Leiter LA, Rubino F, Bhatt DL. Metabolic surgery: weight loss, diabetes, and beyond. *J Am Coll Cardiol* 2018;**71**:670–87.
8. Sailon AM, Wasserburg JR, Kling RR, Pasick CM, Taub PJ. Influence of large-volume liposuction on metabolic and cardiovascular health: a systematic review. *Ann Plast Surg* 2017;**79**:623–30.
9. Boriani F, Villani R, Morselli PG. Metabolic effects of large-volume liposuction for obese healthy women: a meta-analysis of fasting insulin levels. *Aesthetic Plast Surg* 2014;**38**:1050–6.
10. Clark JM, Sanders S, Carter M, et al. Improving the translation of search strategies using the polyglot search translator: a randomized controlled trial. *J Med Libr Assoc* 2020;**108**:195–207.
11. Cumpston M., Li T., Page M.J., et al. Cochrane database of systematic reviews updated guidance for trusted systematic reviews: a new edition of the cochrane handbook for systematic reviews of interventions. 2019. doi:10.1002/14651858.ED000142.
12. Stone JC, Glass K, Clark J, et al. The MethodologicAl STandards for Epidemiological Research (MASTER) scale demonstrated a unified framework for bias assessment. *J Clin Epidemiol* 2021;**134**:52–64.
13. Xu C, Doi SAR. The robust error meta-regression method for dose-response meta-analysis. *Int J Evid Based Healthc* 2018;**16**:138–44.
14. Brightman L, Weiss E, Chapas AM, et al. Improvement in arm and post-partum abdominal and flank subcutaneous fat deposits and skin laxity using a bipolar radiofrequency, infrared, vacuum and mechanical massage device. *Lasers Surg Med* 2009;**41**:791–8.
15. Shek S, Yu C, Yeung CK, Kono T, Chan HH. The use of focused ultrasound for non-invasive body contouring in Asians. *Lasers Surg Med* 2009;**41**:751–9.
16. Choi SY, Kim YJ, Kim SY, et al. Improvement in abdominal and flank contouring by a novel adipocyte-selective non-contact radiofrequency device. *Lasers Surg Med* 2018;**50**:738–44.
17. Boisnic S, Divaris M, Nelson AA, Gharavi NM, Lask GP. A clinical and biological evaluation of a novel, noninvasive radiofrequency device for the long-term reduction of adipose tissue. *Lasers Surg Med* 2014;**46**:94–103.
18. Shek SYN, Yeung CK, Chan JCY, Chan HHL. Efficacy of high-intensity focused ultrasonography for noninvasive body sculpting in Chinese patients. *Lasers Surg Med* 2014;**46**:263–9.
19. Tonucci LB, Mourão DM, Ribeiro AQ, Bressan J. Noninvasive body contouring: biological and aesthetic effects of low-frequency, low-intensity ultrasound device. *Aesthetic Plast Surg* 2014;**38**:959–67.
20. Katz B, Bard R, Goldfarb R, Shiloh A, Kenolova D. Ultrasound assessment of subcutaneous abdominal fat thickness after treatments with a high-intensity focused electromagnetic field device: a multicenter study. *Dermatol Surg* 2019;**45**:1542–1548.
21. Hong JY, Ko EJ, Choi SY, et al. Efficacy and safety of high-intensity focused ultrasound for noninvasive abdominal subcutaneous fat reduction. *Dermatol Surg* 2020;**46**:213–19.
22. Fonseca VM, Campos PS, Certo TF, de-Faria LT, Juliano PB, Cintra DE, et al. Efficacy and safety of noninvasive focused ultrasound for treatment of subcutaneous adiposity in healthy women. *J Cosmet Laser Ther* 2018;**20**:341–50.
23. Arabpour-Dahoue M, Mohammadzadeh E, Avan A, et al. Leptin level decreases after treatment with the combination of Radiofrequency and Ultrasound cavitation in response to the reduction in adiposity. *Diabetes Metab Syndr* 2019;**13**:1137–40.
24. Moreno-Moraga J, Valero-Altés T, Martínez Riquelme A, Isarria-Marcosy MI, Royo De La Torre J. Body contouring by non-invasive transdermal focused ultrasound. *Lasers Surg Med* 2007;**39**:315–23.
25. Mahmoud ELdesoky MT. Mohamed Abutaleb EEl, Mohamed Mousa GS. Ultrasound cavitation versus cryolipolysis for non-invasive body contouring. *Australas J Dermatol* 2016;**57**:288–93.
26. Robinson DM, Kaminer MS, Baumann L, et al. High-intensity focused ultrasound for the reduction of subcutaneous adipose tissue using multiple treatment techniques. *Dermatol Surg* 2014;**40**:641–51.
27. Solish N, Lin X, Axford-Gatley RA, Strangman NM, Kane M. A randomized, single-blind, postmarketing study of multiple energy levels of high-intensity focused ultrasound for noninvasive body sculpting. *Dermatol Surg* 2012;**38**:58–67.
28. Verner I. A novel nonfocused pulsed ultrasound technology for noninvasive circumference reduction. *Dermatol Ther* 2021;**34**. doi:10.1111/DTH.15101.
29. Khedmatgozar H, Yadegari M, Khodadadegan MA, et al. The effect of ultrasound cavitation in combination with cryolipolysis as a non-invasive selective procedure for abdominal fat reduction. *Diabetes Metab Syndr* 2020;**14**:2185–9.

30. An Open-label, Single-center, prospective evaluation of a novel noninvasive ultrasound body sculpting device - PubMed. https://pubmed.ncbi.nlm.nih.gov/29942424/ (accessed 2 Jul 2022).
31. Fritz K, Salavastru C. Long-term follow-up on patients treated for abdominal fat using a selective contactless radiofrequency device. *J Cosmet Dermatol* 2017;**16**:471–5.
32. Guth F, Bitencourt S, Bedinot C, Sinigaglia G, Tassinary JAF. Immediate effect and safety of HIFU single treatment for male subcutaneous fat reduction. *J Cosmet Dermatol* 2018;**17**:385–9.
33. Kwon TR, Yoo KH, Oh CT, et al. Improved methods for selective cryolipolysis results in subcutaneous fat layer reduction in a porcine model. *Skin Res Technol* 2015;**21**:192–200.
34. Abdel-Aal NM, Mostafa MSEM, Saweres JW, Ghait RS. Cavitation and radiofrequency versus cryolipolysis on leptin regulation in central obese subjects: a randomized controlled study. *Lasers Surg Med* 2022. doi:10.1002/LSM.23555.
35. [PDF] CRYO LIPOLYSIS VERSUS COLD LASER ON LIPID PROFILE AND BODY COMPOSITION IN WOMEN WITH CENTRAL OBESITY | Semantic Scholar. https://www.semanticscholar.org/paper/CRYO-LIPOLYSIS-VERSUS-COLD-LASER-ON-LIPID-PROFILE-Al-Agamy-Al-Nahas/dfb47a03dec92b095772b8f36d3c4ee50cb5f5ad (accessed 2 Jul 2022).
36. Klein KB, Zelickson B, Riopelle JG, et al. Non-invasive cryolipolysis for subcutaneous fat reduction does not affect serum lipid levels or liver function tests. *Lasers Surg Med* 2009;**41**:785–90.
37. Klein KB, Bachelor EP, Becker Ev, Bowes LE. Multiple same day cryolipolysis treatments for the reduction of subcutaneous fat are safe and do not affect serum lipid levels or liver function tests. *Lasers Surg Med* 2017;**49**:640–4.
38. Ferraro GA, de Francesco F, Cataldo C, Rossano F, Nicoletti G, D'Andrea F. Synergistic effects of cryolipolysis and shock waves for noninvasive body contouring. *Aesthetic Plast Surg* 2012;**36**:666–79.
39. Jewell ML, Solish NJ, Desilets CS. Noninvasive body sculpting technologies with an emphasis on high-intensity focused ultrasound. *Aesthetic Plast Surg* 2011;**35**:901–12.
40. Guth F, Bitencourt S, Bedinot C, Sinigaglia G, Tassinary JAF. Immediate effect and safety of HIFU single treatment for male subcutaneous fat reduction. *J Cosmetic Dermatol* 2018;**17**:385–9.
41. Kwon TR, Kim JH, Jang YN, et al. Comparison of different energy response for lipolysis using a 1060-nm laser: an animal study of three pigs. *Skin Res Technol* 2021;**27**:5–14.
42. Ybarra J, Blanco-Vaca F, Fernández S, et al. The effects of liposuction removal of subcutaneous abdominal fat on lipid metabolism are independent of insulin sensitivity in normal-overweight individuals. *Obes Surg* 2008;**18**:408–14.
43. Swanson E. The clinical relevance of lower triglyceride and leukocyte levels after liposuction. *Plast Reconstr Surg* 2012;**129**. doi:10.1097/PRS.0B013E31824A62F8.

Journal of Plastic, Reconstructive & Aesthetic Surgery 81 (2023) 83–84

JPRAS
An International Journal of Surgical Reconstruction
www.JPRASurg.com

Invited Commentary

Metabolic changes after surgical fat removal: Current gaps and suggestions for future studies

Saif Badran [a,b,*], **Suhail A. Doi** [b]

[a] *Division of Plastic and Reconstructive Surgery, Washington University in St. Louis School of Medicine, Missouri, USA*
[b] *Department of Population Medicine, College of Medicine, QU Health, Qatar University, Doha, Qatar*

Received 25 December 2022; Accepted 7 April 2023

Dear Editor,

We read with interest the letter by Seretes et al. discussing the findings and limitations of our evidence synthesis regarding the metabolic implications of surgical subcutaneous fat removal (SSFR).[1] It is true that existing studies were of small sample size, heterogeneous in terms of baseline body mass index (BMI), type and amount of SSFR, gender differences, as well as participants' behaviour in terms of diet and exercise.[2] While this has a bearing on the results of this paper, a meta-analysis generates an average effect over the multiple studies and those till date[3–8] have failed to generate consensus because they did not address the heterogeneity in follow-up duration among the included studies. Our dose-response meta-analysis (DRMA)[1] aimed not only to pool previous studies to reach a bigger sample size and stronger conclusion, but also to account for differences in follow-up time. Thus, regardless of the existing heterogeneity in patient characteristics, there was a metabolic effect demonstrable for SSFR and these results are consistent with the observation that even a small amount of fat reduction can have a significant metabolic benefit on insulin sensitivity, inflammation, and blood pressure.[9,10]

With the current advancement in our understanding regarding fat tissue being an active endocrine organ rather than an energy store, as well as the accelerating increase in demand for such body contouring surgeries (that lead to SSFR) to improve body shape quickly, it is essential to further investigate the metabolic changes after these surgeries, not only to confirm the safety of these procedures, but also to help us to understand the mechanisms underpinning the link between obesity and metabolic diseases and the impact of various patient differences on metabolic sequalae. Our meta-analysis is reassuring in that metabolic safety seems plausible and therefore the focus now needs to be on additional sources of population heterogeneity such as existing comorbidities such as diabetes mellitus and history of previous bariatric surgery,[11] which could alter the metabolic trajectory after SSFR. As Seretes aptly concludes, future controlled studies with homogenous samples, proper methodology, and adequate follow-up remain of high importance to clarify the role of different patient factors on

DOI of original article: https://doi.org/10.1016/j.bjps.2023.01.017
Abbreviations: SSFR, Surgical subcutaneous fat removal; NSSFR, Non-surgical subcutaneous fat removal; DRMA, Dose-response meta analysis
* Correspondence to: College of Medicine, Qatar University, Doha, Qatar.
E-mail address: saif_badran@hotmail.com (S. Badran).

https://doi.org/10.1016/j.bjps.2023.04.008

metabolism after surgical[1] (SSFR) and non-surgical[12] (NSSFR) subcutaneous fat removal.

Ethical Approval

Not applicable.

Funding

This project was supported by the Medical Research Office at Hamad Medical Corporation (#01-20-466) and the Qatar National Research Fund (Project #NPRP14S-0406-210153). The responsibility for the paper lies with the authors and there was no influence of the funder.

Conflict of interest statement

None.

Acknowledgements

The authors thank Hamad Medical Corporation (grant ID 01-20-466) and Qatar National Research Fund (grant ID NPRP14S-0406-210153) for their support to this paper.

References

1. Badran S, Habib AM, Aljassem G, et al. Metabolic changes after surgical fat removal: a dose-response meta-analysis. *J Plast Reconstr Aesthet Surg* 2023;**76**:238–50.
2. Badran S, Doi SA, Hamdi M, et al. Metabolic aspects of surgical subcutaneous fat removal: an umbrella review and implications for future research. *Bosn J Basic Med Sci* 2022:1.
3. Seretis K, Goulis DG, Koliakos G, Demiri E. Short- and long-term effects of abdominal lipectomy on weight and fat mass in females: a systematic review. *Obes Surg* 2015;**25**:1950–8.
4. Seretis K, Demiri E. Metabolic effects of large-volume liposuction for obese healthy women: a meta-analysis of fasting insulin levels. *Aesthet Plast Surg* 2015;**39**:278–9.
5. Boriani F, Villani R, Morselli PG. Metabolic effects of large-volume liposuction for obese healthy women: a meta-analysis of fasting insulin levels. *Aesthet Plast Surg* 2014;**38**:1050–6.
6. Danilla S, Longton C, Valenzuela K, et al. Suction-assisted lipectomy fails to improve cardiovascular metabolic markers of disease: a meta-analysis. *J Plast Reconstr Aesthet Surg* 2013;**66**:1557–63.
7. Sailon AM, Wasserburg JR, Kling RR, Pasick CM, Taub PJ. Influence of large-volume liposuction on metabolic and cardiovascular health: a systematic review. *Ann Plast Surg* 2017;**79**:623–30.
8. Seretis K, Goulis DG, Koliakos G, Demiri E. The effects of abdominal lipectomy in metabolic syndrome components and insulin sensitivity in females: a systematic review and meta-analysis. *Metabolism* 2015;**64**:1640–9.
9. Ziccardi P, Nappo F, Giugliano G, et al. Reduction of inflammatory cytokine concentrations and improvement of endothelial functions in obese women after weight loss over one year. *Circulation* 2002;**105**:804–9.
10. Stevens VJ, Obarzanek E, Cook NR, et al. Long-term weight loss and changes in blood pressure: results of the Trials of Hypertension Prevention, phase II. *Ann Intern Med* 2001;**134**:1–11.
11. Badran S, Doi SA, Hammouda A, et al. The impact of prior obesity surgery on glucose metabolism after body contouring surgery: A pilot study. *Biomol Biomed* 2023. https://doi.org/10.17305/bb.2023.8827.
12. Badran S, Doi SA, Iskeirjeh S, et al. Metabolic changes after non-surgical fat removal: a dose response meta-analysis. *J Plast Reconstr Aesthet Surg* 2022. https://doi.org/10.1016/J.BJPS.2022.10.054.

Biomolecules and Biomedicine
ISSN: 2831-0896 (Print) | ISSN: 2831-090X (Online)

Journal Impact Factor® (2021): 3.76
CiteScore® (2021): 5.2
www.biomolbiomed.com | blog.biomolbiomed.com

RESEARCH ARTICLE

NEW AND EMERGING METHODS

Validation of Doi's weighted average glucose as a measure of post-load glucose excursion for clinical use

Saif Badran[1], Suhail A. Doi[1], Atalla Hammouda[2], Omran A. H. Musa[1], Abdella M. Habib[3]*

[1]Department of Population Medicine, College of Medicine, QU Health, Qatar University, Doha, Qatar

[2]Department of Plastic Surgery, Hamad General Hospital, Doha, Qatar

[3]Department of Basic Medical Sciences, College of Medicine, QU Health, Qatar University, Doha, Qatar

***Corresponding author:** Abdella M. Habib; E-mail: ahabib@qu.edu.qa

DOI: https://doi.org/10.17305/bb.2022.8807

Submitted: 18 January 2023/ **Accepted:** 06 March 2023/ **Published online:** 22 March 2023

Conflicts of interest: Authors declare no conflicts of interest.

Funding: SB was supported by the Medical Research Office at Hamad Medical Corporation (#01-20-466). AMH and SD were supported by the Qatar National Research Fund (Project Numbers #NPRP13S-0209-200315 and NPRP14S-0406-210153). The responsibility for the paper lies with the authors and there was no influence of the funder.

ABSTRACT

In this study, we examined the performance of a novel index of glucose excursion (Doi's weighted average glucose; dwAG) in relation to the conventional measure of area under the oral glucose tolerance test (A-GTT) and the homeostatic model assessment for insulin sensitivity (HOMA-S) and pancreatic beta cell function (HOMA-B)**.** A cross-sectional comparison of the new index was conducted using 66 oral glucose tolerance tests (GTTs) performed at different follow-up times among 27 participants who had undergone surgical subcutaneous fat removal (SSFR). Comparisons across categories were made using box plots and the Kruskal-Wallis one-way ANOVA on ranks. Passing-Bablok regression was used to compare the dwAG against the conventional A-GTT. The Passing-Bablok regression model suggested a cutoff for normal values for A-GTT of 15.14 mmol/L·$2h^{-1}$ compared to the dwAG's suggested threshold of 6.8 mmol/L. For every 1 mmol/L·$2h^{-1}$ increase in A-GTT, the dwAG value increased by 0.473 mmol/L. The glucose area under the curve correlated well with the four defined dwAG categories, with at least one of the categories having a different A-GTT curve (KW Chi2 = 52.8 [df = 3], $P < 0.001$). The HOMA-S tertiles were also associated with significantly different levels of glucose excursion measured through both the dwAG value (KW Chi2 = 11.4 [df = 2], $P = 0.003$) and A-GTT measure (KW Chi2 = 13.1 [df = 2], $P = 0.001$). It is concluded that the dwAG value and categories serve as a simple and accurate tool that can be used for interpreting glucose homeostasis across clinical settings.

Keywords: Diabetes mellitus; oral glucose tolerance test; weighted average glucose; dwAG; under the curve; HOMA-S.

Introduction

Diabetes mellitus is a growing global pandemic that is increasing at an alarming rate. It is expected that diabetes prevalence will reach 10.2% (578 million), and that the prevalence of impaired glucose tolerance will reach 8% (454 million) by 2030 [1]. Half of the diabetic population has asymptomatic hyperglycemia [1] and this has led to further research on different diagnostic tools that can shed light on glycemic changes seen in patients with disorders of glucose homeostasis.

A test that has commonly been used to diagnose glycemic disorders is the oral glucose tolerance test (GTT), which is extensively used in both research and clinical practice as an indicator of gestational diabetes [2], but has been replaced by the fasting plasma glucose (FPG) for the diagnosis of type 2 diabetes [3]. In both humans and animals, GTT provides an indication of the relative roles of insulin secretion and insulin resistance in the progression of glucose intolerance. It can provide the best measure of glucose homeostasis and has the potential to diagnose patients with impaired glucose tolerance even with normal FPG levels. This is of value because those patients are at higher risk for developing type 2 diabetes as well as cardiovascular diseases [4].

Doi's weighted average glucose (dwAG) is a novel index that represents a single value summary of the glucose excursion under the GTT. The latter is derived from only 3 time points on the GTT at 0, 60 and 120 minutes and was categorized into 4 levels in a previous study of gestational diabetes. These four categories differentiated between normal, impaired, abnormal, and severely abnormal glycemic states [2]. In this study, we examine the performance of the dwAG value in comparison to the area under the GTT (75 mg oral glucose with 6 time points of glucose measurements) and homeostatic model assessment for insulin sensitivity (HOMA-S) and pancreatic beta cell function (HOMA-B) in a group of participants undergoing surgical subcutaneous fat removal for cosmetic purposes, also known as body contouring surgery. The aim

was to determine whether the values and cutoffs as defined for gestational diabetes also define glucose excursion in a different group of adult subjects outside pregnancy.

MATERIALS AND METHODS

Subjects

We studied 27 consecutive eligible patients who underwent body contouring surgery at the Department of Plastic Surgery, Hamad General Hospital, in the period between July 2021 and June 2022. Sixteen participants were obese (59%) and 4 patients were diagnosed with type 2 diabetes mellitus (15%). Details of the participants are given in Table 1. GTT was performed at 3 different time points before and after surgery (visit one: within 1 week before surgery, visit two: 1 week after surgery, and visit three: 6 weeks after surgery). After taking a detailed medical history and complete physical examination, patients with comorbidities were excluded except for type 2 diabetes mellitus patients who were not on insulin therapy.

Study design

The research design in this study was a cross-sectional comparison of standard and new method of assessing glucose excursion under the GTT. The GTT was administered using 75 mg oral glucose with 6 time points of glucose measurements (fasting [gtt0], 15 minutes [gtt15], 30 minutes [gtt30], 45 minutes [gtt45], 60 minutes [gtt60] and 120 minutes [gtt120] in mmol/L). For each of the GTT's, glucose excursion was computed using:

a) standard method: Tai's trapezoidal rule for area under the GTT [5] expressed as mmol/L/2h using 6 GTT values (at 0, 15, 30, 45, 60 and 120 minutes)

b) new method: Doi's weighted average glucose (dwAG) [2] calculated using the formula $(\text{gtt0} \times 0.28) + (\text{gtt60} \times 0.36) + (\text{gtt120} \times 0.36)$ and expressed as actual glucose values in

mmol/L. The dwAG represents a single value summary of the glucose excursion under the GTT using only the 3 time points (0, 60 and 120 minutes) in routine GTT's for diagnostic use [2]. The dwAG value was categorized into 4 categories: dwAG0 ≤ 6.8, dwAG1 > 6.8 and ≤ 7.5, dwAG2 > 7.5 and ≤ 8.6 and dwAG3 > 8.6 mmol/L based on 4 levels of risk previously defined for women with gestational diabetes [2]. These four levels of dwAG reflect normal, impaired, abnormal, and severely abnormal dwAG values, respectively.

The Oxford HOMA2 Calculator was used to compute HOMA-S and HOMA-B (both anchored at 100% for normal insulin sensitivity) by means of FPG and fasting C-peptide [6].

The GTTs were classified into two patterns or shapes that indicate a higher level of beta cell dysfunction:

a) Those that peaked after 30 minutes (Y/N) defined as a maximum value after 30 minutes (or after 45 minutes if the value at this time only exceeded the 30 minute value by < 0.25 mmol/L) [7].
b) A biphasic GTT defined as a GTT with 120 min glucose ≥ 0.25 mmol/L higher than at 60 minutes [8].

Ethical statement

All subjects signed an informed consent before starting the study, which was approved by the Institutional Review Board at Hamad Medical Corporation and Qatar University (MRC-01-20-466, and QU-IRB 1412-EA/20 respectively), and by the Institutional Bio-safety Committee at Qatar University (QU-IBC-2020/066).

Statistical analysis

Comparisons across categories were made using box plots and the Kruskal-Wallis one-way ANOVA on ranks which extends the Mann–Whitney U test. Passing-Bablok regression was used to compare both methods of computing glucose excursion and is a linear regression procedure with no special assumptions regarding the distribution of the samples and the measurement errors [9]. The result does not depend on the assignment of the methods for glucose excursion to X and Y. A linear regression model with two categorical predictors (peak after 30 minutes and biphasic GTT) was used to assess mean values of dwAG, area under the GTT (A-GTT), HOMA-S and HOMA-B in groups defined by these factors. Finally, the dependence of dwAG on HOMA-S and HOMA-B was modeled in linear regression using restricted cubic splines and using the values of both HOMA-S and HOMA-B indices centered at 100%. Stata version 15 (College Station, TX, USA) was used for all analyses and exact P values were reported throughout.

RESULTS

There were a total of 66 complete GTTs and of these, 47 (71.2%) had peak values after 30 minutes and 9 (13.6%) were biphasic (8/9 also had a peak after 30 minutes). Glucose excursion was computed using the two measures indicated in the methods and a Passing-Bablok regression model suggested a cutoff for normal values for the A-GTT of 15.14 mmol/L·$2h^{-1}$ as the equivalent cutoff to the dwAG value of 6.8 mmol/L. For every 1 mmol/L·$2h^{-1}$ increase in A-GTT, the dwAG value increased by 0.473 mmol/L (Figure 1). The glucose area under the curve correlated well with the dwAG level (4 groups), with at least one of the levels having a different A-GTT (KW Chi2 = 52.8 [df = 3], $P < 0.001$). The median A-GTT in each dwAG category was 13.2, 15.9, 18.3 and 21.0 mmol/L·$2h^{-1}$ in the normal, impaired, abnormal, and severely abnormal dwAG groups, respectively (Figure 2).

The HOMA-S tertiles were associated with different levels of glucose excursion measured through both the dwAG value (KW Chi2 = 11.4 [df = 2], $P = 0.003$) and A-GTT value (KW Chi2 = 13.1 [df = 2], $P = 0.001$) (Figure 3). The IQRs for the dwAG across the insulin sensitivity tertiles were 6.8 to 9.4, 6.1 to 7.6, and 5.3 to 7.0 mmol/L, respectively. For A-GTT, the IQRs were 15.4 to 21.5, 13.3 to 18.5, and 12.2 to 16.5 mmol/L·$2h^{-1}$, respectively. The impact on glucose excursion was seen more prominently once insulin sensitivity was lowest (in the first tertile; HOMA-S median -53.35%, IQR -69.7% to - 49.1%).

HOMA-B alone (in a non-linear regression model) explained 42% of the variation in dwAG values, whereas HOMA-S explained 9% of the variation in dwAG values in a similar model. The combination of both HOMA-B and HOMA-S in a non-linear regression model (using restricted cubic splines) contributed to explaining 66% of the variation in dwAG values suggesting that the combination was what defined the bulk of the variation in dwAG values. This is shown graphically in Figure 4, which shows that dwAG depends on both beta cell function and insulin sensitivity, and that dwAG increases as both insulin sensitivity and beta cell function decline.

The mean dwAG value in those GTTs with a peak at 30 minutes and that were monophasic was 6.4 mmol/L. There was a mean increase in dwAG of 1.4 mmol/L ($P = 0.032$) in those GTTs with a peak after 30 min but no biphasic shape and a mean increase of 3.0 mmol/L in GTTs with both a later peak and biphasic shape ($P = 0.002$). With the A-GTT the mean changes followed a similar trend but with less statistical evidence against the model hypothesis at this sample size. HOMA-B declined on average by 19.8% ($P = 0.262$) in the late peak only group and by 29.3% ($P = 0.285$) in the combined late peak and biphasic group. The respective changes in HOMA-S for these groups were -3% and -3.7%, respectively, suggesting that these shape changes reflected beta cell function. None of the GTTs from a patient with a history of bariatric surgery demonstrated a

biphasic pattern (P = 0.028, Fishers exact test), but a peak after 30 minutes occurred with equal frequency in those with or without a history of bariatric surgery.

DISCUSSION

This study, for the first time, introduces a novel tool to define glucose homeostasis in adult population, and demonstrates an excellent correlation with the A-GTT and is well discriminated by tertiles of HOMA-S. The implication here is that the dwAG, which combines fasting, 1h and 2h plasma glucose values, is a sufficient criterion for measuring glucose excursion in adults, which in this paper refers specifically to a group of non-pregnant adults who underwent body contouring surgery. The dwAG was responsive to GTTs with peaks after 30 minutes or with a biphasic shape and this was not so clearly evident with the A-GTT. The time to glucose peak >30 minutes has previously been shown to be an independent indicator of prediabetes and lower beta cell function in an otherwise healthy multi-ethnic adult cohort [7]. It is known that the glucose peak occurs most frequently at 30 minutes (60.5%) and is accompanied by a synchronous peak of insulin [10]. Thus, both a later peak and a biphasic shape indicate worse beta cell function [8, 11].

It was noted that none of the GTTs showed a biphasic pattern in subjects who had a history of bariatric surgery, which is not surprising given the fact that meal-induced secretion of glucagon-like peptide-1 (GLP-1) could be up to 10-fold higher in patients after gastric bypass or sleeve gastrectomy surgeries compared to non-surgical individuals. One possible mechanism (among others) that has been put forward is accelerated nutrient transit from stomach to the gut, leading to enhanced secretion of GLP-1 [12]. The latter is specific to bariatric surgery and occurs before weight loss; given that our patients had bariatric surgery more than 18 months preceding the GTT, the effect is sustained. The latter is different from the favorable effects of bariatric surgery on

peripheral insulin sensitivity which is shared with those of calorie restriction [13] and is only improved in proportion to weight loss [14, 15].

The implication from the observations in these patients with or without history of bariatric surgery is that the measure of glucose excursion using the dwAG value shares elements of the two major metabolic impairments associated with glucose homeostasis: an increase in insulin resistance and impaired beta cell function [16, 17]. This was demonstrated in this study (Figure 4), where the dwAG was about 5 mmol/L when both HOMA indices were normal (100%). There was a linear increase in dwAG when insulin sensitivity declined and a non-linear increase in dwAG when beta cell function declined. This explains why the dwAG or area under the GTT curve may be a better indicator of transitioning to type 2 diabetes mellitus [18] or future cardiovascular disease and mortality [19] than low insulin sensitivity alone. As indicated in our results, the dwAG correlates better with shape parameters than A-GTT and this was evident in post-bariatric subjects with much better beta cell function.

This study provides firm support to the dwAG as an alternative and novel method to formally assess glucose excursion under the GTT. Although it was developed for gestational diabetes [2], it is shown here that it can have broader application. This study confirms that the same groupings from normal to severely abnormal glucose excursion hold in this population of adults outside of pregnancy and, as expected, correlates with HOMA insulin sensitivity and beta cell function. While the GTT is no longer used as a mainstay in diabetes diagnosis [20, 21], it continues to be used as an index of glucose excursion, which represents the balance of insulin sensitivity and beta cell function. While those with abnormal dwAG values (dwAG2) had a mean FPG of 5.6 mmol/L which coincides with the ADA threshold for impaired fasting glucose (IFG), these two tests, nevertheless, provide different levels of glucose homeostasis assessment because

the GTT combines information from both insulin sensitivity and beta cell function [22], whereas the FPG is responsive primarily to insulin secretion relative to the level of insulin resistance [23] and is ideally suited to diabetes diagnosis as it indicates decompensated insulin resistance.

The strengths of the present study include a first-time comparison of the A-GTT to a novel index of glucose excursion using the conventional GTT used in clinical practice, the computation of the A-GTT from six time-points of the GTT, and the comparison of both the conventional and novel indices to HOMA beta cell function and insulin sensitivity in the same model. Potential limitations include the fact that we have not yet acquired data on various hormones of interest during GTT (which is currently ongoing) and the use of a single GTT for the comparisons in individuals, which may have less reproducibility but, on the positive side, mimics the clinical use of these indices in practice.

CONCLUSION

The dwAG represents a single value summary of glucose excursion under the GTT and serves as a simple but accurate tool that can be used for glucose homeostasis interpretation. It was initially concieved as a tool that could be used to define glucose homeostasis in pregnancy and, in that study, correlated with adverse perinatal outcomes. It has now been independently validated as equivalent to the conventional A-GTT (based on six time-points) measure of glucose excursion in this study in a different population of non-pregnant adults and correlates well with both HOMA insulin sensitivity and HOMA beta cell function.

ACKNOWLEDGEMENTS

The authors thank the Department of Plastic Surgery & Qatar Metabolic Institute at Hamad General Hospital and the volunteers for their contribution,whose participation made this study possible.

REFERENCES

[1] Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9(th) edition. Diabetes Res Clin Pract. 2019;157:107843.

[2] Doi SAR, Bashir M, Sheehan MT, Onitilo AA, Chivese T, Ibrahim IM, et al. Unifying the diagnosis of gestational diabetes mellitus: Introducing the NPRP criteria. Prim Care Diabetes. 2022;16(1):96-101.

[3] Inzucchi SE. Clinical practice. Diagnosis of diabetes. N Engl J Med. 2012;367(6):542-50.

[4] Perry RC, Baron AD. Impaired glucose tolerance. Why is it not a disease? Diabetes Care. 1999;22(6):883-5.

[5] Tai MM. A mathematical model for the determination of total area under glucose tolerance and other metabolic curves. Diabetes Care. 1994;17(2):152-4.

[6] OXFORD. Homeostasis Model Assessment (HOMA2) Calculator 2004 [cited 2023. Available from: https://www.dtu.ox.ac.uk/homacalculator/.

[7] Chung ST, Ha J, Onuzuruike AU, Kasturi K, Galvan-De La Cruz M, Bingham BA, et al. Time to glucose peak during an oral glucose tolerance test identifies prediabetes risk. Clinical endocrinology. 2017;87(5):484-91.

[8] Manco M, Nolfe G, Pataky Z, Monti L, Porcellati F, Gabriel R, et al. Shape of the OGTT glucose curve and risk of impaired glucose metabolism in the EGIR-RISC cohort. Metabolism. 2017;70:42-50.

[9] Passing H, Bablok. A new biometrical procedure for testing the equality of measurements from two different analytical methods. Application of linear regression procedures for method comparison studies in clinical chemistry, Part I. J Clin Chem Clin Biochem. 1983;21(11):709-20.

[10] Nolfe G, Spreghini MR, Wietrzycowska Sforza R, Morino G, Manco M. Beyond the morphology of the glucose curve following an oral glucose tolerance test in obese youth. European journal of endocrinology. 2012;166(1):107-14.

[11] Wang X, Zhao X, Zhou R, Gu Y, Zhu X, Tang Z, et al. Delay in glucose peak time during the oral glucose tolerance test as an indicator of insulin resistance and insulin secretion in type 2 diabetes patients. Journal of diabetes investigation. 2018;9(6):1288-95.

[12] Smith EP, Polanco G, Yaqub A, Salehi M. Altered glucose metabolism after bariatric surgery: What's GLP-1 got to do with it? Metabolism. 2018;83:159-66.

[13] Markovic TP, Jenkins AB, Campbell LV, Furler SM, Kraegen EW, Chisholm DJ. The determinants of glycemic responses to diet restriction and weight loss in obesity and NIDDM. Diabetes care. 1998;21(5):687-94.

[14] Lin E, Liang Z, Frediani J, Davis Jr SS, Sweeney JF, Ziegler TR, et al. Improvement in β-cell function in patients with normal and hyperglycemia following Roux-en-Y gastric bypass surgery. American Journal of Physiology-Endocrinology and Metabolism. 2010;299(5):E706-E12.

[15] Lima MMO, Pareja JC, Alegre SM, Geloneze SR, Kahn SE, Astiarraga BD, et al. Acute effect of roux-en-y gastric bypass on whole-body insulin sensitivity: a study with the euglycemic-hyperinsulinemic clamp. The Journal of Clinical Endocrinology & Metabolism. 2010;95(8):3871-5.

[16] Kanauchi M, Kimura K, Kanauchi K, Saito Y. Beta-cell function and insulin sensitivity contribute to the shape of plasma glucose curve during an oral glucose tolerance test in non-diabetic individuals. Int J Clin Pract. 2005;59(4):427-32.

[17] Abdul-Ghani MA, Jenkinson CP, Richardson DK, Tripathy D, DeFronzo RA. Insulin secretion and action in subjects with impaired fasting glucose and impaired glucose tolerance: results from the Veterans Administration Genetic Epidemiology Study. Diabetes. 2006;55(5):1430-5.

[18] Tabák AG, Herder C, Rathmann W, Brunner EJ, Kivimäki M. Prediabetes: a high-risk state for diabetes development. Lancet. 2012;379(9833):2279-90.

[19] Unwin N, Shaw J, Zimmet P, Alberti KG. Impaired glucose tolerance and impaired fasting glycaemia: the current status on definition and intervention. Diabet Med. 2002;19(9):708-23.

[20] Bartoli E, Fra GP, Carnevale Schianca GP. The oral glucose tolerance test (OGTT) revisited. Eur J Intern Med. 2011;22(1):8-12.

[21] Genuth S, Alberti KG, Bennett P, Buse J, Defronzo R, Kahn R, et al. Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care. 2003;26(11):3160-7.

[22] Kanauchi M, Kimura K, Kanauchi K, Saito Y. Beta-cell function and insulin sensitivity contribute to the shape of plasma glucose curve during an oral glucose tolerance test in non-diabetic individuals. International journal of clinical practice. 2005;59(4):427-32.

[23] Carnevale Schianca GP, Mella R, Scaglia E, Bigliocca M, Colli E, Fra GP, et al. Expanding the clinical use of standard OGTT: the percentage increment of 2 h with respect to fasting glucose as an index of β-cell dysfunction. Diabetes/Metabolism Research and Reviews. 2011;27(3):262-8.

TABLES AND FIGURES WITH LEGENDS

Table 1: Baseline characteristics of study participants

Factor	Level/units	Visit 1	Visit 2	Visit 3
		N=27	N=22	N=19
Sex	M	6 (22.22%)	6 (27.27%)	3 (15.79%)
	F	21 (77.78%)	16 (72.73%)	16 (84.21%)
BMI category	Normal	4 (14.81%)	3 (13.64%)	2 (10.53%)
	Overweight	7 (25.93%)	6 (27.27%)	5 (26.32%)
	Obese	16 (59.26%)	13 (59.09%)	12 (63.16%)
Bariatric surgery status	No prior history	17 (62.96%)	13 (59.09%)	13 (68.42%)
	Had a prior history	10 (37.04%)	9 (40.91%)	6 (31.58%)
Fat percent, median (IQR)	%	37.00 (32.90, 42.20)	37.00 (32.90, 42.90)	39.60 (33.60, 44.00)
Biphasic shape of GTT	No	23 (85.19%)	19 (86.36%)	15 (88.24%)
	Yes	4 (14.81%)	3 (13.645)	2 (11.76%)
Peak glucose after 30min on the GTT	No	7 (25.93%)	5 (22.73%)	4 (23.53%)
	Yes	20 (74.07%)	17 (77.27%)	13 (76.475)
GTT0, median (IQR)	mmol/L	5.30 (4.90, 5.80)	5.45 (5.00, 5.70)	5.20 (4.90, 9.00)
GTT15, median (IQR)	mmol/L	7.90 (6.80, 9.70)	7.45 (7.00, 8.30)	8.00 (6.20, 9.00)
GTT30, median (IQR)	mmol/L	8.60 (7.10, 11.20)	8.40 (7.70, 10.30)	8.95 (6.80, 10.70)
GTT45, median (IQR)	mmol/L	10.40 (7.50, 12.00)	9.55 (8.40, 10.10)	8.10 (6.40, 10.70)
GTT60, median (IQR)	mmol/L	8.90 (7.20, 12.60)	8.75 (7.60, 11.10)	8.35 (7.10, 11.50)
GTT120, median (IQR)	mmol/L	6.70 (4.20, 8.80)	6.40 (5.30, 8.60)	5.75 (4.70, 8.20)

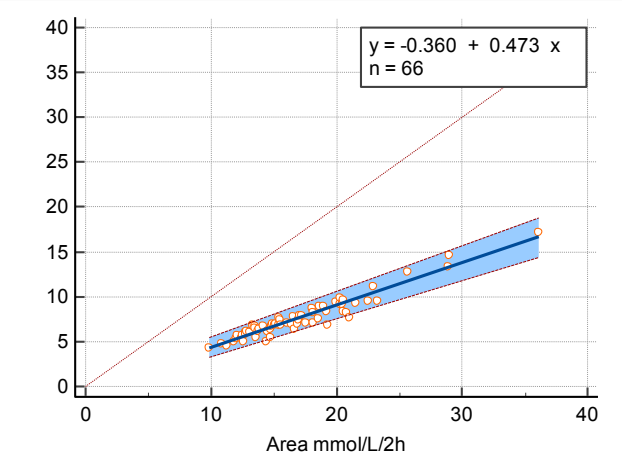


Figure 1. Passing-Bablok regression plot showing data and fit for the weighted average glucose measure of glucose excursion predicted from area under the GTT (glucose). Cusum test for linearity, No significant deviation from linearity ($P = 0.83$); Spearman rank correlation coefficient 0.934 (95% confidence interval 0.894 to 0.959). GTT: glucose tolerance test

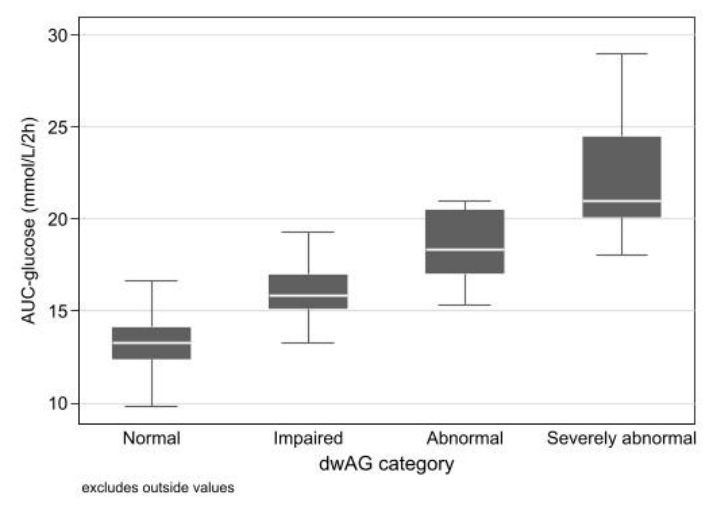


Figure 2: Association between the area under the GTT and dwAG category measure of glucose excursion. GTT: glucose tolerance test

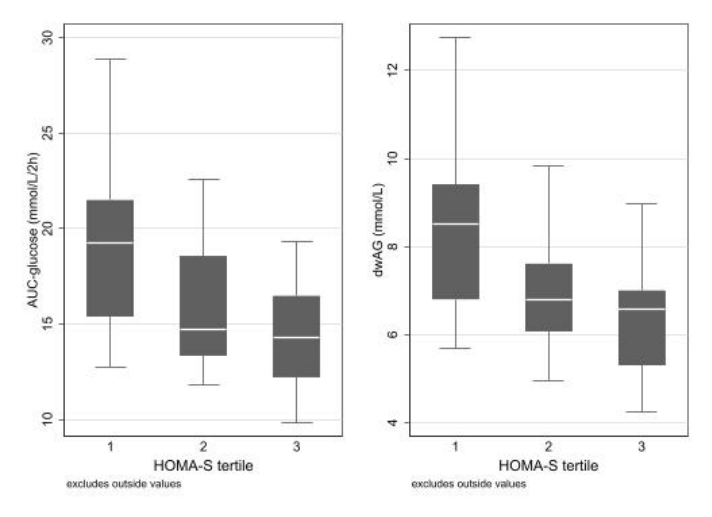


Figure 3: Association between glucose excursion (left: Tai's area under the GTT; right: Doi's weighted average glucose) and innsulin sensitivity tertile.

*HOMA-S tertile: Homeostatic Model Assessment for insulin sensitivity tertiles 1, 2 and 3

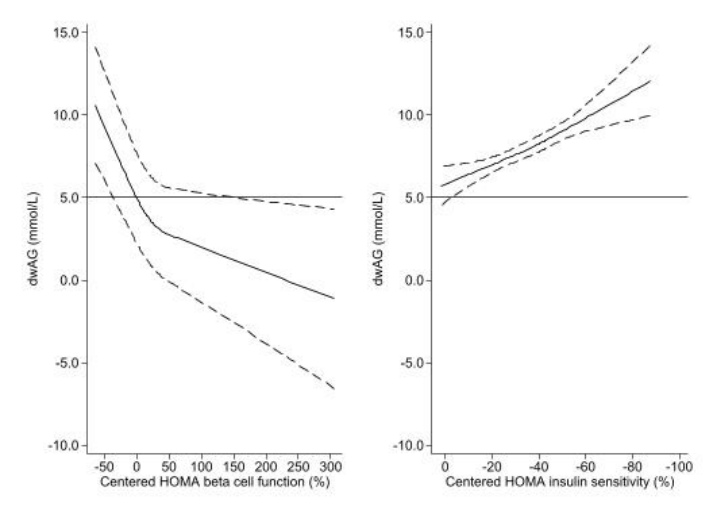


Figure 4. Relationship of HOMA insulin sensitivity (%) and HOMA beta cell function (%) to the dwAG (mmol/L) demonstrating that both are important in determining the dwAG value. The values of HOMA are centered at 100%, and when both are normal (0%) the dwAG value is about 5 mmol/L. As HOMA insulin sensitivity decreases the dwAG rises linearly and this is mitigated by an increase in beta cell function which drops the dwAG value.

Biomolecules & Biomedicine

RESEARCH ARTICLE

The impact of prior obesity surgery on glucose metabolism after body contouring surgery: A pilot study

Saif Badran[1], Suhail A. Doi[1], Atalla Hammouda[1], Hoda Khoogaly[2], Mohammad Muneer[1], Meis Alkasem[2], Abdul-Badi Abou-Samra[2,3], and Abdella M. Habib[4*]

Body contouring surgery enhances physical appearance by means of surgical subcutaneous fat removal (SSFR). However, it remains unclear how SSFR may affect glucose metabolism and its broader effects on the endocrine system, especially in individuals who have undergone obesity (bariatric) surgery. This study aimed to evaluate the impact of SSFR on glucose excursion and insulin resistance in such patients, by examining them over three visits (within 1 week before surgery, 1 week after surgery, and 6 weeks after surgery). The independent impact of SSFR and history of obesity surgery on glucose homeostasis was evaluated in 29 participants, of whom ten patients (34%) had a history of obesity surgery. Indices of glucose metabolism were evaluated using cluster robust-error logistic regression. Results indicated that SSFR led to a gross improvement in insulin resistance at 6 weeks after the surgery in all patient's irrespective of BMI, type 2 diabetes mellitus (T2D) status, or history of obesity surgery (OR 0.22; $P = 0.042$). However, no effect was observed on glucose excursion except for a transient increase at visit 2 (1 week after surgery) in those without prior obesity surgery. Interestingly, participants with a history of obesity surgery had approximately half the odds being in the upper tertile for HOMA-IR (OR 0.44; $p = 0.142$) and ten-folds lower odds of having severely abnormal glucose excursion (OR 0.09; $p = 0.031$), irrespective of their BMI, T2D status, or time post SSFR. In conclusion, this study showed that body contouring surgery through SSFR resulted in (at least) short-term improvement in insulin resistance (independent of the participant's BMI, T2D status, or history of obesity surgery) without affecting glucose excursion under the GTT. On the contrary, obesity surgery may have a long-term effect on glucose excursion, possibly due to sustained improvement of pancreatic β-cell function.

Keywords: Obesity, obesity surgery, bariatric surgery, body contouring surgery, surgical fat removal, insulin resistance, glucose homeostasis, metabolism.

Introduction

Currently, there is a significant drift toward people seeking body contouring surgical interventions, such as dermo-lipectomy and liposuction, to quickly improve body appearance. This increase in demand can be attributed to several factors, including sedentary lifestyle, consumption of high energy diets, media emphasis on fitness and health, as well as the current paucity of effective and safe pharmacological treatment for overweight and obesity [1]. An additional push behind these body contouring surgeries is the recent advancement in safety and popularity of obesity surgeries, such as Roux-en-Y gastric bypass and sleeve gastrectomy, both of which are currently the most effective surgical interventions for treating obesity and type 2 diabetes (T2D). However, these procedures usually followed by a subsequent surgical intervention to remove excess residual subcutaneous fat and redundant skin to improve physical appearance [2, 3]. Surgical subcutaneous fat removal (SSFR), a main consequence of body contouring surgery, differs from other modalities of reducing body fat (such as diet, exercise, and obesity surgeries) since SSFR results in a sudden loss of adipocytes from the abdominal subcutaneous fat (ASF) compartment. On the other hand, other forms of fat reduction all result in a gradual decrease of both subcutaneous and intraabdominal adipocytes in terms of both size and quantity [4]. The metabolic impacts of the large volume subcutaneous fat removal during body contouring surgery are not known fully [5–7]. Several studies have investigated the latter, using different tests that assess glucose homeostasis, such as the homeostasis model assessment-estimated insulin resistance (HOMA-IR) [8–10] and fasting insulin levels [11, 12]. Fewer studies have assessed both fasting and postprandial glucose homeostasis using the insulin tolerance test [13], oral glucose tolerance test (OGTT) [14, 15], or the gold standard glucose clamp test [16, 17]. The existing studies have

[1]Department of Population Medicine, College of Medicine, QU Health, Qatar University, Doha, Qatar; [2]Qatar Metabolic Institute, Hamad Medical Corporation, Doha, Qatar; [3]Department of Medicine, Weill Cornell Medicine Qatar, Qatar Foundation, Doha, Qatar; [4]College of Medicine, QU Health, Qatar University, Doha, Qatar.

*Correspondence to Abdella Habib: ahabib@qu.edu.qa

DOI: 10.17305/bb.2022.8827

been summarized in one systematic review and five meta-analyses [6, 7, 18–21], and these syntheses suggest a possible improvement in insulin sensitivity, but a major challenge in interpreting these results is that they did not account for the heterogeneity of patients in terms of baseline body mass index (BMI), T2D status, and prior obesity (bariatric) surgery. This is of high importance to delineate the independent effect of SSFR on glucose homeostasis. To evaluate the latter, we decided to assess the independent impact of SSFR on both glucose excursion (which is the sum of pancreatic-β cell function and insulin resistance) and insulin resistance (HOMA indices) while accounting for preoperative BMI, T2D status, and prior bariatric surgery history.

Materials and methods

Subjects

We studied 29 consecutive eligible patients who were planned to undergo SSFR that included either abdominoplasty or lower body lift surgery (liposuction cases were excluded) at Hamad General Hospital, in the period between July 2021 and December 2022. All subjects had a stable weight for at least six months before the surgery with a fluctuation of less than 3% of body weight. Patients with comorbidities were excluded except for T2D. Diabetic patients on insulin therapy were excluded. Patients with a history of obesity surgery were excluded if the surgery was less than two years before the body contouring surgery.

Study design and reporting

The research design in this study was a quasi-experiment with three time points. A quasi-experimental design lacks individual patient randomization, but it has allocation of treatment by the researcher, and the longitudinal nature of this design means that the same patients act as their own control. This design was chosen because the classical experimental design (randomized controlled trial) is not appropriate for this type of study. Outcome variables of interest were measured at three time points which were the patient hospital visits (visit one: within 1 week before surgery, visit two: 1 week after surgery, and visit three: 6 weeks after surgery). The TREND reporting guideline for nonrandomized/quasi-experimental study designs was used to guide the reporting in this paper (see Supplementary material) [22].

Patient measurements

Collected outcome variables during the three visits included patient age, gender, comorbidities and medications, history of obesity surgery, vital signs, body fat composition measurements using bioelectrical impedance analysis (TANITA® segmental body composition scale) before and after surgery, details of the surgical procedure, including type of surgery and the weight of fat mass removed (in grams), OGTT using 75-gm oral glucose with six time points of glucose measurements (fasting (gtt0), 15 min (gtt15), 30 min (gtt30), 45 min (gtt45), 60 min (gtt60), and 120 min (gtt120) in mmol/L), fasting insulin (pmol/l) and c-peptide (nmol/l), hemoglobin A1c [HBA1c; (%)], lipid profile (LDL, HDL, and triglyceride in mmol/L), c-reactive protein [CRP; (mg/L)], interleukin-6 [IL-6; (pg/mL)], vitamin D (ng/mL). The HOMA-IR (anchored at 1 for normal insulin sensitivity) was calculated by means of the fasting plasma glucose and fasting c-peptide using the University of Oxford HOMA2 calculator [23]. For each of the GTT's, glucose excursion was computed using Doi's weighted average glucose (dwAG) [24, 25] and was categorized into four categories: dwAG0 $\leq$ 6.8, dwAG1 $>$ 6.8 & $\leq$ 7.5, dwAG2 $>$ 7.5 & $\leq$ 8.6, and dwAG3 $>$ 8.6 mmol/L based on four levels of risk previously defined for women with gestational diabetes [24]. The four levels of dwAG reflect normal, impaired, abnormal, and severely abnormal dwAG, respectively. The dwAG has been validated [25] against the area under the GTT curve.

Blood samples and assays

Fasting blood samples were collected, immediately processed, and stored frozen at −80 °C pending analysis. All assays were performed at the central laboratory of Hamad Medical Corporation, a laboratory accredited by the College of American Pathologist (CAP) and Joint Commission International (JCI).

Plasma glucose was measured using a hexokinase-based enzymatic method, the coefficient of variation for the assay was 1.2% at a mean glucose value of 5.3 mmol/L during the study period. Total cholesterol, triglycerides, and high-density lipoprotein cholesterol (HDL-C) levels were measured enzymatically. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation. Serum 25(OH)D concentration (included both vitamin D2 and vitamin D3 fractions) was measured using electrochemiluminescence immunoassay (Vitamin D Total II, Roche, North America, USA). Plasma insulin and C peptide concentrations were measured on EDTA plasma (0.1 mL) using a sandwich-based assay on microparticles detected by fluorescence according to the manufacturer recommendations (insulin and C peptide Elecsys kits, Roche, North America, USA). The detection ranges were between 0.2–1000 mIU/mL and 0.01–40 ng/mL, for insulin and c peptide, respectively. The intra-assay and inter-assay variations were less than 5% for both assays. The plasma concentration of CRP was measured using a particle-enhanced immunoturbidimetric assay following the manufacturer recommendation (cobas CRP Test, Roche Diagnostics, North America, USA); the CRP in the diluted plasma binds with the CRP antibody on latex particles; the concentration of CRP is calculated as a function of the changed absorbance measured at 525 nm and 625 nm which is in relation to the amount of agglutination. The detection range is 3.0–400 mg/L and intra- and inter-assay variations are less than 4%. IL-6 was measured by a non-competitive (sandwich) chemiluminescent immunoassay (Elecsys® IL-6, Roche Diagnostic, North America USA). The assay measures a range of 1.5-5000 pg/mL, with an inter-assay precision of 17.4% (at 1.82 pg/mL) and 2.0% (at 4461 pg/mL) and a stated reference value <7 pg/mL.

All subjects had an OGTT with a 75-g glucose challenge and blood sampling at 0, 15, 30, 60, 90, and 120 min. Blood samples during the OGTT were collected in plain microtubes, rapidly centrifuged in a micro-centrifuge, and the supernatant serum

was assayed for glucose concentrations using Analox (Analox Instrument Ltd, GM9, UK).

Ethical statement

This study was approved by the Institutional Review Board at Hamad Medical Corporation and Qatar University (MRC-01-20-466 and QU-IRB 1412-EA/20, respectively), and by the Institutional Bio-safety Committee at Qatar University (QU-IBC-2020/066). All subjects signed an informed consent before starting the study.

Statistical analysis

Descriptive statistics were computed (median and interquartile range or number and percent) to report patient variables across time points. Because the data collected over time (three time points) are correlated, the methods used for longitudinal data analysis accounted for the correlated nature of the data. A cluster robust error logistic regression analysis was conducted to assess predictors of glucose excursion with the clusters being the individual patient. Two outcomes were analyzed in two separate analyses, with outcomes being either upper tertile HOMA-IR (model 1) or severely abnormal (dwAG3) glucose excursion (model 2). Only patient characteristics deemed important prognostically for these outcomes were adjusted for in these models. The mass of fat removed was not included in the models because it was correlated with the degree of obesity and thus a proxy for it. Predictive margins from the logistic model were computed as a way of presenting model results in the scale of interest (probability), not in the estimation scale (logit) as the latter is more informative than odds ratios. A predictive margin is a generalization of an adjusted mean applied to the nonlinear model (logistic regression model) thus using the estimated model to make predictions on different values of a covariate to evaluate its effect on the outcome. Stata version 15 (College Station, TX, USA) was used for all analyses and exact *P* values were reported throughout.

Results

Patients studied

The study included 29 patients (22 females and 7 males), all patients had at least one postoperative visit (15 patients completed both second and third visit, 7 patients completed the second visit only, and 7 patients completed the third visit only). Ten patients (37%) had a history of obesity surgery (six sleeve gastrectomy, two bypass surgery, two sleeve plus bypass surgery). Eleven patients (38%) were either lean or overweight, and the remaining 18 patients (62%) were obese. Five patients (17%) had T2D on oral medications, and none were on insulin therapy. A detailed medical history and complete physical examination revealed no other serious comorbidities or organ dysfunction in any participant. Average ASF removed during surgery was 2400 (range 1300–3600) g. Preoperatively, the median dwAG value was 7.0 mmol/L (interquartile range (IQR) 6.4–8.3), and median HOMA-IR was 1.6 (IQR 1.3–2.1). The Tanita full body composition analysis, complete lipid profile, and basic laboratory results are reported in Table 1. While the mean fat% and fat mass remain unchanged, on average, across visits, in a paired-difference linear regression analysis we find that for every percent difference in fat% the excised tissue in body contouring surgeries increased by 206.1 g (95% CI 26.1 g, 386.1 g).

Model 1 (HOMA-IR): Predictors of insulin resistance

The risk of severe insulin resistance (defined as having an upper tertile HOMA-IR level) was assessed in relation to SSFR, history of bariatric surgery, T2D status, and baseline BMI independently (Table 2). The median for HOMA-IR in the upper tertile (across all time points) was 2.18 (IQR 1.96–3.30).

The odds of having upper tertile HOMA-IR (independent of the T2D status, BMI, and history of obesity surgery) was 30% higher (OR 1.30; $p = 0.688$) in the first week after SSFR but had dropped 78% below base value (OR 0.22; $p = 0.042$) by 6 weeks after SSFR (Table 2). The interpretation of the latter is that at 1 week after surgery the estimated OR suggested some worsening of HOMA-IR due to postoperative inflammatory status [26] but with little evidence against the null hypothesis at this sample size ($p = 0.688$). However, at 6 weeks, there was a clinically and statistically significant drop in HOMA-IR and the odds of upper tertile HOMA-IR dropped almost five-folds over the baseline.

On the contrary, those with a history of obesity surgery (irrespective of SSFR, BMI, and T2D status) had a 56% decrease in odds of upper tertile HOMA-IR (OR 0.44) compared to those without prior obesity surgery, but this time with some evidence against the null hypothesis at this sample size ($p = 0.142$). Diabetic status showed a four-folds higher odds of having upper tertile HOMA-IR (OR 3.99; $p = 0.086$). However, BMI had a weak independent correlation with insulin resistance status (OR 1.38; $p = 0.615$). This model showed the goodness of link (linktest in Stata) and goodness of fit (Area under ROC curve= 0.709).

Model 2 (dwAG3): Predictors of abnormal glucose excursion

The risk of having a severely abnormal glucose excursion on the GTT (defined as dwAG3) was assessed in relation to SSFR, history of bariatric surgery, as well as diabetic and obesity status independently (Table 2). The median dwAG in this severely abnormal group across all time points was 9.51 (IQR 9.15–11.93).

The odds of having severely abnormal dwAG (independent of the T2D status, BMI, and history of obesity surgery) was two-fold higher (OR 2.2; $p = 0.256$) in the first week after SSFR but had returned to the base value (OR 1.05; $p = 0.956$) by 6 weeks after SSFR. The interpretation of the latter is that at 1 week after surgery the estimated OR suggested some worsening due to postoperative inflammatory status [26] but there was weak evidence ($p = 0.256$) against the null hypothesis at this sample size.

On the contrary, those with prior obesity surgery had an almost ten-fold decrease in odds of a severely abnormal dwAG status (OR 0.09; $p = 0.031$) compared to those without prior obesity surgery (irrespective of SSFR, obesity, and T2D status).

Diabetic status as expected showed an extremely high odds of having severely abnormal dwAG (OR 66.01; $p = 0.001$). However, obesity status showed weak association with the risk of having a severely abnormal glucose excursion on the GTT (OR 0.78; $p = 0.795$) suggesting that abdominal fat mass and

Table 1. Characteristics of the study population

Factor	Level	Visit 1	Visit 2	Visit 3
Number of participants		29	22	22
Age (years)		43.0 (38.0, 50.0)	41.0 (37.0, 50.0)	43.0 (38.0, 51.0)
Sex	Male	7 (24.1%)	6 (27.3%)	5 (22.7%)
	Female	22 (75.9%)	16 (72.7%)	17 (77.3%)
Diabetic status	No	24 (83%)	20 (91%)	18 (82%)
	Yes	5 (17%)	2 (9%)	4 (18%)
dwAG value (mmol/L)		7.0 (6.4, 8.3)	6.9 (6.4, 8.7)	7.1 (5.7, 8.2)
AUC-glucose (mmol/L/2h)		16.6 (13.5, 20.4)	15.8 (14.4, 19.0)	15.4 (12.9, 18.2)
HOMA-IR		1.6 (1.3, 2.1)	1.7 (1.3, 2.0)	1.5 (1.2, 1.7)
History of bariatric surgery	Yes	10 (34%)	9 (41%)	7 (32%)
	No	19 (66%)	13 (59%)	15 (68%)
BMI category	< 30	11 (38%)	9 (41%)	7 (32%)
	≥ 30	18 (62%)	13 (59%)	15 (68%)
BMI (kg/m^2)		31.7 (29.1, 33.6)	31.7 (29.1, 34.2)	32.0 (29.3, 34.2)
Bioelectrical impedance measures				
Body fat percent (%)		37 (33.6, 42.2)	37 (32.9, 42.9)	38.9 (34.1, 44.0)
Fat mass (kg)		32.4 (26.6, 37.4)	32.1 (26.6, 40.3)	32.5 (26.9, 37.4)
Total body water percent		44.4 (41.4, 47.1)	44.4 (41.4, 47.2)	43.8 (40.8, 46.1)
Basal metabolic rate (kJ/day)		5933 (5644, 6556)	5897.5 (5523, 6556)	6070.5 (5653, 7130)
Visceral fat rating		9 (6, 11)	8.5 (6, 12)	9 (6, 12)
Routine metabolic profile				
HbA1c (%)		5.4 (5.2, 5.6)	5.4 (5.2, 5.6)	5.3 (5.2, 5.6)
CRP (mg/L)		1 (1, 2.8)	1 (1, 2.9)	1 (1, 2.8)
IL-6 (pg/ml)		3 (1, 5)	3.5 (2, 5)	3 (1, 4)
Vitamin D (ng/ml)		26 (19, 36)	26.5 (21, 40)	25 (18, 40)
Cholesterol (mmol/L)		4.3 (3.8, 4.9)	4.3 (3.8, 4.8)	4.4 (3.7, 4.8)
Triglyceride (mmol/L)		0.8 (0.6, 1)	0.9 (0.6, 1)	0.8 (0.6, 1)
HDL (mmol/L)		1.3 (1.1, 1.7)	1.3 (1.1, 1.6)	1.2 (1.1, 1.7)
LDL (mmol/L)		2.8 (1.9, 3.4)	2.8 (1.9, 3.4)	2.8 (1.9, 3.3)

dwAG: Doi's weighted average glucose; HOMA-IR: Homeostasis model assessment-estimated insulin resistance; BMI: Body mass index; HbA1c: Hemoglobin A1c; CRP: c-reactive protein; IL-6: Interleukin-6; HDL: High-density lipoprotein; LDL: Low-density lipoprotein.

Table 2. Predictors of insulin resistance (model 1: HOMA-IR) or abnormal glucose excursion (model 2: dwAG3)

Variable	Model 1 (HOMA-IR) ** OR (95% CI)	*P* values	Model 2 (dwAG3) ** OR (95% CI)	*P* values
Time post SSFR				
1 week after surgery*	1.30 (0.36, 4.67)	0.688	2.20 (0.56, 8.56)	0.256
6 weeks after surgery*	0.22 (0.05, 0.95)	0.042	1.05 (0.17, 6.34)	0.956
Risk factors				
History of bariatric surgery	0.44 (0.14, 1.32)	0.142	0.09 (0.01, 0.80)	0.031
Diabetes mellitus	3.99 (0.82, 19.34)	0.086	66.01 (6.61, 435.47)	<0.001
Obese	1.38 (0.40, 4.78)	0.615	0.78 (0.12, 4.94)	0.795

* Compared to pre-surgery. ** Model 1: OR of upper tertile HOMA-IR; Model 2: OR of severely abnormal dwAG (dwAG3). HOMA-IR: Homeostasis model assessment-estimated insulin resistance; dwAG: Doi's weighted average glucose; SSFR: Surgical subcutaneous fat removal.

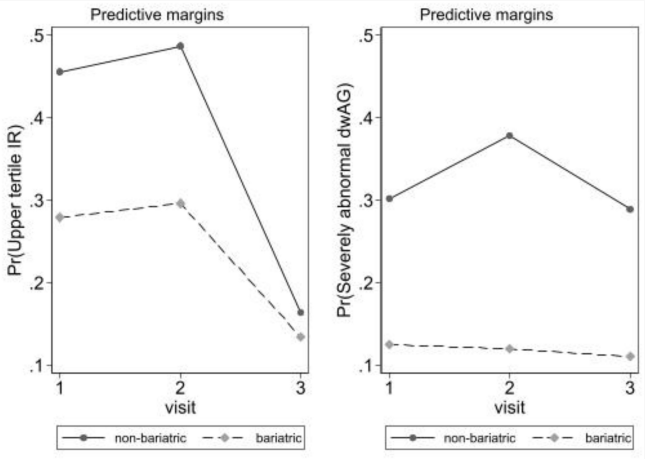


Figure 1. Predictive margins after logistic regression in Table 2. The left panel depicts insulin resistance (model 1; HOMA-IR) and right panel depicts glucose excursion under the GTT (model 2; dwAG). HOMA-IR: Homeostasis model assessment-estimated insulin resistance; dwAG: Doi's weighted average glucose.

associated adipose fat dysfunction may be stronger predictors of insulin resistance status compared to total fat mass [27]. This model showed goodness of link (linktest in Stata) and goodness of fit (Area under ROC curve = 0.764).

The impact of prior bariatric surgery on glucose homeostasis changes after SSFR

The impact of prior bariatric surgery on changes in glucose homeostasis (both insulin resistance and glucose excursion under the GTT) after SSFR was examined using predictive margins after logistic regression from models 1 & 2. Figure 1 depicts the proportions under the models described in previous sections. This analysis aims to compare the changes in proportions of patients with either upper tertile insulin resistance or severely abnormal (dwAG3) glucose excursion under the GTT in those with the history of bariatric surgery vs bariatric surgery naïve participants. The left panel depicts results for upper tertile insulin resistance (model 1) and the right panel depicts results for dwAG3 glucose excursion under the GTT (model 2).

In the left panel (Figure 1), there is an increase in proportions with upper tertile insulin resistance by visit 2 and this is seen in both those with and without bariatric surgery history. Marked improvement then follows in visit 3 (again in both groups with and without history of bariatric surgery) suggesting that insulin sensitivity has improved markedly by 6 weeks (more so in bariatric surgery naïve participants). This also correlates with the previous finding above, where SSFR resulted in a transient worsening in insulin resistance at visit 2 (1 week after surgery) possibly due to the postoperative inflammatory status [26], followed by significant improvement at visit 3 (6 weeks after surgery).

The right panel in Figure 1 depicts the proportions in relation to severely abnormal glucose excursion (dwAG3) and here the picture is different. Those with a history of bariatric surgery have no real change in probability of this degree of glucose excursion over time while those without a prior history of bariatric surgery demonstrate a rise in the proportion with severely abnormal glucose excursion by visit 2 (which parallels the increase in HOMA-IR) and then returns to baseline by visit 3.

In both the left and right panels, those with a history of bariatric surgery have both lower proportions with gross insulin resistance as well as with severely abnormal glucose excursion at all time points. It is clear that the main impact of SSFR is on insulin resistance (HOMA-IR) in all subjects, but that the glucose excursion effect is markedly attenuated in those with a history of bariatric surgery.

These results clearly suggest that SSFR improves insulin sensitivity in those with or without bariatric surgery, but only impacts glucose excursion under the GTT in bariatric surgery naïve participants, suggesting that bariatric surgery results in sustained improvements in this area possibly related to better pancreatic β-cell function (and less so in terms of HOMA-IR) [28].

Discussion

Obesity surgery is an efficient treatment for obesity and related metabolic diseases [29]. Because of the rapid and massive weight loss following the surgery, many patients tend to require

body contouring plastic surgery to remove redundant abdominal skin and excess subcutaneous abdominal fat for aesthetic purposes. The precise mechanisms by which obesity surgery affords the protections and the consequences of surgical (and non-surgical) fat removal on human metabolism are not fully clear yet [5–7]. This study answered a few of the pertinent questions through examination of the early postoperative changes in glucose homeostasis after SSFR at three time points. A clear protective effect of prior obesity surgery on glucose excursion during the GTT was demonstrated using a novel index, the dwAG. This effect was found to be independent of time post SSFR, BMI, and diabetic status. Abnormal glucose excursion has been associated with different metabolic risk profiles and increased future risk of T2D [30]. Therefore, our results suggest that obesity surgery offers this protection, independent of BMI. The mechanism underpinning this protection on abnormal glucose excursion seems to work through both effects on insulin resistance as well as pancreatic β cell function because the OGTT combines both insulin resistance and the β cell function status [31]. The implication is that glucose excursion under the OGTT curve provides a predictive test for the future development of T2D, independent of BMI. The latter is related to the overall shape of the glucose excursion curve and thus the slower the glucose curve returns to the fasting glucose level, the worse the metabolic profile with greater insulin resistance and/or worse pancreatic β cell function, and higher risk of future development of T2D [30, 32].

Insulin resistance, which is defined as a suboptimal response to normal blood levels of insulin, is what links overweight and obesity to worsening pancreatic β cell function, T2D and its associated metabolic consequences such as cardiovascular diseases. In this study, subjects with a history of obesity surgery had a markedly lower glucose excursion even at visit 2 when HOMA-IR increased, strongly suggesting that the obesity surgery effect is mediated through sustained improvement in pancreatic β cell function. This is interesting because obesity surgery is known to improve glucose homeostasis before significant weight loss ensues [32, 33] and this also occurs with calorie restriction [34]. The mechanisms by which pancreatic cell health and function are improved remain unknown [35] though it has been suggested that gut hormones, especially glucagon-like peptide-1 [36], may modulate this effect. Better understanding of what happens in the aftermath of obesity surgery will provide novel insights into our understanding of the management of chronic metabolic sequalae of obesity, especially T2D.

The removal of about 2–3 kg of ASF (through SSFR) was associated with a net benefit in terms of insulin resistance post SSFR as indicated in Table 2 and Figure 1 at 6 weeks. This improvement in insulin resistance may be linked to SSFR-associated changes in the secretion of certain adipokines, such as leptin and IL-6 [37, 38]. These two adipokines are secreted from subcutaneous fat stores rather than the visceral fat stores, due to their larger mass and higher secretion rate [38]. They both act centrally (in the hypothalamus) and peripherally in various tissues, such as adipocytes, pancreas, liver, and skeletal muscles [39], to promote insulin action and sensitivity, thereby maintaining glucose homeostasis. However, the impact of these primary adipokines may be influenced by other factors, particularly in cases of elevated leptin levels in obesity, and these additional factors may counteract the favorable effects of leptin [40, 41].

There is no doubt that leptin exerts an insulin-sensitizing effect since leptin administration exerts an insulin-sensitizing effect in those with low leptin states, including lipoatrophy states [43] and hypoleptinaemic states are also associated with insulin resistance [41, 43] which can be ameliorated by leptin treatment [43, 44]. Thus, a decrease in leptin levels is expected after SSFR, but the underlying mechanism for the paradoxical improvement in insulin sensitivity remains unknown. One explanation could be that leptin resistance is a consequence of deficiency of some other adipokine that is deficient in obesity and rises after SSFR. This would ease leptin from its resistant state, even as its own levels decrease. The mechanisms involved however need further investigation to establish a link with the two main adipokines—leptin and IL-6, which are the most abundant adipokines secreted from white adipose tissue [45].

Conclusion

In conclusion, this study demonstrates an improvement in insulin resistance after SSFR, independent of BMI, diabetic status, or obesity surgery status. Furthermore, this study sheds new light on the possibility that the long-term impact of obesity surgery may primarily target improvement in pancreatic β-cell function, regardless of SSFR. However, the intricate interplay between SSFR and obesity surgery in obesity and T2D remains to be fully elucidated.

Acknowledgments

The authors thank the Department of Plastic Surgery & Qatar Metabolic Institute at Hamad General Hospital and the volunteers whose participation made this study possible for their contribution.

Conflicts of interest: Authors declare no conflicts of interest.

Funding: SB was supported by Hamad Medical Corporation (MRC-01-20-466). AMH and SD were supported by the Qatar National Research Fund (Projects #NPRP13S-0209-200315 and #NPRP14S-0406-210153). The responsibility for the paper lies with the authors and there was no influence of the funder

Data availability: Data is available upon reasonable request from the corresponding author.

Submitted: 18 January 2023
Accepted: 06 March 2023
Published online: 22 March 2023

References

[1] Pitanguy I. Evaluation of body contouring surgery today: a 30-year perspective. Plast Reconstr Surg 2000 Apr;105(4):1499–514. https://doi.org/10.1097/00006534-200004040-00039.

[2] Kitzinger HB, Abayev S, Pittermann A, Karle B, Kubiena H, Bohdjalian A, et al. The prevalence of body contouring surgery after gastric bypass surgery. Obesity Surg 2012;22(1):8–12. https://doi.org/10.1007/S11695-011-0459-1.
[3] Borud LJ and Warren AG. Body contouring in the postbariatric surgery patient. J Am Coll Surg 2006 Jul;203(1):82–93. https://doi.org/10.1016/J.JAMCOLLSURG.2006.01.015.
[4] Rodriguez A, Catalan V, Gomez-Ambrosi J, Fruhbeck G. Visceral and subcutaneous adiposity: are both potential therapeutic targets for tackling the metabolic syndrome? Curr Pharm Des 2007 Jun;13(21):2169–75. https://doi.org/10.2174/138161207781039599.
[5] Badran S, Doi SA, Hamdi M, Hammouda A, Alharami S, Clark J. Metabolic aspects of surgical subcutaneous fat removal: an umbrella review and implications for future research. Bosn J Basic Med Sci 2023 Mar;23(2):235–47. https://doi.org/10.17305/BJBMS.2022.8175.
[6] Badran S, Habib AM, Aljassem G, Musa OAH, Clark J, Hamdi M, et al. Metabolic changes after surgical fat removal: a dose-response meta-analysis. J Plast Reconstr Aesthet Surg 2023 Jan;76:238–50. https://doi.org/10.1016/j.bjps.2022.10.055.
[7] Badran S, Doi SA, Iskeirjeh S, Aljassem G, Jafarian N, Clark J, et al. Metabolic changes after nonsurgical fat removal: a dose response meta-analysis. J Plast Reconstr Aesthet Surg 2023 Feb;77:68–77. https://doi.org/10.1016/j.bjps.2022.10.054.
[8] Giugliano G, Nicoletti G, Grella E, Giugliano F, Esposito K, Scuderi N, et al. Effect of liposuction on insulin resistance and vascular inflammatory markers in obese women. Br J Plast Surg 2004;57(3):190–4. https://doi.org/10.1016/J.BJPS.2003.12.010.
[9] Esposito K, Giugliano G, Giugliano D. Metabolic effects of liposuction—yes or no? N Engl J Med 2004 Sep;351(13):1354–7. https://doi.org/10.1056/NEJM200409233511320.
[10] Robles-Cervantes JA, Yánez-Diaz S, Cárdenas-Camarena L. Modification of insulin, glucose and cholesterol levels in nonobese women undergoing Liposuction: is liposuction metabolically safe? Ann Plast Surg 2004 Jan;52(1):64–67. https://doi.org/10.1097/01.SAP.0000096448.59407.43.
[11] Giese SY, Bulan EJ, Commons GW, Spear SL, Yanovski JA. Improvements in cardiovascular risk profile with large-volume liposuction: a pilot study. Plast Reconstr Surg 2001;108(2):510–9. https://doi.org/10.1097/00006534-200108000-00035.
[12] Giese SY, Neborsky R, Bulan EJ, Spear SL, Yanovski JA. Improvements in cardiovascular risk profile after large-volume lipoplasty: a 1-year follow-up study. Aesthet Surg J 2001;21(6):527–31. https://doi.org/10.1067/MAJ.2001.120434.
[13] Martínez-Abundis E, Molina-Villa CA, González-Ortiz M, Robles-Cervantes JA, Saucedo-Ortiz JA. Effect of surgically removing subcutaneous fat by abdominoplasty on leptin concentrations and insulin sensitivity. Ann Plast Surg 2007 Apr;58(4):416–9. https://doi.org/10.1097/01.SAP.0000240033.00047.CC.
[14] Samdal F, Birkeland KI, Ose L, Amland PF. Effect of large-volume liposuction on sex hormones and glucose- and lipid metabolism in females. Aesthetic Plast Surg 1995 Mar;19(2):131–5. https://doi.org/10.1007/BF00450248.
[15] Mohammed BS, Cohen S, Reeds D, Young VL, Klein S. Long-term effects of large-volume liposuction on metabolic risk factors for coronary heart disease. Obesity (Silver Spring) 2008 Dec;16(12):2648–51. https://doi.org/10.1038/OBY.2008.418.
[16] Klein S, Fontana L, Young VL, Coggan AR, Kilo C, Patterson BW. Absence of an effect of liposuction on insulin action and risk factors for coronary heart disease. N Engl J Med 2004 Jun;350(25):2549–57. https://doi.org/10.1056/NEJMOA033179.
[17] D'Andrea F, Grella R, Rizzo MR, Grella E, Grella R, Nicoletti G, et al. Changing the metabolic profile by large-volume liposuction: a clinical study conducted with 123 obese women. Aesthetic Plast Surg 2005 Dec;29(6):472–8. https://doi.org/10.1007/S00266-005-0089-X.
[18] Sailon AM, Wasserburg JR, Kling RR, Pasick CM, Taub PJ. Influence of large-volume liposuction on metabolic and cardiovascular health: a systematic review. Ann Plast Surg 2017 Dec;79(6):623–30. https://doi.org/10.1097/SAP.0000000000001195.
[19] Seretis K, Goulis DG, Koliakos G, Demiri E. The effects of abdominal lipectomy in metabolic syndrome components and insulin sensitivity in females: a systematic review and meta-analysis. Metabolism 2015 Dec;64(12):1640–9. https://doi.org/10.1016/J.METABOL.2015.09.015.
[20] Boriani F, Villani R, Morselli PG. Metabolic effects of large-volume liposuction for obese healthy women: a meta-analysis of fasting insulin levels. Aesthetic Plast Surg 2014 Sep;38(5):1050–6. https://doi.org/10.1007/S00266-014-0386-3.
[21] Danilla S, Longton C, Valenzuela K, Cavada G, Norambuena H, Tabilo T, et al. Suction-assisted lipectomy fails to improve cardiovascular metabolic markers of disease: a meta-analysis. J Plast Reconstr Aesthet Surg 2013 Nov;66(11):1557–63. https://doi.org/10.1016/J.BJPS.2013.07.001.
[22] Haynes AB, Haukoos JS, Dimick JB. TREND reporting guidelines for nonrandomized/quasi-experimental study designs. JAMA Surg 2021 Sep;156(9):879–80. https://doi.org/10.1001/JAMASURG.2021.0552.
[23] Diabetes trials unit : home page. [cited 2022 May 5]. Available from: https://www.dtu.ox.ac.uk/
[24] Doi SAR, Bashir M, Sheehan MT, Furuya-Kanamori L, Abou-Samra A-B, McIntyre DA, et al. Unifying the diagnosis of gestational diabetes mellitus: Introducing the NPRP criteria. Prim Care Diabetes 2022 Feb;16(1):96–101. https://doi.org/10.1016/J.PCD.2021.08.006.
[25] Badran S, Doi S, Hammouda A, Musa O, Habib A. Validation of Doi's weighted average glucose as a measure of post-load glucose excursion for clinical use. Biomol Biomed Online ahead of print. https://doi.org/10.17305/bb.2022.8807.
[26] Tewari N, Awad S, Duška F, Williams JP, Bennett A, Macdonald IA, Lobo DN. Postoperative inflammation and insulin resistance in relation to body composition, adiposity and carbohydrate treatment: A randomised controlled study. Clin Nutr 2019 Feb;38(1):204–212. https://doi.org/10.1016/j.clnu.2018.01.032
[27] Klöting N, Fasshauer M, Dietrich A, Kovacs P, Schön MR, Kern M. Insulin-sensitive obesity. Am J Physiol Endocrinol Metab 2010 Sep;299(3):E506–15. https://doi.org/10.1152/AJPENDO.00586.2009.
[28] Jørgensen NB, Bojsen-Møller KN, Dirksen C, Martinussen C, Svane MS, Kristiansen VB, et al. Sustained improvements in glucose metabolism late after Roux-En-Y gastric bypass surgery in patients with and without preoperative diabetes. Sci Rep 2019 Oct;9(1):1–10. https://doi.org/10.1038/s41598-019-51516-y.
[29] Sjöström L. Review of the key results from the Swedish obese subjects (SOS) trial—a prospective controlled intervention study of bariatric surgery. J Intern Med 2013 Mar;273(3):219–34. https://doi.org/10.1111/JOIM.12012.
[30] Andrade Mesquita LD, Pavan Antoniolli L, Cittolin-Santos GF, Gerchman F. Distinct metabolic profile according to the shape of the oral glucose tolerance test curve is related to whole glucose excursion: a cross-sectional study. BMC Endocr Disord 2018 Aug;18(1):56. https://doi.org/10.1186/S12902-018-0286-7.
[31] Bartoli E, Fra GP, Schianca GPC. The oral glucose tolerance test (OGTT) revisited. Eur J Intern Med 2011;22(1):8–12. https://doi.org/10.1016/J.EJIM.2010.07.008.
[32] Douros JD, Niu J, Sdao S, Gregg T, Fisher-Wellman K, Bharadwaj M, et al. Sleeve gastrectomy rapidly enhances islet function independently of body weight. JCI Insight 2019 Mar;4(6):e126688. https://doi.org/10.1172/JCI.INSIGHT.126688.
[33] Oppenländer L, Palit S, Stemmer K, Greisle T, Sterr M, Salinno C, et al. Vertical sleeve gastrectomy triggers fast β-cell recovery upon overt diabetes. Mol Metab 2021 Dec;54:101330. https://doi.org/10.1016/J.MOLMET.2021.101330.
[34] Sathananthan M, Shah M, Edens KL, Grothe KB, Piccinini F, Farrugia LP, et al. Six and 12 weeks of caloric restriction increases β cell function and lowers fasting and postprandial glucose concentrations in people with type 2 diabetes. J Nutr 2015;145(9):2046–51. https://doi.org/10.3945/JN.115.210617.
[35] Douros JD, Tong J, D'Alessio DA. The effects of bariatric surgery on islet function, insulin secretion, and glucose control. Endocr Rev 2019 May;40(5):1394–423. https://doi.org/10.1210/ER.2018-00183.
[36] Sridharan K, Kalayarasan R, Kamalanathan S, Sahoo J, Kar SS, Nandhini LP, et al. Change in insulin resistance, beta cell function, glucagon-like peptide-1 and calcitonin levels two weeks after bariatric surgery. Diabetes Metab Syndr 2019 May;13(3):2142–7. https://doi.org/10.1016/J.DSX.2019.05.002.
[37] Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature 2006;444(7121):840–6. https://doi.org/10.1038/nature05482.
[38] Harmelen VV, Reynisdottir S, Eriksson P, Thörne A, Hoffstedt J, Lönnqvist F, et al. Leptin secretion from subcutaneous and visceral adipose tissue in women. Diabetes 1998;47(6):913–7. https://doi.org/10.2337/DIABETES.47.6.913.
[39] Margetic S, Gazzola C, Pegg GG, Hill RA. Leptin: a review of its peripheral actions and interactions. Int J Obes Relat Metab Disord 2002 Nov;26(11):1407–33. https://doi.org/10.1038/sj.ijo.0802142.

[40] Paz-Filho G, Mastronardi C, Wong M-L, Licinio J. Leptin therapy, insulin sensitivity, and glucose homeostasis. Indian J Endocrinol Metab 2012;16(S3):S549–55. https://doi.org/10.4103/2230-8210.105571.
[41] German JP, Wisse BE, Thaler JP, Oh-I S, Sarruf DA, Ogimoto K, et al. Leptin deficiency causes insulin resistance induced by uncontrolled diabetes. Diabetes 2010 Jul;59(7):1626–34. https://doi.org/10.2337/DB09-1918.
[42] Bindlish S, Presswala LS, Schwartz F. Lipodystrophy: syndrome of severe insulin resistance. Postgrad Med 2015 Jan;127(5):511–6. https://doi.org/10.1080/00325481.2015.1015927.
[43] Mulligan K, Khatami H, Schwarz J-M, Sakkas GK, DePaoli AM, Tai VW, et al. The effects of recombinant human leptin on visceral fat, dyslipidemia, and insulin resistance in patients with human immunodeficiency virus-associated lipoatrophy and hypoleptinemia. J Clin Endocrinol Metab 2009;94(4):1137–44. https://doi.org/10.1210/JC.2008-1588.
[44] Rodríguez AJ, Neeman T, Giles AG, Mastronardi CA, Paz-Filho G. Leptin replacement therapy for the treatment of non-HAART associated lipodystrophy syndromes: a meta-analysis into the effects of leptin on metabolic and hepatic endpoints. Arq Bras Endocrinol Metab 2014;58(8):783–97. https://doi.org/10.1590/0004-2730000003174.
[45] Khan M, Joseph F. Adipose tissue and adipokines: the association with and application of adipokines in obesity. Scientifica (Cairo) 2014;2014:1–7. https://doi.org/10.1155/2014/328592.

Related articles published in BJBMS

1. Emerging roles of sortilin in affecting the metabolism of glucose and lipid profiles

   Xin Su et al., BJBMS, 2022

2. The effects of exercise on vascular markers and C-reactive protein among obese children and adolescents: An evidence-based review

   Norizam Salamt et al., BJBMS, 2020

3. The relationship between vitamin D status, physical activity and insulin resistance in overweight and obese subjects

   Gülis Kavadar et al., BJBMS, 2015

APPENDICES

Appendix A: NPRP research grant

NPRP14-S No.: 0406-210153

QNRF – NATIONAL PRIORITY RESEARCH PROGRAM - STANDARD

NPRP-S ID	NPRP14S-0406-210153
Project title in English	Metabolic Changes After Surgical Fat Removal, a quasi-experiment with four-time points
Project title in Arabic (optional)	التغييرات الأيضية بعد الإزالة الجراحية للدهون. شبه تجربة ذات أربع نقاط زمنية
Type of Application	○ Resubmission
Type of research	○ Experimental development / Translational Research
Priority Theme	3. Health 3.1 Research that leads to early detection, better prevention, improve diagnostics and treatments of chronic diseases with a high prevalence in Qatar - mainly diabetes and its complications
Submitting Institution	Qatar University
Lead PI (title, name, position)	Suhail A.R. Doi *MBBS, MMed, MClinEpid, PhD, FRCP* Head, Department of Population Medicine, College of Medicine, Qatar University
List of participants (PIs' names, collaborative institutions, PIs' residency)	PI name / PI Institution / PI residency Abdella M. Habib / QU-CMED / Qatar Mohamed Elrayess / QU-BRC / Qatar Meis Alkasem / HMC-QMI / Qatar Ropesh Krishnankutty / HMC-iTRI / Qatar
Co-Funding/cost sharing	- No Co-fund from a third-party institution. - Cost sharing from HMC- QMI (132,000 USD)
Total funding requested	**$499,488 USD** — **Project duration**: 36 months

Contents

Research Plan

1. PROPOSAL SUMMARY

Obesity is a prevalent disease among the Qatari population affecting more than half of the adult population, which makes it a national priority. This increase in body weight is a major risk factor leading to the development of insulin resistance, metabolic syndrome, and diabetes mellitus (type 2). Although obesity is a preventable disease, maintaining a normal body weight can be very challenging and difficult. This has resulted in the increase in demand for cosmetic fat removal surgery. The current drift towards surgical fat removal (AKA body contouring surgeries) has been driven by the increase in expertise with these procedures in Qatar, the high prevenance of obesity and the free access to cosmetic surgeries for citizen. This has led to a corresponding increase in health cost burden in Qatar.
Although it is well known that excess fat tissue leads towards the development of insulin resistance and its other metabolic sequelae such as diabetes mellitus and cardiovascular disease; what remains unknown however are the health implications for those undergoing fat removal surgeries. In other words, are there metabolic benefit or harm? While several studies have looked at metabolic parameters pre and post fat removal surgeries, these are few and inconclusive. Additionally, we still lack data on proteomic, metabolomic, lipidomic and clinical biochemistry changes before and after surgical fat removal. A particular characteristic of these patients is the sudden large volume removal of excess fat, which is not seen in other modalities of weight loss such as diet, and bariatric surgeries.

Through a study of blood and adipose tissue, this research proposal aims to identify:
1) The clinical improvements in biochemical profiles of patients undergoing excess fat removal as a function of time and its potential associations with the percentage of fat removal and other clinical phenotypes.
2) Novel biomarkers for the varying degrees of insulin resistance observed in these patients for a diabetic and non-diabetic group.
3) Critical underlying mechanisms for clinical benefits observed in patients after the sudden removal of excess body fat.

The resulting data will be processed by applying an extensive epidemiological analysis to understand the change in insulin resistance and glycemic as well as body mass trajectories after surgery. It is anticipated that the results of this proposal will provide critical comprehensive data. This, in turn, will enable us not only to further understand novel pathways through which insulin resistance develops and its clinical consequences in obese patients but will also provide us with data that can be used to develop promising diagnostic and therapeutic tools to tackle these cluster of clinical consequences. As such, it is likely to contribute to improvements in the management of obesity, thereby reducing the national health cost burden. The results from this proposed research project will likely enhance the delivery of vital healthcare services for the Qatari population and will increase Qatar's capacity in this field.

2. REBUTTAL (if applicable)

First reviewer feedback:

A. Liposuction has been clinically proven to have no beneficial effect on systemic insulin sensitivity. It is therefore very unclear why this is being included as an intervention.

Response: Several studies have measured changes in insulin resistance status after SFR using different tests such as measuring fasting glucose and insulin levels [46- 47] , HOMA levels [48], insulin tolerance test (ITT) [49], and the gold standard hyper insulinemic glucose clamp test [50]. Four out of the latter five studies demonstrate an increase in insulin sensitivity contrary to what the reviewer asserts. The problem to date has been the small sample sizes, inconsistency among studies in terms of diabetic status, and degree of obesity and tests used and thus no conclusion has been reached to date. [50].

of bariatric surgery. To address the above hypothesis, we will recruit the following patients' groups only: 1. Obese non-diabetic (OND) groups 2. Obese with Diabetes (OD) groups.

B. Not sure why the investigators chose to call the research design to be a quasi-experiment with four-time points. Although stated that a randomized controlled trial is not appropriate, the proposed studies are still longitudinal studies as patients will be followed up and compared to their baseline before the contouring surgery. The main concern that the current design is too ambitious to include broadly Obese non-diabetic (OND) groups, Obese with Diabetes (OD) groups and then the following subgroups: 1) OND without bariatric surgery 4) OD without bariatric surgery 2) OND with RYGB 5) OD with RYGB 3) OND with GS 6) OD with GS The team should focus on group 1 and 2 (no bariatric surgery) to establish the impact of contouring surgery first then a separate study can be designed to examine the combined effect with Bariatric surgery.

Response: A quasi-experimental design lacks individual patients' randomization, but it has allocation of treatment by the researcher, and the longitudinal nature of this design means that the same patients act as their own control. This design was chosen because the classical experimental design (randomized controlled trial) is not appropriate for this type of study.

Kindly note that the project has been changed to focus on group 1 and 2 (no bariatric surgery) to establish the impact of contouring surgery first.

Third reviewer feedback:

A. A plan for communication and exploitation of results is provided but is rather limited for the breadth and significance of the project.

Response: Results of this study will be sued to update the health system (surgical departments among governmental and private hospitals) regarding the non-cosmetic impact on patients and may serve to modify selection criteria for this procedure, to those who would benefit most, or avoid harm. Dissemination of results based on the data will be through peer-reviewed publications and conference presentations. Given the importance of our research, particular attention will be focused on the wider dissemination of the research findings.

Kindly see updates of section **6.4** below for further details.

B. Specific deliverables regarding the public dissemination of the project results are not included in the workplan.

Response: Specific deliverables have been added at the end of each workplan below.

3. RENEWAL JUSTIFICATION (if applicable)

Not applicable.

4. OBJECTIVES AND SIGNIFICANCE

4.1. SCIENTIFIC OR TECHNICAL OBJECTIVES

A. Background

Overweight and obesity have reached pandemic levels and currently affect all age groups and socioeconomic classes worldwide [1]. Obesity prevalence has almost tripled in the last 50 years according to the World Health Organization and this, in turn, has led to more fatality than malnutrition and underweight combined [2]. The rising obesity rate has led to a substantial rise in metabolic diseases such

as diabetes mellitus type 2 (T2D), hypertension, cardiovascular disease, non-alcoholic hepato-steatosis and dyslipidemia [3]. About 70% of Qatar's adult population is overweight or obese (as discussed at the Qatar Diabetes Leadership Forum on 13th Feb 2020). Qatar is now ranked fifth globally in terms of incidence of obesity [1], which makes further research focused on the field of obesity and associated metabolic diseases including diabetes as a national priority as indicated in the Qatar National Health Strategy 2018 – 2022.

Lipids comprise a wide range of molecules such as phospholipids, fatty acids, and triglycerides [4]. These molecules represent a highly efficient energy resource. Recent studies have advanced our view of adipose tissue from being simply a store for energy, into an active endocrine organ, which secretes several metabolically active adipocytokines such as leptin, adiponectin, and resistin. The latter play an essential rule in glucose hemostasis and energy metabolism in our body [5]. These molecules have been ascribed to have a critical role in energy homeostasis through communication with organs that maintain system-wide metabolic homeostasis such as the liver. Of the adipocyte-derived factors, adiponectin, and leptin are among the essential adipocytokine hormones. Indeed, adiponectin analogs are now considered one of the promising new therapeutic targets for obesity-linked hyperglycemia, that mitigates obesity and improves insulin sensitivity [6-7].

Insulin resistance, as a consequence of such dysregulation associated with obesity, is what links the latter to T2D. Insulin resistance leads to dysregulation of glucose homeostasis via a combination of impaired glucose clearance and elevated glucose production in the liver. The insulin resistance itself is thought to be a consequence of adipocyte mass. Too little fat mass, as seen in patients with lipodystrophy, results in a severe form of insulin resistance and too much adipose mass can also result in a similar condition [8]. The primary reason for the latter form of insulin resistance may be hypoxia in adipose tissue that leads to inflammatory lipotoxicity [9].

Currently it is unknown if the removal of excess subcutaneous fat tissue through surgical fat removal (SFR; aka body contouring surgeries such as abdominoplasty) ameliorates the mass of hypoxic fat thus reducing its consequences. Such surgeries have become very common because, although obesity is a preventable disease, maintaining a normal body weight can be very challenging and difficult and the increase in demand for SFR has been driven by patients seeking an improved physical appearance [10]. The current drift towards surgical fat removal (AKA body contouring surgeries) has been driven by the increase in expertise with these procedures in Qatar, the high prevenance of obesity and the free access to cosmetic surgeries for citizen.

A typical example of these body contouring surgeries is the abdominoplasty (aka Tummy Tuck) surgery which suddenly removes around 2-3kg of subcutaneous fat tissue, and usually followed by tightening the abdominal wall muscles, to correct if there is a divarication of recti muscles, especially in females with a history of multiple pregnancies [11-12]. Suction-assisted lipectomy represent another common example of surgical fat removal, that target subcutaneous fat from unwanted area such as the abdominal wall and flanks. The accelerating demand for these surgical procedures, has gradually moved practice from removing a small amount of intractable fat tissue, to removal of a large volume (more than four liters of fat) of subcutaneous fat tissue [13], which eventually can result in a significant metabolic effect [14].

SFR classically involves abdominal and thigh fat removal, although other sites may less commonly also be targets for surgery [12]. When abdominal fat is the target of SFR, it should be noted that only subcutaneous fat mass is removed. Interestingly, the distribution of fat depots in humans determines metabolic outcomes.

Abdominal (or upper-fat) distribution is correlated more strongly with obesity-associated metabolic risks and consequences more than the gluteo-femoral (or lower-fat) distribution in the gluteal and thigh regions [15-17]. Central obesity in the abdominal area, represents one of the essential components of metabolic syndrome, along with insulin resistance, elevated serum triglyceride, blood pressure, and low high-density lipoproteins [5]. Abdominal obesity is distributed into two major compartments, subcutaneous and intra-abdominal. The latter is divided into retroperitoneal and intraperitoneal fat compartments. Intraperitoneal fat is known as visceral fat and represents both the mesenteric as well as the omental fat cells [18].

Some studies have proposed that both subcutaneous as well as intraabdominal fat play a role in metabolic risk [14]. Others have linked the metabolic risk of obesity mainly to the visceral adipose tissue, because it is directly involved in the delivery of free fatty acids as well as inflammatory protein such as interleukin-6 (IL-6), to the liver via the portal circulation [18-19]. However, subcutaneous fat may also play a role given that more than 80% of these free fatty acids and other inflammatory proteins reach the liver via the systemic circulation [20-21]. This is supported by studies that found intrahepatic triglyceride rather than visceral fat is a better marker for obesity associated metabolic risk [22]. Therefore, it has recently been

suggested that the metabolic risk in obesity is a shared effect of molecules secreted by both these compartments. Thus, there is an expectation that SFR may alter glucose homeostasis and insulin resistance as a direct consequence of surgical subcutaneous fat removal.

Research has found that even a small weight loss (of up to 10 percent) can result in a significant improvement of obesity linked metabolic abnormalities such as insulin resistance, high blood pressure, abnormal inflammatory markers level, and associated dyslipidemia [6, 23-27]. Additionally, the development in the knowledge of the metabolic consequences of excess body fat and observations after bariatric surgeries [5], have suggested that there could possibly be a similar effect after SFR. This has been examined in several studies, which measure hormonal changes before and after SFR at different time points. These studies have been small and heterogenous and have reported inconsistent effects on metabolic parameters such as insulin resistance, adipocytokine levels and inflammation [28-39] .

To improve power and resolve inconsistency, these small studies have been combined and analyzed in several systematic reviews (SR) and meta-analyses (MA). The first was conducted in 2013 [40], and since then another five syntheses have been published [41- 45]. These syntheses can be classified into those that investigate time trends, and those that looked at fixed time outcomes after surgery. Only one synthesis examined the time trend after SFR, however they looked at the changes in weight and fat mass only [45]. The remaining syntheses looked at metabolic changes without considering the heterogeneity in follow up duration across studies. These metabolic changes include insulin resistance, adipocytokine levels and inflammatory markers.

Several studies have measured changes in insulin resistance status after SFR using different tests such as measuring fasting glucose and insulin levels [46-47] , HOMA levels [48], insulin tolerance test (ITT) [49], and the gold standard hyper insulinemic glucose clamp test [50]. Apart from the glucose clamp test, most of these tests are not accurate in assessing the change in insulin sensitivity, and a study that used the glucose clamp test, had a small sample size and a lot of variability among participants in terms of diabetic status, and degree of obesity [50]. The challenge behind using accurate tests such as the hyper insulinemic glucose clamp and the intravenous glucose tolerance test is the fact that they are very demanding [51].

Across three MAs and two SRs examining the effect of SFR on insulin sensitivity, most of the evidence suggests a possible improvement in obesity associated insulin sensitivity, however there was a lack of clarity regarding the extent of the effect, and clinical significance. This was because there were major problems in design and analysis of the MAs and therefore results couldn't be interpreted. In terms of the SRs there was no clarity on the extent of the changes across the studies, since there was a focus on statistical significance only. It is clear that the impact of SFR on insulin resistance remains unknown given the data reported in Table 1. Although syntheses were inconsistent, there was a trend towards improvement in insulin sensitivity, but the clinical extent or duration of any improvement remains unclear.

Patients seeking body contouring surgeries that target the abdomen and thigh regions will have a BMI in the overweight to the obese range with different degrees of insulin resistance. The previous literature has suggested that almost all people start to have insulin resistance when their BMI starts to cross 23. Obesity causes an increase in the efflux of fatty acids from the adipocytes, which will be converted into a triglyceride molecule and this results in the production of many metabolites and intermediates that cause insulin signaling impairment and eventually insulin resistance. The latter, in turn, causes an increase in visceral fat such as omental fat and also results in fatty changes in the liver. Thus, in our study, we will be measuring the changes in insulin resistance after removing an average of 2-3 kg of subcutaneous fat cells, and we will try to understand the mechanism behind the observed differences. Furthermore, insulin resistance in overweight and obese patients is modulated by intermediates in lipid metabolism. To understand why certain patients, have a high BMI but still maintain a lower degree of insulin resistance, these intermediates need to be studied. This can be achieved through proteomic and metabolomic investigation to know which intermediates might be associated with insulin resistance. Such information will be of value in providing diagnostic and therapeutic benefit as well as for generating tools for early detection of diabetes and metabolic disorders. Another exciting field of this research proposal is to find if some of these metabolites are associated with more improvement in the insulin sensitivity status after the body contouring surgeries.

The main difference between SFR and other modalities of fat loss (such as diet, exercise, or bariatric surgeries) is that non-SFR modalities result in a gradual decrease in both the subcutaneous and intra-abdominal fat tissue. This gradual reduction occurs through a decrease in the size of the adipocytes while with SFR there is actual loss of subcutaneous adipocytes number, but without impact on intraabdominal adipocytes [14]. In summary, the precise effect of a sudden removal of a patient's body fat on metabolism

are still not fully understood, particularly in terms of changes in insulin resistance, adipocytokine levels, inflammatory markers, appetite, satiety, and mental wellbeing.

	Study	Design and objective	Participants and follow up	Main finding	Remaining evidence gaps
1.	Sailon et al. 2017 [41]	A total of 10 studies, published between 2000 and 2009, examined the effect of large volume liposuction (more than 3.5 liters) on insulin resistance.	A total of 346 participants, with variable duration of follow up duration between 3 weeks and 6 months after SFR.	Author reported conflicting results but stated that surgical fat removal by large volume liposuction can improve insulin sensitivity. No clear extend of change was reported.	This review focused examining the statistical significance of these changes post SFR, without reporting the extent of change, or its clinical importance. The review had substantial heterogeneity in terms of participants baseline characteristics, included studies sample size, and different assessment tools for insulin resistance.
2.	Seretis et al. 2015 [42]	A total of 4 studies, published in the period between 2007 and 2014, assessed the effect of SFR on insulin resistance. Studies examined the effect of SFR by comparing it to non-surgical procedure, as well as to other surgeries that doesn't target the subcutaneous fat tissue.	A total of 140 subjects. Three of the studies had a follow up of around 2 months, while the fourth had a follow up of 2 years.	Fasting glucose levels changes after SFR were not statistically significant (1.42, 95% CI: −1.57, 4.40). Changes in insulin sensitivity were also assessed either by insulin tolerance test or HOMA index, however the result reported lack of significant change after SFR (0.14, 95% CI -0.69-0.96).	This meta-analysis included 4 studies that were so contrived in terms of control group that no conclusion was possible. The small number of studies limited it's validity and prevented subgroup analysis according to certain confounders such as age or BMI.
3.	Boriani et al., 2014 [43]	A total of 5 prospective studies, published between 2001 and 2008, were examined for changes in insulin resistance after SFR.	A total of 190 participants with a range of follow up between 3 months and 1 year.	Fasting insulin levels were significantly higher before SFR by a WMD of 3.49 mIU/ml [95% CI 1.12, 5.87].	There was a degree of heterogeneity among studies ($p = 0.02$, $I^2 = 67$ %). Fasting insulin levels was used as a surrogate for insulin resistance, which is an indirect measure.
4.	Daniilla et al., 2013 [52]	A total of 5 studies were included, published between 1995 and 2008. All of the studies were designed as quasi experiments.	A total of 111 participants with range of follow up between 3 weeks and 6 months. One study had a follow up of 1 year, but it included 9 participants only.	Analysis reported that SFR result in decreased fasting insulin levels, and the amount of reduction was associated with the amount of aspirated fat, independent with the baseline BMI. No significant change was reported in HOMA levels after SFR.	Although this MA studied the effect of time on the SFR induces changes in insulin resistance, the sample size of the included studies was small.

B. Objectives

This proposal aims to address the following hypotheses concerning sudden excess fat removal by surgical fat removal in obese patients.

Hypothesis-1. Removal of excess fat during body contouring surgery alone can result in measurable clinical benefit (e.g., Satiety, eating behavior, Mental wellbeing, OMICS and biochemical indices of insulin resistance and glucose homeostasis).

Hypothesis-2. Clinical benefits of excess fat removal are likely to be greater in obese patients with type 2 diabetes compared to non-diabetic obese.

In our study, we will be initially limiting the population of studied patients to naive patients who never had bariatric surgery before so the impact of the contouring surgery can be easily determined separate from the impact of bariatric surgeries. Once this is established then we will extend our studies to the combination of SFR with and without history of a bariatric surgery. To address the above hypothesis, we will recruit the following patients' groups:

3. Obese non-diabetic (OND) groups 4. Obese with Diabetes (OD) groups

Thus, in these patient groups we will address the following previously unaddressed important questions relating to the above hypotheses:

1) Does the sudden excess fat removal by body contouring surgery alone result in clinical benefit?
- Over what time-frames post-surgery does this occur?
- Can these be correlated to the degree of insulin resistance and/or to the percentage of body fat removed?
- If there is clinical benefit, what is the underlying molecular mechanisms?
- Can we identify novel biomarkers through transcriptomic, proteomic, lipidomic and biochemical profiling?

2) Are the clinical benefits associated with the removal of excess body fat different in non-diabetic obese vs diabetic-obese patients?

In summary, through a study of blood and adipose tissue, this research proposal aims to identify-
1) The clinical improvements in biochemical/OMIC profiles of patients undergoing excess body fat removal as a function of time and its potential correlation with the percentage of fat removed and clinical phenotypes.
2) Novel biomarkers for the varying degrees of insulin resistance observed in these patients for diabetic and non-diabetic groups.
3) Critical underlying mechanisms for clinical benefits observed in patients after the sudden removal of excess body fat.

This project will be conducted with specific aims and will involve mainly primary data collection but also secondary data collection from existing research studies.

C. Aims:

1. To determine if insulin resistance, glycemic status, appetite and mental well-being are modulated by such a sudden change in the non-visceral fat after surgical fat removal.
2. To determine using biochemical and OMIC profiling if there could be any novel biomarkers that distinguish between the patients with varying degrees of insulin sensitivity and other clinical phenotypes described above.
3. To understand the mechanisms through which the changes observed in aim one is mediated, thus lending itself as a foundation for further investigation into newer therapeutic approaches for mitigating the development of type 2 diabetes mellitus.

Aim one:
The following approach will be utilized to determine if clinical improvements are modulated by such a change in the non-visceral fat after the body contouring surgeries as below:
1A. Non-diabetic patients: to determine if insulin resistance is modulated by such a change in the non-visceral fat after the body contouring surgeries in the abdomen and thigh regions. This will be ascertained by measuring glycemic changes before and after the surgery over four timelines (pre-operative, immediate post-operative, short term and long-term post-operative). Glycemia related changes will be assessed using well known baseline measurements (HOMA, HbA1c, relevant hormones (GLP-1, PYY, GIP, insulin-like 5, ghrelin, leptin, adiponectin, vitamin D, midnight salivary cortisol, IL-6 and TNF-alpha), fatty acids and the oral glucose tolerance test (OGTT). The OGTT will use 4 time points (0, 0.5, 1 & 2 hours) with measurement of c-peptide and glucose simultaneously.
1B. Diabetics: to determine the impact on glycemic status after such a change in the non-visceral fat, using similar measurements as above (excluding the OGTT).
1C. Measure the amount of change in anthropometric/ fat mass measurements (height, weight, BMI, waist circumference and body fat), as well as measure the changes in the Mental Health Questionnaire (PHQ-9) [23] for depression, the Appearance Anxiety Inventory Questionnaire for body dysmorphic disorder [24], the Generalized Anxiety Disorder-7 Questionnaire (GAD-7), the Council of Nutrition Appetite Questionnaire (CNAQ) [26] after 6 months of undergoing surgical fat removal. Fat mass measurements will be done using the Tanita electrical impedance method.

Aim Two:
To identify novel biomarkers of changes seen in Aim 1 through epidemiological linkage of clinical data with the signatures derived from proteome, lipidome and steroid hormone profiles of fat tissue and blood of patients with varying degrees of insulin sensitivity. The goal is to translate this profiling into a diagnostic and therapeutic tool for managing insulin resistance among overweight and obese patients. This will be achieved by the following studies on fat tissue and blood samples recruited during and post-surgery (only blood):

2A. Proteomics: From fat tissue lysates and serum
1- Prepare extracts for proteome and lipidome profiling. Fat tissue and serum samples will be extracted to obtain hydrophobic and lipophilic fractions. Extracts will be centrifuged to obtain soluble fractions, which then will be used for a) direct mass spectrometry profiling and/or b) separations by electrophoresis (for proteins) or chromatography (for lipids) followed by mass spectrometry.
2- Study the relative expression of proteins, lipids with emphasis on fatty acids and steroids, in adipocytes, by applying chromatography, electrophoresis and mass spectrometry. Extracts may contain complex mixtures, and a separation of the mixture components would be required. For proteins, we will use 1D- and 2D-electrophoresis. For lipids, we will use reverse phase (RP) chromatography by using a C18-RP column. Electrophoresis and chromatography allow quantification and measurement of relative quantities of proteins and lipids. For mass spectrometry measurements, we will use relative ion count (for unknown molecules) and comparison with external standards (for known molecules).
3- Generate representative profiles of proteins and lipids for studied clinical conditions. Standardization of extraction, separation and mass spectrometry protocols will allow to generate representative profiles. Profiles of clinical samples will be integrated to obtain representative profiles. For profiles of GLP-1, PYY, GIP, insulin-like 5, ghrelin, leptin, adiponectin, vitamin D, midnight salivary cortisol, IL-6 and TNF-alpha, and c-peptide, external standards will be used to ensure secure identification and relative quantification. External standards will also be used to generate fragmentation spectra with our mass spectrometry instrument (Ultraflextreme).
4- Report systemic analysis of the profiles for correlations with the studied clinical conditions. Representative profiles of medical conditions will be compared to identify unique components and molecules changing levels of expression. Molecules with change in expression for at least 50% of control values will be considered. For integration of data for systemic analysis, we will use open source tools, e.g. Cytoscape, String, FunCoup.

2B. Metabolomics: From cultured preadipocytes:
1- Isolate stromal vascular fraction from adipose tissue and expand preadipocytes cultures.
2- Study the adipogenic capacity of isolated preadipocytes.
3- Measure cytokines/adipokines secreted from expanded preadipocyte cultures.

4- Measure oxidative stress and insulin signaling from expanded preadipocytes cultures.

Aim three:
To understand the mechanisms behind clinical changes observed in objective one, by applying novel epidemiological methods to analyze data collected through aims 1 & 2 thus creating an opportunity for discovery of newer therapeutic approaches for mitigating the development of type 2 diabetes mellitus, and this will be achieved through:

3A- Epidemiological analyses of changes in measured hormones, and profiles (proteomic, metabolomic and gene expression) before and after the surgery (immediate post-operative, short term after 6 weeks and long term after 6 months).
3B- Analytic examination of the magnitude of these changes with the clinical changes described in Aim 1 and the amount of fat tissue removed from the surgery.

4.2. ADVANCES ON STATE-OF-THE ART

This research is aiming to target the uncertainties in the metabolic changes after a sudden reduction in the amount of subcutaneous fat tissue by surgical methods. This in turn will help the team understand the underlying mechanism behind the insulin resistance trajectories among overweight and obese patients which is a major cause of morbidities and mortalities among the Qatari population and on the global level as well. The team is well positioned to apply epidemiological, proteomic and metabolomic techniques in the elucidation of the aims of the project.

This research output aims ultimately to increase our knowledge and improve our clinical practice in managing obesity-associated insulin resistance and other metabolic complications, which has a direct consequence for the health system by potentially suggesting ways through which higher accuracy and specificity in the treatment and detection of these diseases can proceed. Eventually, this will have a positive impact on the cost burden of treating these obesity-related diseases and complications. The innovation in this program of work outlined in this research proposal is not limited to theory-driven data, but the aim is to be clinically translated into novel diagnostic and therapeutic targets that are clinically feasible to tackle these metabolic diseases.

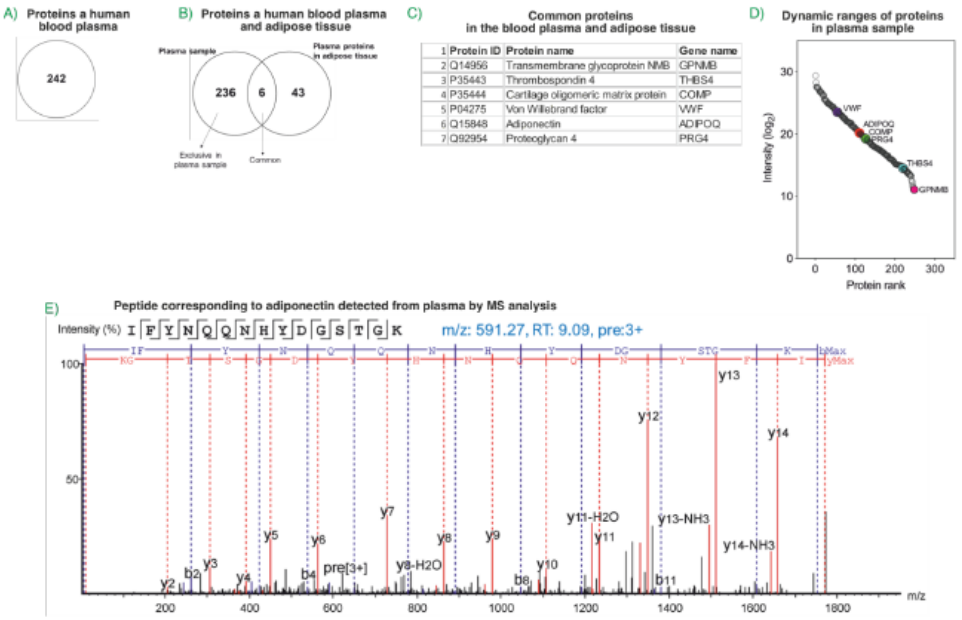
4.3. PRELIMINARY DATA OR STUDIES

A. Sample collection

Over the last year, Institutional Review Board (IRB) and Institutional Biosafety Committee (IBC) approvals were obtained from the affiliated partners (Hamad Medical Corporation and Qatar University). Recently patient's recruitment has started after obtaining the required site approvals from HMC. Over the last 3 months, 7 patients were recruited; and blood & fat samples were collected and stored. All patients were followed up for 6 weeks (third time point).

B. Proteomic analysis from blood sample

An example of a proteomic analysis from a serum sample, using Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS), is depicted below in Figure 1:



	Protein ID	Protein name	Gene name
2	Q14956	Transmembrane glycoprotein NMB	GPNMB
3	P35443	Thrombospondin 4	THBS4
4	P35444	Cartilage oligomeric matrix protein	COMP
5	P04275	Von Willebrand factor	VWF
6	Q15848	Adiponectin	ADIPOQ
7	Q92954	Proteoglycan 4	PRG4

Figure 1: Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) data analysis and visualization of plasma proteomic profile.
(A) The number of proteins identified in human blood plasma after depletion.
(B) Venn diagram showing the unique proteins identified in the plasma vs adipose tissue (from the human protein atlas database).
(C) The common proteins in both samples, such as adiponectin
(D) The wide dynamic range of quantified proteins present in the blood plasma sample and adipose tissue (from the human protein atlas database), is highlighted.
(E) Peptides corresponding to the adiponectin detected in the plasma.

C. Isolation of stromal vascular fraction and expansion of preadipocyte cultures

Stromal vascular fraction (SVF) was obtained from all collected adipose tissues. Preadipocyte cultures were expanded from SVF (Figure 2) and aliquots were stored in liquid nitrogen for future experiments.

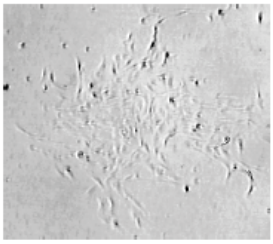


Figure 2: An expanded colony of preadipocytes from adipose tissue-derived stromal vascular fraction.

D. Study the adipogenic capacity of isolated preadipocytes.

Adipogenic capacity was assessed in expanded preadipocyte cultures using established protocols [53] in the presence of inflammatory (IL-6) and oxidative stress (4-HNE) conditions used to study adipogenesis in its pathophysiological milieu. Our preliminary data showed no effect of 4-HNE and IL-6 treatment on preadipocyte proliferation assessed by Alamar blue (Figure 3A) and counting of DAPI-stained nuclei (Figure 3B). However, data showed reduced adipogenic capacity with IL-6 (p=0.1, Figure 3C) and 4-HNE (p=0.2, Figure 3D). Data also suggest a slight increase in the size of differentiated adipocytes in response to IL-6 (p=0.09) and 4-HNE (p=0.09) (Figure 3E), suggesting a hypertrophic phenotype.

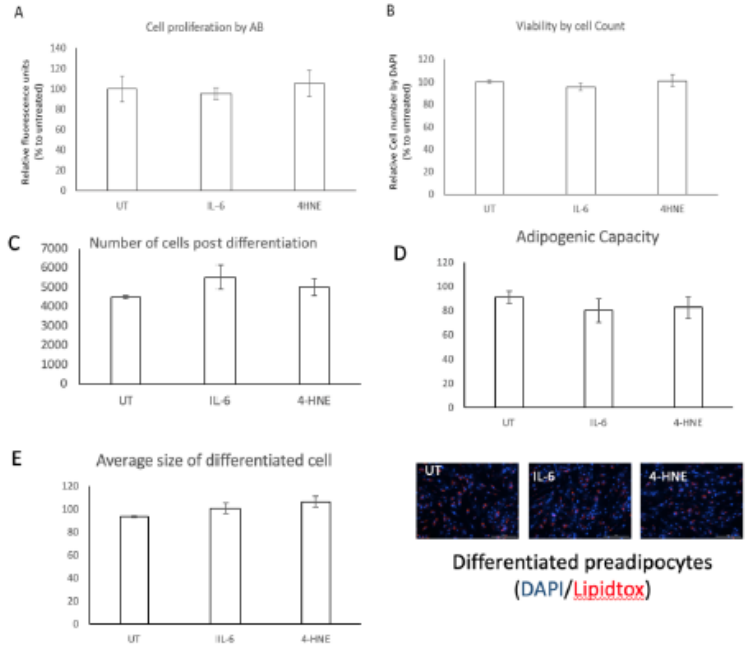


Figure 3: Proliferation and differentiation of SVF-derived preadipocytes in presence of IL-6 and 4-HNE treatment. SVF-derived cells (passages 1–3) were grown in stromal medium for 4 days then proliferation was assessed using Alamar blue (A) and DAPI staining (B). Cells were also grown in stromal media overnight then incubated in differentiation medium (DMEM-F12 containing 3% (vol./vol.) FBS, 33 µmol/l biotin, 17 µmol/l D-pantothenate,1 µmol/l dexamethasone, 250 µmol/l methylisobutylxanthine, 0.1 µmol/l human insulin and 5 µmol/l of PPARγ agonist, rosiglitazone) for 7 days, followed by 12 days in maintenance medium containing the same components as the differentiation medium, except for methylisobutylxanthine and rosiglitazone. To investigate IL-6 mediated insulin resistance, cells were grown as above, with 20 ng/ml IL-6 for the entire differentiation/maintenance periods with medium change every 2-3 days. For investigating 4-HNE-mediated insulin resistance, cells were grown as above, with 10 micromole 4-HNE for the entire differentiation/maintenance periods. Adipogenic capacity was assessed using lipidtox staining. Adipogenic capacity was assessed in untreated (UT), IL-6 and 4-HNE treated cells by measuring number of differentiated cells (C), % of differentiated cells (lipidtox/DAPI positive cells) (D) and cell size as assessed by Cytation 5 software (E). Images of UT, IL-6 and 4-HNE treated cells are shown in E (DAPI in blue and lipitox in red).

E. Additional preliminary data on related topics:

The research team has contributed to a large volume of data generated in this area relating to clinical endocrinology, diabetes, clinical epidemiology and research synthesis [54-142], clinical biochemistry 131-195], proteomics [196-236] and metabolomics [237-241] in leading journals in their field. The research team has an extensive and wide spectrum of skills in the field of endocrinology & diabetes, proteomics, genetics

and plastic surgery which will meet the required remit of this research project. In terms of subject matter expertise, the team is led by a clinical endocrinologist and clinical epidemiologist (LPI Doi) who will coordinate the extensive data analysis required for the project and its resulting publications. Other members of the research team include experts in diabetes (Consultant Abou-Samra), biochemistry (PI Habib), proteomics (Consultant Souchelnytskyi) and metabolomics (PI El Rayess), thus the team is well placed as content experts in this project.

LPI Doi and Consultant Abou-Samra are not only top tier researcher in the field of clinical endocrinology, but also the LPI has worked as a top tier researcher in clinical epidemiology thus bringing methodological expertise to this project in addition to content expertise. They have thus contributed many papers (listed above) in high impact journals in the field of obesity and diabetes. LPI Doi has previously conducted a related epidemiological study to this project to address the examination of the fasting and the 2-h plasma glucose in the light of beta-cell functional impairment [63]. In addition, he is successfully leading an NPRP-10 project, Translating Research Evidence into Practice for Gestational Diabetes and Refining Tools for Meta-analytic Research Synthesis, which has produced robust outcomes in year 1 of the project in terms of high yield publications [242-246].

Key investigators Habib, Souchelnytskyi & Elrayes have participated in previous funded projects some including NPRP projects. Altogether they form a team with world expertise in biochemistry/proteomics/metabolomics. For example, Consultant Souchelnytskyi is a world expert in proteomics and is the Head of the QU Proteomics Core facility. This facility has the necessary instrumentation and has developed applications which would be used in this project. Consultant Souchelnytskyi had conducted an NPRP project that focused on studying the differences in proteome profiles of human cancers, e.g. breast cancer, lymphoma, brain cancers. He has experience in development of new markers and drug targets, based on OMICs profiling. PI Elrayess has previously established and validated the protocols described in objective 3B as part of a QNRF funded grant (NPRP6) investigating insulin-resistance related impaired adipogenesis in obese participants. He will utilize the wealth of previous data and the technical expertise of his laboratory to compare differences between fat cells from abdominal surgeries versus fat cells from thigh surgeries to facilitate meeting the objectives of this project.

5. METHODOLOGY AND PROJECT STRUCTURE

5.1. METHODOLOGY

A. Research design:

The research design will be a quasi-experiment with four-time points. A quasi-experimental design lacks individual patients' randomization, but it has allocation of treatment by the researcher, and the longitudinal nature of this design means that the same patients act as their own control. This design was chosen because the classical experimental design (randomized controlled trial) is not appropriate for this type of study.

B. Research set up:

The methodology in this project will leverage the unique position of Qatar where body contouring surgeries occur almost daily in each governmental and private hospital in Qatar due to the combination of relatively low health care costs and a high socio-economic status of the relevant populations receiving body contouring surgery. Consultant Hammouda and RA Badran will be involved with all patient surgeries recruited to this study (surgical resident) and will manage the recruitment process for the patients in concert with Consultant Hammouda on this project. Recruitment will happen during the routine preoperative visits, during which the research protocol will be explained, and the patient will be given a copy of the research information sheet and research consent. Patient participation will be completely optional and will not affect their care in any way, and withdrawal or continuation within this project will be treated identically.

In this research design the outcome variables of interest will be measured before and at three time points after the surgical intervention (interrupted time series design; preoperative "baseline phase", immediate postoperative, short term phase and long-term phase) as below:

1- Preoperative Phase: within 1 week before the surgery.
2- Immediate Phase: within the first post-operative week.
3- Short term Phase: during the short term follow up clinic visit; between 2-6 weeks after surgery.
4- Long term phase: during the long term follow up clinic visit; after 6 months post-surgery.

All patients will be consented before starting the project by one of the research team. Patients in each of the following encounters will be asked to go to Qatar Metabolic Institute for blood samples collection, he will be instructed to come fasting for 8 hours with the help of the PI Alkasem and Consultant Abou Samra. The patient will have an IV canula and blood samples will be collected for the OGTT and other tests. Patient medical history in addition to the questionnaires used in this study (CNAQ, PHQ-9, GAD-7 & body dysmorphism questionnaire) will be assessed before the surgery, 6 weeks after surgery, and 6 months after the surgery. Blood samples collected will be sent to Qatar University laboratory for analysis and the planned profiling by one of the PI's of the study.

PI's Krishnankutty & Habib, and Consultants Souchelnytskyi & Steinhoff , will assist with the proteomic analyses. The tissue samples will be extracted with solvents to obtain fractions of proteins (hydrophilic) and lipids (hydrophobic). This extraction protocol will be subjected to quality controls, to ensure high levels of extraction. These protocols have been developed for solid tumors and cultured cells; we tested these protocols with animal (sheep) fat tissue. Matrix-assisted laser desorption ionization (with a time of flight analyzer; MALDI-ToF) mass spectrometry profiling of the extracts confirmed feasibility of this work. Obtained mass spectra allow us to conclude that the available technologies can deliver informative results.

Our experience of analysis and clinical correlation studies are confirmed in publications [169-209]. The figure-1 & 2 below depicts that the method has the ability to detect more than 100 molecules in a single mass spectrometry run. This was obtained in a trial run using human blood plasma (figure-1) and fat tissue extract (sheep) figure-2. Note that we will have multiple fractions to run (10-50) per sample which will provide a rich source of detected molecules (proteins, peptides, metabolites).

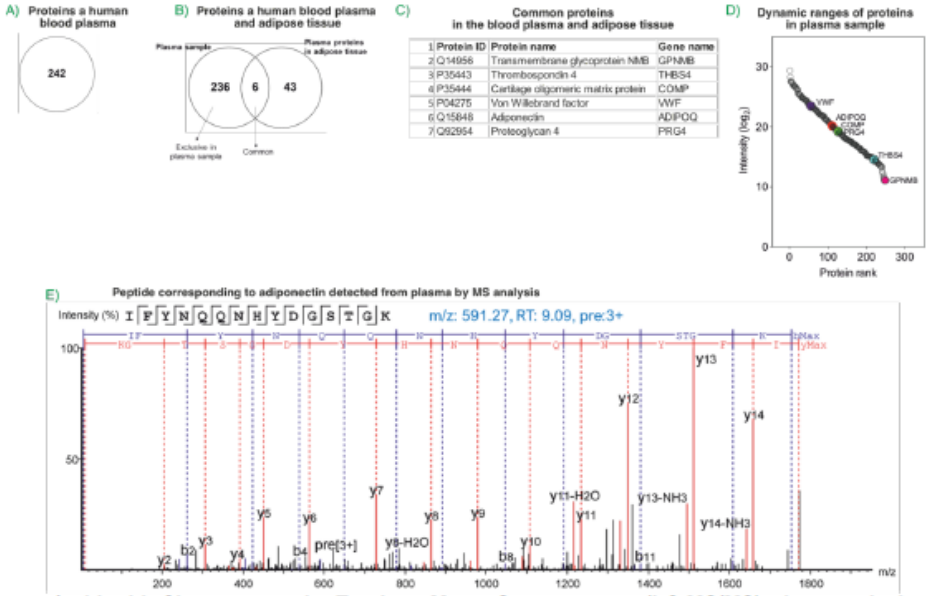


Figure 1: Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) data analysis and visualization of plasma proteomic profile.

(A) The number of proteins identified in human blood plasma after depletion. (B)Venn diagram showing the unique proteins identified in the plasma vs adipose tissue (from the human protein atlas database). C) The common proteins in both samples, such as adiponectin (D) The wide dynamic range of quantified proteins present in the blood plasma sample and adipose tissue (from the human protein atlas database), is highlighted. (E) Peptides corresponding to the adiponectin detected in the plasma.

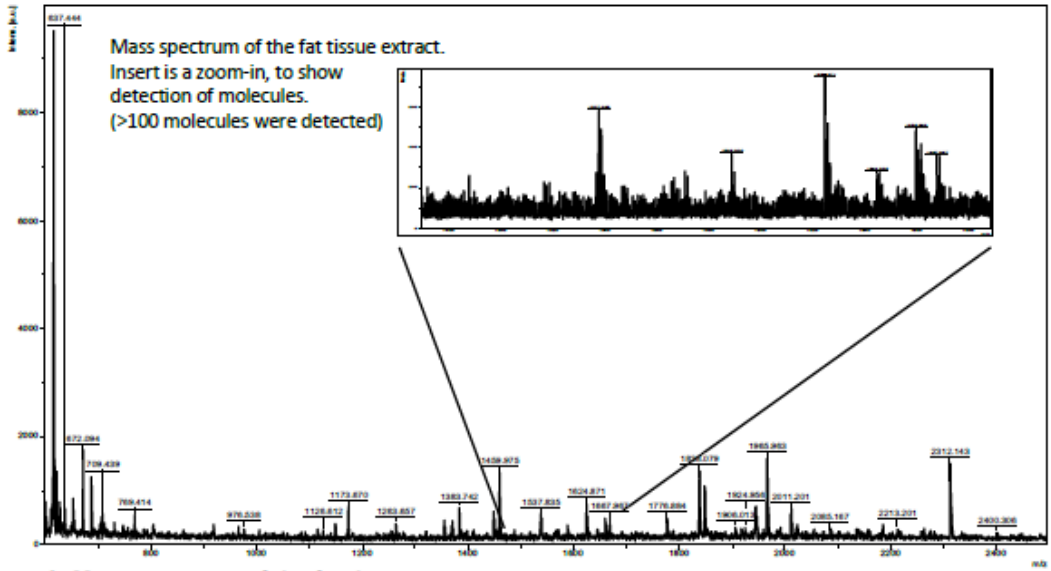


Figure 2: Mass spectrum of the fat tissue extract.

Separation of proteins will be performed by 2-dimencional gel electrophoresis. To detect 3,000 to 5,000 proteins in a sample and measure differences in their expression which is the routine at the Proteomics Core facility. Differentially expressed proteins will be selected for identification by MALDI TOF/TOF mass spectrometry at Ultraflextreme (Bruker). Peptide mass fingerprinting and fragmentation by post-source decay. Separation of lipids will be by FPLC (Akta). We will optimize the chromatographic matrix, with reverse phase matrix to be the first choice. Chromatographic fractions will be prepared for further mass spectrometry identification, by drying to decrease the volume and quality control of composition. Identification of lipids will be performed by MALDI TOF/TOF mass spectrometry.

For identifications, we will use such databases as NCBInr (for protein ID searches) and primarily METLIN database (http://metlin.scripps.edu) for mass spectrometry spectra matching for metabolites/lipids. For lipids we will also use LipidMaps (http://www.lipidmaps.org/data/index.html), SphinGOMAP (http://sphingomap.org/) and Lipid Bank (http://lipidbank.jp/index00.shtml). Integration of data will be performed with use of such systems biology tools as Cytoscape, FunCoup and KEGG. To evaluate clinical relevance of obtained signatures, we will correlate components of the signatures with available clinical information on pathogenicity, disease-relevance, prognosis, prediction and targeting by drugs, We will use NCBI databases with clinical information, e.g. ClinVar.

For identifications, we will use such databases as NCBInr (for protein ID searches) and primarily METLIN database (http://metlin.scripps.edu) for mass spectrometry spectra matching for metabolites/lipids. For lipids we will also use LipidMaps (http://www.lipidmaps.org/data/index.html), SphinGOMAP (http://sphingomap.org/) and Lipid Bank (http://lipidbank.jp/index00.shtml). Integration of data will be performed with use of such systems biology tools as Cytoscape, FunCoup and KEGG. To evaluate clinical relevance of obtained signatures, we will correlate components of the signatures with available clinical information on pathogenicity, disease-relevance, prognosis, prediction and targeting by drugs, We will use NCBI databases with clinical information, e.g. ClinVar.

C. population:

Patients undergoing body-contouring surgeries at the Department of Plastic Surgery in Hamad General Hospital in the period 2021-2023.

D. Inclusion criteria:

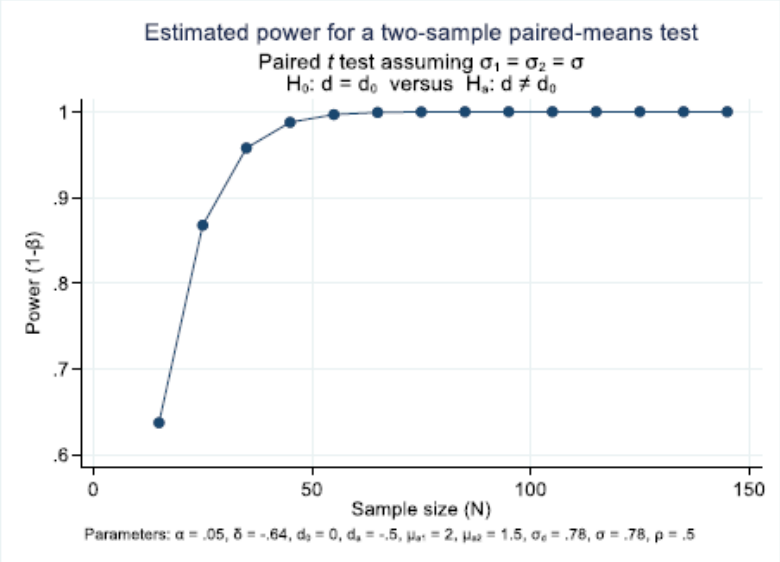
- Abdominoplasty surgeries: aims to remove the excess fat and skin from the abdominal area [247].
- Lower Body Lifting Surgeries which aim to remove the excess fat and skin tissue in the lower trunk circumferentially, the gluteal area and the thighs [248].
- Thighplasty: aims to remove excess fat and skin tissue from the thigh region [249].
- BMI 25-32.
- Age 18 - 65y.

E. Exclusion criteria:

-Patients with a history of bariatric surgeries (gastric band, sleeve gastrectomy, by-pass surgery)
-Patients declining participation in the study or asking to be withdrawn at any time.
-Patients who underwent bariatric surgery less than 18 months before the body contouring surgery.
-co-morbidities (except diabetes).
-Diabetic nephropathy (eGFR <60ml/min).
-Age <18 or >65y.
-Body contouring surgeries outside the abdomen or thigh.

F. Sample size

Our primary outcome is the change in insulin resistance after surgical fat removal (SFR). We consider a minimum clinically significant change in HOMA2 IR to be between 15%-25% [250] from a baseline of 2.0 (change of approximately 0.5). The variance of HOMA2 IR was derived from a previous study of ours were the HOMA IR was approximately normally distributed in subjects with values < 3.5 with a variance of 0.61[63]. For an alpha of 0.05, we estimate a sample size of 35 (given the conservative difference of 0.5 in HOMA-IR) will give us 90% power to detect a statistically significant difference should a true difference of this magnitude exist. Given two groups (diabetic and non-diabetics), and an expected 30% drop out rate, we will recruit 100 subjects.



5.2. RESEARCH PLAN REQUIREMENTS REGARDING THE SECTIONS ON THE PROTECTION OF HUMAN SUBJECTS SECTION; AND/OR ON THE VERTEBRATE ANIMAL CARE AND USE.

The local ethics committee approval of the study and patients will be sought from Hamad Medical Corporation as well as Qatar University. Consent will be taken at the plastic surgery clinic, Hamad General Hospital by the consultants / resident on this project who is taking care of the patient after a full explanation of the study. Participants will be informed that their data will be used during the entire period of research without any link to their profile. The Information sheet and the consent form will be given to the participant and explained carefully at the first outpatient clinic visit preoperatively. Signing of consent will be done at the admission encounter or the next clinic visit, whichever comes first.

5.3. PROJECT MANAGEMENT

A. Setting

This Study will involve HMC facilities at the Department of Plastic Surgery in Hamd General Hospital (Consultant Hammouda and RA Badran), Qatar Metabolic Institute (PI ALkasem and Consultant Abou-Samra), and Translational Research Institute (PI krishnankutty and Consultant Steinhoff). It will also involve Qatar University facilities at the College of Medicine (facilitated by LPI Doi, PIs Habib and Consultant Souchelnytskyi) and the Biomedical Research Institute (facilitated by PI Elrayess).

B. Data collection & handling of confidentiality

The data set will be collected primarily from patients, with some secondary data collection. The primary data will include clinical and laboratory data as outlined in the methods. All data collected will be coded with links to actual patient information kept confidentially in a secure location at Hamad General Hospital. Only the KI will have access to the patient identification details. Data will be de-identified before release from HGH.

C. Data analysis

The members of the research team have a long-standing track record of research collaboration across different teams. Data will be analyzed extensively and collaboratively with the health system at the Department of Population Medicine at Qatar University. The Department is well positioned for the requisite analytical and design expertise (LPI Doi, Principal Supervisor) who has not only the relevant expertise but also is the author of several analytic models in Medicine and has written a book on Methods of Clinical Epidemiology [225].

In brief, because the data collected over time (four-time points) are correlated, the methods used for longitudinal data analysis will account for the correlated nature of the data. There are many methods through which this can be achieved, but in this study the plan will be to use cluster robust analysis. In this method, we consider statistical inference in regression models where observations can be grouped into clusters, with model errors uncorrelated across clusters but correlated within clusters. The LPI has discussed the use of such modeling previously in relation to meta-regression [226] and a variant of this regression approach will be used here. Stata version 15 (College Station, TX, USA) will be used for all analyses. All statistical and epidemiological analyses will be done under oversight from the LPI.

5.4. TECHNICAL DESCRIPTION BY WORK PACKAGE

5.4.1. Work Packages (WP) 1:

WP#	Work Package Title	Start Month	End Month
1.	Research Synthesis	Jan 2022	Sep 2022

Participant Name	Efforts Inside Qatar	Efforts Outside Qatar	Total Efforts in Days
LPI Doi	40	0	40
PI Habib	20	0	20
Consultant Abou-Samra	10	0	10
RA 1	240	0	240
RA 2	240	0	240

Objectives of this work package
To compare using a systematic review and meta-analysis, the changes in insulin resistance and glycemic status in patients before and after surgical fat removal from abdomen & thigh regions.

Description of work
One scoping review and meta-analyses will be conducted to achieve the objective. The tasks involved include: -T1.1. building the search strategy and retrieving all relevant publications (2 months). -T1.2. screening and selection of publications (2 months). -T1.2. data extraction and analysis (2 months). -T1.4. write-up and submission of the manuscript to a journal (3 months).
Deliverables
2 publications submitted to a journal – Year 1/ Month 9.

Performance Site(s)
Qatar University (CMED).

5.4.2. Work Packages (WP) 2:

WP#	Work Package Title	Start Month	End Month
2.	Quasi-experimental trial	Jan 2022	Dec 2024

Participant Name	Efforts Inside Qatar	Efforts Outside Qatar	Total Efforts in Days
LPI Doi	*30*	*0*	*30*
PI Habib	*30*	*0*	*30*
PI Elrayess	*50*	*0*	*50*
PI Alkasem	*75*	*0*	*75*
PI Krishnankutty	*25*	*0*	*25*
Cons. Abou samra	*20*	*0*	*20*
Cons. Steinhoff	*20*	*0*	*20*
RA 1	*240*	*0*	*240*
RA 2	*240*	*0*	*240*

Objectives of this work package
A) Patient recruitment & management as well as clinical data collection and collection of clinical laboratory data. B) Use of information in A) to determine if insulin resistance, glycemic status, appetite and mental well-being differ across patient phenotypes, and evaluate trajectories over time (pre surgery & post-surgery at three time points)

Description of work
WP2 will be carried out throughout the research project, the tasks involved include: -T2.1. Getting the IRB approvals from Hamad Medical Corporation and Qatar University (9 months). -T2.2. Recruiting patients at Hamad General Hospital and data collection from questionnaires and blood tests collected from the patients at 4-time points (15 months). -T2.3. Clinical patient data and clinical laboratory data extraction and analysis (4 months). -T2.4. Write-up and submission of the manuscript (8 months).

Deliverables
One publication submitted – Year 3/Month 6. One publication submitted – Year 3/Month 12.

Performance Site(s)

Hamad Medica Corporation (Surgery Dep. + QMI+ iTRI) & Qatar University (CMED +BRC)

5.4.3. Work Packages (WP) 3:

WP#	Work Package Title	Start Month	End Month
3.	Laboratory study	Jan 2022	Dec 2024

Participant Name	Efforts Inside Qatar	Efforts Outside Qatar	Total Efforts in Days
LPI Doi	*20*	*0*	*20*
PI Habib	*40*	*0*	*40*
PI Elrayess	*25*	*0*	*25*
PI Krishnankutty	*50*	*0*	*50*
Cons. Abou samra	*20*	*0*	*20*
Cons. Steinhoff	*30*	*0*	*30*
RA 1	*240*	*0*	*240*
RA 2	*240*	*0*	*240*

Objectives of this work package
To determine how clinical parameters in WP2 are modulated using proteomic/metabolomic profiling. This will provide a good source of data for discovery of novel biomarkers and elucidate mechanisms that can be translated into use for early detection and diagnosis of dysmetabolic traits. This work package will consist of: A) Profiling of fat tissue lysate and serum B) Culturing preadipocytes: D) Epidemiological analyses linking these data with clinical parameters

Description of work
WP3 will be carried out throughout the duration of the research project, the tasks involved include: -T3.1. Getting the IRB approvals from Hamad Medical Corporation and Qatar University (9 months). -T3.2. Recruiting patient's fat tissue samples from Hamad General Hospital and send them to Qatar Biomedical Science labs for analysis (9 months). -T3.3. Data extraction and analysis (6 months). -T3.4. write-up and submission of the manuscript to a journal (12 months).

Deliverables
One publication submitted to a journal – Year 3/Month 6 One publication submitted to a journal – Year 3/Month 12

Performance Site(s)
Hamad Medica Corporation (QMI+ iTRI) & Qatar University (CMED +BRC)

5.5. WPs SCHEDULE, DELIVERABLES AND MILESTONES

Table 1: List of work packages

WP number	WP title	Responsible person	Person-days inside Qatar	Person-days outside Qatar	Start date	End date
1	Research synthesis	LPI	550	0	Jan 2022	Sep 2022
2	Quasi-experimental trial	LPI	775	0	Jan 2022	Dec 2024
3	Laboratory study	PI Habib	605	0	Jan 2022	Dec 2024
Total			**1930**	**0**		

Table 2: List of deliverables

WP #	Deliverable number	Deliverable title	Responsible Person	Type of deliverable	Delivery date
WP1	2 papers	Scoping review + meta-analysis	LPI	Publications in a peer review Journals	Sep 2021
WP2	2 papers	Papers on clinical changes	LPI	Publications in a peer review Journals	During the second and third year
WP3	2 papers	papers on relationship between clinical parameters and biochemical / OMICS data	PI Habib	Publications in a peer review Journals	During the second and third year

Table 3: Estimated timeline of the project

WPs & Tasks	Year 1												Year 2												Year 3											
	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12
WP1																																				
T1.1																																				
T1.2																																				
T1.3																																				
T1.4																																				
WP2																																				
T2.1																																				
T2.2																																				
T2.3																																				
T2.4																																				
WP3																																				
T3.1																																				
T3.2																																				
T3.3																																				
T3.4																																				

6. EXPECTED IMPACT OF THE PROJECT

6.1. OUTPUTS AND OUTCOMES

It is anticipated that at least 2 peer-reviewed review and meta-analysis papers with targeted clinical impact will be published. Given the relevance of the results and the impact that these will have on clinical decision making and public health policies, high impact medical journals (e.g., BMJ, Lancet) will be targeted.

2 additional peer-reviewed articles outlining the clinically relevant changes in the hormonal profiles and their clinical implications after the body contouring surgeries as well as an understanding of the trajectories of these changes will be published in specialized endocrinology and plastic surgery journals (such as PRS or Clin Endocrinol).

Another 2 peer-reviewed articles are expected to be published making use of epidemiological linkage of the clinical and proteomic/metabolomic data. These will be planned to be published in high impact endocrinology and metabolism journals (such as J Clin Endocrinol Metab).

Given the position of the LPI, and the trans-disciplinary team across five institutions (CMED-QU, BRC-QU, HGH-HMC, QMI-HMC, iTRI-HMC), this proposal will promote a culture of collaborative research work and create a culture of scholarship that will progress the educational agenda of Qatar.

The research papers are expected to generate new knowledge that will have a direct bearing on our understanding of the mechanisms for the development of insulin resistance and subsequent metabolic complications in overweight/obese populations. This is expected to lead to identification of novel methods of early detection for people at risk which aligns with the priorities of the Qatar National Diabetes Research Agenda. The impact on the Qatari population is expected to be significant given that the prevalence of overweight/obesity in this population is about 70% (as discussed at the Qatar Diabetes Leadership Forum on 13th Feb 2020).

The surgeries that we are assessing are very frequently performed in Qatar (almost daily across hospitals in the country – public and private) and therefore it is important to document and assess the metabolic consequences of these surgeries. The data on the latter are very minimal and this project will bring conclusiveness to this area. The data collected will guide policy in this area.

6.2. ALIGNMENT TO NPRP-S PRIORITY THEMES

This proposal falls within the National Priorities Research Program 13 (NPRP 13) biomedical and health pillar priority theme of non-communicable diseases. The priorities under this pillar are 2.2.3 Diabetes, 2.2.2 Cardiovascular and 2.2.4 Mental health all of which are the priority themes of this project. This theme presents a number of challenges and this project has the capacity to impact all the specific priorities including prevention, diagnosis, early detection, epidemiology and treatment. This will optimize effective delivery of health care and related systems and services and improve the health and wellbeing of the Qatar population through better use of research output.

There is a pressing need to ensure that we expand research input to cope with the high impact of such metabolic disorders and to study the metabolic effect of these body contouring surgeries which is gaining accelerating popularity in Qatar. This, in turn, will be an opportunity to improve our clinical practice so that Qataris can continue to enjoy a productive and fulfilling life with the best efficiencies for support and health services, and on the budget. Importantly, it will provide robust evidence that can be used to guide health modeling, support public health messages, develop preventative interventions and even therapeutic modalities. As such it is likely to contribute to major health care advances thereby providing a better quality of life for the population.

6.3. SOCIAL, HEALTH, ECONOMIC, AND ENVIRONMENTAL IMPACT

Based on the current literature it is not clear if surgical fat removal for cosmetic reasons has a neutral, adverse or beneficial impact on metabolic health of a patient. This is a critical question to be answered for Qatar, because this is a common procedure amongst the Qatari population, given the free access to this surgical procedure. There is a need to invest scientific effort towards answering this question, in order to ensure that patients are not harmed by this procedure. In addition, if benefits are found, this can then have potential implications for type 2 diabetes in terms of understanding interaction with fat tissue related hormones and further our medical knowledge of the interaction between fat mass and various hormonal regulation.

Additionally, Qatar University (QU) intends to become the most research-intensive university in the region. Qatar University (QU) has been ranked 332nd in the QS World University Rankings 2019, among the top 1,000 universities in the world, and 36th in the "QS Top 50 Under 50" 2019 ranking. It has been steadily increasing in rank across reputable international rankings. QU-CMED facilitates national and international collaboration with world research leaders and fosters the career development of staff through providing opportunities for training (e.g. academic leadership) and funding for attendance at national and international conferences. The current proposal is integrated within QU's broader strategic recognition of core responsibilities around providing research leadership, addressing complex problems, and extending benefits to the community that accompanies the development and maintenance of a pervasive research culture. QU has systematically and deliberately invested in the development of a health cluster across the colleges of Medicine, Health Sciences and Pharmacy. The present proposal fits with existing QU research strengths in terms of advancing the fields of diabetes & metabolic diseases, clinical epidemiology and the field of molecular medicine.

The funding sought in the current proposal would provide the required level of research support for LPI Doi in his capacity as an academic staff member and Head of the Department of Population Medicine, to deliver on the mission of this research-intensive Department located within the QU-CMED and thus strengthen Qatar's research infrastructure. It will also support the role of QU-CMED in post-graduate education.

Key elements of the mission of the College of Medicine, in line with Hamad Medical Corporation's priorities, are to better the health of the population through leveraging research findings and to promote and improve the physical as well as mental health and wellbeing of the Qatari population. The project will contribute directly to this mission through better evidence generation across a multitude of unanswered questions to generate new data that will link clinical, biochemical, molecular and mental health parameters (such as depression, generalized anxiety and body dysmorphic disorder scores) after these body contouring surgeries. These findings will generate new evidence regarding mood in relation to molecular changes that are measured through proteomic analyses. In so doing, the capacity for informed decision making through leveraging of research output becomes more robust and reliable contributing to our ability to make the best use and interpretation of knowledge in the country, potentially informing policy and practice.

The proposed project can provide a very strong platform for the continuation, consolidation, and expansion of this work, and through this have an impact on the National Health Strategy (NHS) of Qatar as outlined by the Ministry of Public Health (MOPH). Research translation is a key aspect of the MOPH health strategy as that is what guides policy and practice and is evidenced by being a key element within the NHS. In addition to its direct alignment with the strategic priorities of Qatar Foundation, the proposed research will allow existing national and international collaborative relationships with other research institutions to be strengthened through collaborative analyses of large datasets. As Head of the Department of Population Medicine, LPI Doi can continue to influence research translation in this area of national importance thus creating further opportunities for collaborative research translation activities to be initiated and developed within CMED and these outputs will be invaluable to the various researchers in these streams. They would also be valuable to researchers across QU such as in Biomedical Sciences, Public Health, Academic Departments of Surgery & Medicine and therefore this project has strategic importance well beyond CMED thereby contributing to cross- and inter-disciplinary research at QU. This funding can also support the strategic requirements of both the CMED and QU by providing access to opportunities that LPI Doi can leverage for the broader interest of the Qatari research community.

6.4. COMMUNICATION AND EXPLOITATION OF RESULTS

Results of this study will be sued to update the health system (surgical departments) regarding the non-cosmetic impact on patients and may serve to modify selection criteria for this procedure, to those who would benefit most, or avoid harm. Dissemination of results based on the data will be through peer-reviewed publications and conference presentations. Given the importance of our research, particular attention will be focused on the wider dissemination of the research findings. Where possible open access options will be chosen and results will be communicated to the broader community through the general media, public seminars and talks to interest groups and leaders especially within the NHS of the MOPH in Qatar. With the support of QU, it is anticipated that the research team will organize local seminars and workshops on key methodologies utilized as part of the educational service for medical and postgraduate students.

Special interest will be to use this project as a promotion for further collaborative studies among the involved parties, as well as an opportunity to advertise our postgraduate projects that include masters and PhD. programs at Qatar University. This will aim to generate not only advanced clinical knowledge but also will help the development of future researchers that will continue to support the health advancement of this country.

7. RISK ASSESSMENT AND MITIGATION

A. Informed consent:
The local ethics committee approval of the study and patients will be managed according to the Declaration of Helsinki. Consent will be taken at the plastic surgery clinic - Hamad General hospital by the consultant/ doctor who is taking care of the patient after a full explanation of the study. Subjects will be informed that their data will be used during the entire period of research without any link to their profiles. The Information sheet and the consent form is going to be given and explained carefully to the patient at the outpatient clinic visit preoperatively. Signing of the consent form will be later on at the admission encounter or the next clinic visit.

B. Patient Risk:
Risks associated are minimal and limited to taking an additional blood sample from the patient using the same puncture site for the routine blood workup, this causes very rarely: minor bruising, small hematoma, diaphoresis, and hypotension. To minimize these risks, Hamad Medical Corporation policies will be used during blood sampling.

C. Bio Specimen & Sample Collection:
Samples collected from the patient will include blood and fat samples which are planned to be stored for analysis in batches. Storage of fat and blood samples will be at -80-degrees Celsius at Qatar University, College of Medicine laboratories. No link between bio-specimens and patient details or information will be circulated to PIs or placed on data collection sites (electronic or on paper). The sample will be coded, and the code system will be saved in a different place inside Hamad General Hospital and only the Clinical staff and the LPI will have access to identifying information when needed for follow-up.

D. Data Collection, Management & Confidentiality:
After taking consent from the patient, a coding system will be used, and each participant will be given a research participation number to be used throughout the research project. Consent will be saved as a hard copy in a secure place dedicated to the principal investigator inside Hamad Medical Corporation.
The coding system that links between the patient details in the consent and the research number will be stored at the Department of Plastic Surgery on a secure Hamad Medical Corporation computer. Another hard copy for the coding system will be stored in an allocated place inside Hamad General Hospital. The datasheet will be stored in soft and hard copies, using only the coding system identifiers. No subject identifiers will be used outside Hamad Medical Corporation.

E. Subject Withdrawal/ Withdrawal of Consent:
A subject can withdraw from the study at any time during the study. But their plan of care will follow the hospital protocol and their withdrawal from the study will not affect their plan of care.

F. Adverse Event Reporting:
Risks of the research will be minimal and limited to the very rare skin ecchymosis, small hematoma or dizziness, which will be treated at the time of the event and will be dealt with as per Hamad Medical Corporation's safety protocol for venipuncture sampling. These minor events will be reported to the Medical Research Center on the regular follow up reports. All adverse events will be monitored to ensure that they are consistent with those encountered during usual care

G. Ethical Considerations:
Our study will be conducted in full compliance with principles of the "Declaration of Helsinki", Good Clinical Practice (GCP) and within the laws and regulations of the Ministry of Public Health (MOPH) in Qatar. The study will only be conducted after review and approval from the relevant ethics review committees.

8. RESEARCH TEAM DESCRIPTION

8.1. DESCRIPTION, SUITABILITY AND COMPLEMENTARITY OF THE RESEARCH TEAM MEMBERS

A. LPI

The project will be led by Suhail A.R. Doi MBBS, MMed, MClinEpid, PhD, FRCP(Edin) (LPI), Head, Department of Population Medicine, College of Medicine, Qatar University who is a Professor of Clinical Epidemiology and also a board-certified Clinical Endocrinologist listed on the specialist register of the General Medical Council (UK) and a Fellow of the Royal College of Physicians of Edinburgh. (see section 5.3). A key element of this project will be to extend and strengthen existing collaborative links with researchers in Qatar, this will include working closely with the research team.

QUALIFICATION OF THE LPI

LPI Doi MBBS, MMed, MClinEpid, PhD, FRCP(Edin) is a consultant endocrinologist (with expertise in diabetes mellitus and metabolic disorders) and Head of the Department of Population Medicine at the College of Medicine, Qatar University (with expertise in clinical epidemiology, statistical approach to research synthesis and meta-analysis). LPI Doi is an internationally recognised researcher in research synthesis and endocrinology, he has published widely and has more than 200 publications listed on PubMed (h-index 40 and >6000 citations), written a core text on clinical epidemiology and edited a book on the Methods of Clinical Epidemiology as part of the Springer Series in Epidemiology and Public Health. He has also written a book chapter on Medical Therapy for Surgical Patients in Clinical Surgery: A practical Guide published by Hodder Arnold publishers (UK).

In 2009, LPI Doi took up his first primarily academic position at the University of Queensland in Australia and since then he has worked extensively to develop the interface between clinical practice and clinical epidemiology (relative to opportunity since he relinquished a full time clinical consultant role in 2009 to further his research interest) and create new research tools. These include collaborations with several leading researchers in Australia including leading epidemiologists Dr Jan Barendregt & Professor Gail Williams and mathematicians Professor Shahjahan Khan. His methods are currently being applied to the analysis of data from the Burden of Disease group at the Institute of Health Metrics and Evaluation at the University of Washington (Professor Theo Vos). More importantly, his work has generated cross-disciplinary interest in application of the methods in medicine from Surgeons (Dr Metrakos from McGill University), Cardiologists (Dr Gerald Kaye from Queensland Health), Endocrinologists (Dr Anthony Russell from Queensland Health) Medical Physicists (Dr Tomas Kron from the Physical Sciences Department, Peter MacCallum Cancer Centre) and Medical Epidemiologists (Dr Per Hall from the Karolinska Institute). LPI Doi has published with all of the latter researchers in the area of research translation in medicine and given the fact that his methods focus also has a focus on application makes him ideally positioned for this funding bid with a view to furthering key contributions to the research methods that further research translation in medicine.

LPI Doi is on the editorial board of the Journal of Clinical Epidemiology ranked first in the category Medical and Health Sciences as well as Statistics Editor for British Journal of Nutrition (Cambridge) as well as member of the Australasian Epidemiological Association (AEA) and the Convener of the Clinical Epidemiology and Research Synthesis Methods Special Interest group (CERSSIG) of the AEA which is an initiative to foster research and knowledge transfer in methods to facilitate translation of research findings that directly translate to gains in terms of community health and well-being. LPI Doi is also a peer reviewer for various funding agencies in medical research such as the MRC (UK) and the NHMRC (Australia). He has been invited as a speaker to many international conferences and this project will continue to enable such engagements by funding travel for LPI Doi to conduct research with colleagues at partner organizations and to fund dissemination of new data at international venues such as those organized by the European Cooperation in Science and Technology to which he is an invited speaker in Athens in February 2020. Dr Doi's engagement with industry has led to new tools already being used to characterize research translation but the support from this research project will enable further development and demonstration of the validity of the methods. His ability to continue to work closely with methodological experts and application users will provide LPI Doi access to unique opportunities to further develop his clinical, biostatistical and mathematical skills towards metabolic problems which will progress our understanding of real-life solutions to these. With the focus on collaboration with clinical and basic science partners, the present project is strongly and uniquely placed to inform Qatari policy relevant to translational research in this area. Given that LPI Doi brings in both mathematical/epidemiological as well as endocrine/metabolic expertise to bear, QU is therefore very supportive of LPI Doi's research agenda and intends to support this application in any way possible.

B. PIs

1. **PI Habib** was appointed as an Assistant Professor of Biochemistry at the Qatar University, College of Medicine in 2017; and he is also a visiting faculty at University College London (UCL). Before joining Qatar University, he undertook post-doctoral training at the University of Cambridge and UCL, the U.K. and post-graduate training at Cold-Spring Harbor Laboratory, USA. He holds a PhD in Clinical Biochemistry from the University of Cambridge in 2010 and a bachelor's degree from Imperial College London, U.K. His research activities relate to human sensory science, primarily to the nutrient-sensing endocrine cells in the intestine and the genetics of sensory neurons particularly in the context of appetite regulation and diabetes. PI Habib has co-authored in top-tier scientific journals including Nature Medicine, Cell Metabolism and Brain. His publications have been cited 563 times in one year (2019). His most recent results from work studying families with rare Mendelian genetic disorder in which two novel genes were discovered, ZFHX2 in 2018, and FAAH-OUT in 2019. These discoveries attracted worldwide media attention including Nature, Science and is ranked #18 in The New York Times the most-read stories of 2019.

2. **PI Elrayess** is an Assistant Research Professor and a principal investigator at QU with over 18 years of post-doctoral experience spent mostly in industry where he led projects focusing on target validation, seed finding and lead optimization. Over the past 6 years, PI Elrayess has successfully led two NPRP projects that resulted in over 10 publications, and a provisional patent as well as his role as a PI in a third NPRP funded project in collaboration with PI Mazloum. PI Elrayess has a lot of experience in research related to preadipocyte differentiation in relation to insulin resistance and molecular mediators underlying increased risk. His novel findings linking impairment of preadipocyte differentiation to increased risk of IR and T2D in obesity has now received worldwide recognition with over 100 citations in the past 3 years. He has supervised 6 post-graduate students (2 PhDs and 4 MSc students) and has managed multiple research as well as service-based projects.

3. **PI Alkasem** is a Post-Doctoral Research Scientist at Qatar Metabolic Institute (QMI)-AHS Hamad Medical Corporation. She graduated from the Faculty of Medicine at Aleppo University in 2013 with a national exam score of 234/240 ranking First among the high school students and worked for 1 year of internship at Aleppo University Hospital in Syria from 2011 to 2012.She was a Research Associate from March 2013 to 2018 in Qatar Metabolic Institute (QMI)-AHS before she joined the Post-Doctoral Research Scientist. She has attended several of training in Hamad Medical Corporation like Collaborative Institutional Training Initiative Program (CITI): Conflicts of Interest, Biomedical and Social Behavioral Researchers (HIPS) HMC Biomedical Researchers (Basic Course), HMC Clinical Trials Investigators (GCP) and HMC Hazardous materials responders (2016) And Attended multiple conferences in Syria, Qatar and USA for continuing medical education. Also, she attended PTCR online course for 6 months. Dr.Meis contributed to multiple

clinical studies and clinical trials like PPM-0102-160028 - Genetic versus Environmental Basis for Familial Diabetes in Qatar (Qatar National Research Fund – QNRF Personalized Medicine Program).And she has over 15 of publications and Conference Abstracts.

4. **PI Krishnankutty** is a Biotechnology professional with expertise in Protein Biochemistry and Proteomics. Skilled in various protein purification methods, biochemical assays, protein characterization using mass spectrometry-based proteomics approaches. Interested in biomedical research and keen in contributing to the research projects oriented on 'bench to bedside' themes. Specialities: Action oriented, Innovative, Leadership, Project Management. Currently he works as Research Scientist at iTRI-HMC. Previous posts include (Postdoctoral Associate at Weill Cornell Medical College in Qatar, Lunds Universitet, and University of Georgia Complex Carbohydrate Research Center). Dr. Krishnankutty have several publications in high impact factor journals.

C. Other research staff (RAs)

RA Saif Badran is a senior plastic surgery trainee at Hamad General Hospital (HGH). Dr. Badran is a second year Ph.D. scholar in Clinical Epidemiology at Qatar University, member of the Royal College of Surgeons (Edinburgh), and the Scientific Reference and Research Taskforce (Ministry of Public Health- Qatar). He graduated from the faculty of medicine at the University of Jordan in 2015, with a Certificate of Merit and High Appreciation for his extra-curricular activities in the field of community service. He had worked as a surgical trainee at the American University of Beirut Medical Center (AUBMC) before he joined the residency program of Plastic, Reconstructive and Burn Surgery at HGH in 2016. Dr. Badran is currently being nominated as the Plastic Surgery Department Academic Chief Resident, Plastic Surgery Quality and Patient Safety (QPS) team leader, Plastic Surgery Representative for the Clinical Practice Guideline (CGG) committee. He was nominated as the trainee's council Quality and Patient Safety (QPS) committee chairperson of Hamad Medical Corporation (2019-2020). Dr. Badran has been awarded a certificate of excellence at his training program for two consecutive years 2018&2019 and was nominated the Rising Star Certificate for as the best performing plastic surgery trainee in 2020. He has attended several training clerkships and courses in several countries like USA, Germany, Lebanon, Jordan and India. Dr. Badran has over 15 published articles in the field of plastic and reconstructive surgery, clinical epidemiology and COVID19, with many national presentations and several international conference presentations.

8.2 RELEVANT PUBLICATIONS

1. **Doi, S.A.** and G.M. Ward, Examination of the fasting and 2-h plasma glucose in the light of impairment in beta-cell function: what does the epidemiological data tell us? Endocrine, 2015. 48(1): p. 170-8. [63]
2. Mousa H, Elgamal M, Marei RG, Souchelnytskyi N, Lin KW, **Souchelnytskyi S**, Acquisition of Invasiveness by Breast Adenocarcinoma Cells Engages Established Hallmarks and Novel Regulatory Mechanisms. Cancer Genomics Proteomics, 2019. 16(6): p. 505-518. [210]
3. Grosse J, Heffron H, Burling K, Akhter Hossain M, **Habib AM**, Rogers GJ, Richards P, Larder R, Rimmington D, Adriaenssens AA, Parton L, Powell J, Binda M, Colledge WH, Doran J, Toyoda Y, Wade JD, Aparicio S, Carlton MB, Coll AP, Reimann F, O'Rahilly S, Gribble FM, Insulin-like peptide 5 is an orexigenic gastrointestinal hormone. Proc Natl Acad Sci U S A, 2014. 111(30): p. 11133-8. [137]
4. Al-Sulaiti H, Diboun I, Banu S, Al-Emadi M, Amani P, Harvey TM, Dömling AS, Latiff A, **Elrayess MA,** Triglyceride profiling in adipose tissues from obese insulin sensitive, insulin resistant and type 2 diabetes mellitus individuals. J Transl Med, 2018. 16(1): p. 175. [130]
5. Caruso M, Ma D, Msallaty Z, Lewis M, Seyoum B, Al-janabi W1, Diamond M, **Abou-Samra AB,** Højlund K, Tagett R, Draghici S, Zhang X, Horowitz JF, Yi Z. Increased interaction with insulin receptor substrate 1, a novel abnormality in insulin resistance and type 2 diabetes. Diabetes, 2014. 63(6): p. 1933-47. [106].

The complete list of publications from the research team can be accessed via:

1. LPI Doi
https://www.ncbi.nlm.nih.gov/pubmed/?term=doi+sa+OR+suhail+doi

2. PI Habib
https://www.ncbi.nlm.nih.gov/pubmed/?term=habib+am%5Bau%5D+AND+(cambridge+OR+UCL+OR+qatar+OR+basal+OR+%22King%27s+College%22+OR+%22University+College%22+or+%22Royal+london%22)+NOT+%22St+Helier%22

3. PI Elrayes
https://www.ncbi.nlm.nih.gov/pubmed/?term=Elrayess+M

4.PI Krishnankutty
https://pubmed.ncbi.nlm.nih.gov/?term=roopesh+krishnankutty

5.PI Alkasem
https://pubmed.ncbi.nlm.nih.gov/?term=meis+alkasem

6.Consultant Abou Samra
https://pubmed.ncbi.nlm.nih.gov/?term=abou+samra+%5BAU%5D

7.Consultant Steinhoff
https://pubmed.ncbi.nlm.nih.gov/?term=martin+steinhoff

8.Consultant Hammouda
https://pubmed.ncbi.nlm.nih.gov/?term=Atalla+hAMMOUDA

8.3. CONSULTANTS AND SERVICE PROVIDERS

1. **Consultant Abou-Samra** is MD, PhD physician scientist, with extensive research history at several international institutions, including University of Lyon, France, the National Institute of Health, Bethesda, Maryland, Harvard Medical School and the Massachusetts General Hospital and the Wayne State University School of Medicine. His last appointment prior to joining HMC was Chief of Endocrinology, Diabetes and Metabolic Diseases and Director of the clinical endocrine fellowship program at Wayne State University, Detroit, Michigan. Dr. Abou-Samra has received multiple recognitions for his scientific contributions and led several research projects funded by the National Institutes of Health. He is known for his molecular and clinical research on G protein-coupled receptors, insulin action and nutritionally regulated genes. Dr. Abou-Samra published over 140 original papers in peer-reviewed journals and contributed to five USA patents. He was member of the endocrine NIH study section and member of the editorial boards for several international journals. In January 2013, Dr. Abou-Samra joined Hamad Medical Corporation as the Chairman of the Department of Internal Medicine and Professor of Medicine at Weill Cornell Medical College in Qatar. Dr. Abou-Samra is Co-Chair for the Qatar National Diabetes Committee with the mandate of developing a national strategy for diabetes in Qatar and Chairman for the Qatar Metabolic Institute.

2. **Consultant Souchelnytski** is Professor at the College of Medicine of Qatar University. He has an extensive experience in discovery and development of markers for early detection, diagnostic, prognosis and selection of treatment of cancer. He has 2 patents on markers discovery and 3 patents on use of signaling mechanisms for drug development. He has participated in studies for preparation of commercialization of some of the markers. PI Souchelnytskyi has a broad experience of proteomics and systems biology technologies. He belongs to top 2.5% of international ranking out of more than 11 million scientists worldwide at ResearchGate. Prof. Serhiy Souchelnytskyi has experience of leading research consortia and participating in national and international programs. Examples are FP7 European Union Marie Curie RTN network (EpiPlast Carcinoma), recent EU Cooperation on Science and Technology action, and numerous prestigious national and international grants. PI Souchelnytskyi has also experience of supervising commercialization efforts. He had in past a company producing growth factors and providing biomedical services, and recently he started a company working on personalization of cancer treatment.

3. **Consultant Steinhoff** received his double PhD 's from University of Marburg, Germany and UCSF, USA respectively. He is currently Chairman for Department of Dermatology and Venerology, Hamad

Medical Corporation, Medical School, Qatar University &Weill Cornell University Doha, Qatar. He also, worked as Chairman, Director at Department of Dermatology, UCD Charles Institute of Dermatology, University College Dublin, Ireland. He had received number of honors and awards like Allergy Award [1996], Research Award Roche-Posay [2000], Oskar-Gans main scientific award, German Society of Dermatology [2001], Research Award of the Rosacea-Foundation, USA [2003], Victor von Bruhns Research Award of the Society for Wound Healing, Weimar, Germany [2004], Honor award: "Berlin Society of Dermatology" Berlin, Germany [2006], Research Award from National Rosacea Society (NRS), USA [2009, 2011], SFI-Pfizer Innovation Research Award from Minister of Health (D. English), Ireland [2016] and many more. His clinical research interests include Complex general dermatology, Atopic dermatitis, Rosacea/Acne, Melanoma, Wound healing, sclerotherapy. Dermatology Consultant for other Departments: Internal medicine, transplantation, cancer clinic, surgery. He has given more than 200 national/international invited lectures including Natl Acac Sciences New York.

4. **Consultant Hammouda** finished his plastic surgery training program at Hamad Medical Corporation in 2004, since then he continuously worked as a consultant and a supervisor for the training residents. Dr. Hammouda currently acts as a senior consultant in plastic surgery specializing in body contouring surgeries. He was nominated as the Department of Plastic Surgery Head and Acting Program Director in 2019. Dr. Hammouda has several publications and conference presentations in his field.

8.4. CO-FUNDING AND COST SHARING

The Health System is the end user in this project and will have direct benefit if this research uncovers novel biomarkers that facilitate early diagnosis or treatment. This project will also allow decision makers within the health system to assess the impact of these procedures on the metabolic health of the populations they serve. This project will also serve to facilitate a culture of research and inquiry within the health system. This will also further inter-institutional collaboration across various entities in Qatar (CMED-QU, BRC-QU, HGH-HMC, QMI-HMC & iTRI-HMC). The Health system will provide support in-kind cost sharing for this project in terms of patient recruitment, facilities and expertise.

Cost sharing: Hamad Medica Corporation (Qatar Metabolic institute)

Co-Funding Type	Cost category	Description	Amount (USD)	Duration (months)	Year(s) of project	Inside/Outside Qatar
In-kind	Personnel	Prof. Abdul Badi Abou Samra, (Consultant QMI-HMC)	$14,400.00 $14,400.00 $14,400.00	36	Year 1 Year 2 Year 3	Inside Qatar
In-kind	Personnel	Dr. Mels Jasem Alkasem (PI QMI-HMC)	$30,000.00 $30,000.00 $30,000.00	36	Year 1 Year 2 Year 3	Inside Qatar
		Total	$132,000.00			

9. REFERENCES

1. M. P. Czech, "Insulin action and resistance in obesity and type 2 diabetes," Nature Medicine, vol. 23, no. Nature Publishing Group, pp. 804–814, Jul. 11, 2017, doi: 10.1038/nm.4350.
2. Obesity and overweight." https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight (accessed Mar. 14, 2021).
3. H. Cao, "Adipocytokines in obesity and metabolic disease," Journal of Endocrinology, vol. 220, no. 2. NIH Public Access, p. T47, Feb. 2014, doi: 10.1530/JOE-13-0339.

4. J. P. Bergé and G. Barnathan, "Fatty acids from lipids of marine organisms: Molecular biodiversity, roles as biomarkers, biologically active compounds, and economical aspects," Advances in Biochemical Engineering/Biotechnology, vol. 96. Springer, Berlin, Heidelberg, pp. 49–125, Aug. 24, 2005, doi: 10.1007/b135782.
5. K. Seretis, D. G. Goulis, G. Koliakos, and E. Demiri, "The effects of abdominal lipectomy in metabolic syndrome components and insulin sensitivity in females: A systematic review and meta-analysis," Metabolism: Clinical and Experimental, vol. 64, no. 12. W.B. Saunders, pp. 1640–1649, Dec. 01, 2015, doi: 10.1016/j.metabol.2015.09.015.
6. K. Esposito, G. Giugliano, N. Scuderi, and D. Giugliano, "Role of adipokines in the obesity-inflammation relationship: The effect of fat removal," Plastic and Reconstructive Surgery, vol. 118, no. 4. Plast Reconstr Surg, pp. 1048–1057, Sep. 2006, doi: 10.1097/01.prs.0000232281.49432.ce.
7. L. J. Scott, "Liraglutide: A review of its use in the management of obesity," Drugs, vol. 75, no. 8. Springer International Publishing, pp. 899–910, May 30, 2015, doi: 10.1007/s40265-015-0408-8.
8. J. K. Kim, O. Gavrilova, Y. Chen, M. L. Reitman, and G. I. Shulman, "Mechanism of insulin resistance in A-ZIP/F-1 fatless mice," Journal of Biological Chemistry, vol. 275, no. 12, pp. 8456–8460, Mar. 2000, doi: 10.1074/jbc.275.12.8456.
9. C. M. Kusminski et al., "MitoNEET-driven alterations in adipocyte mitochondrial activity reveal a crucial adaptive process that preserves insulin sensitivity in obesity," Nature Medicine, vol. 18, no. 10, pp. 1539–1551, Oct. 2012, doi: 10.1038/nm.2899.

10. M. M. Finucane et al., "National, regional, and global trends in body-mass index since 1980: Systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9·1 million participants," The Lancet, vol. 377, no. 9765, pp. 557–567, 2011, doi: 10.1016/S0140-6736(10)62037-5.
11. H. B. Kitzinger et al., "After massive weight loss: Patients' expectations of body contouring surgery," Obesity Surgery, vol. 22, no. 4, pp. 544–548, Apr. 2012, doi: 10.1007/s11695-011-0551-6.
12. K. Almutairi, J. A. Gusenoff, and J. P. Rubin, "Body Contouring," Plastic and Reconstructive Surgery, vol. 137, no. 3. Lippincott Williams and Wilkins, pp. 586e–602e, Mar. 01, 2016, doi: 10.1097/PRS.0000000000002140.
13. L. Cårdenas-Camarena, A. Tobar-Losada, and A. M. Lacouture, "Large-volume circumferential liposuction with tumescent technique: A sure and viable procedure," Plastic and Reconstructive Surgery, vol. 104, no. 6, pp. 1887–1899, 1999, doi: 10.1097/00006534-199911000-00046.
14. A. M. Sailon, J. R. Wasserburg, R. R. Kling, C. M. Pasick, and P. J. Taub, "Influence of Large-Volume Liposuction on Metabolic and Cardiovascular Health: A Systematic Review," Annals of Plastic Surgery, vol. 79, no. 6. Lippincott Williams and Wilkins, pp. 623–630, Dec. 01, 2017, doi: 10.1097/SAP.0000000000001195.
15. M. F. Herrera et al., "Potential additional effect of omentectomy on metabolic syndrome, acute-phase reactants, and inflammatory mediators in grade III obese patients undergoing laparoscopic Roux-en-Y gastric bypass: A randomized trial," Diabetes Care, vol. 33, no. 7, pp. 1413–1418, Jul. 2010, doi: 10.2337/dc09-1833.
16. A. M. Burgos, "A Prospective Randomized Study Comparing Patients with Morbid Obesity Submitted to Laparotomic Gastric Bypass with or without Omentectomy Attila Csendes & Fernando Maluenda &," doi: 10.1007/s11695-008-9660-2.
17. A. Thörne, F. Lönnqvist, J. Apelman, G. Hellers, and P. Arner, "A pilot study of long-term effects of a novel obesity treatment: Omentectomy in connection with adjustable gastric banding," International Journal of Obesity, vol. 26, no. 2, pp. 193–199, 2002, doi: 10.1038/sj.ijo.0801871.
18. S. Klein, "Is visceral fat responsible for the metabolic abnormalities associated with obesity? Implications of omentectomy," Diabetes Care, vol. 33, no. 7. American Diabetes Association, pp. 1693–1694, Jul. 01, 2010, doi: 10.2337/dc10-0744.
19. L. Fontana, J. C. Eagon, M. E. Trujillo, P. E. Scherer, and S. Klein, "Visceral fat adipokine secretion is associated with systemic inflammation in obese humans," Diabetes, vol. 56, no. 4, pp. 1010–1013, Apr. 2007, doi: 10.2337/db06-1656.
20. S. Klein, "The case of visceral fat: argument for the defense," Journal of Clinical Investigation, vol. 113, no. 11, pp. 1530–1532, Jun. 2004, doi: 10.1172/jci22028.
21. S. Nielsen, Z. K. Guo, C. M. Johnson, D. D. Hensrud, and M. D. Jensen, "Splanchnic lipolysis in human obesity," Journal of Clinical Investigation, vol. 113, no. 11, pp. 1582–1588, 2004, doi: 10.1172/JCI21047.

22. E. Fabbrini et al., "Intrahepatic fat, not visceral fat, is linked with metabolic complications of obesity," Proceedings of the National Academy of Sciences of the United States of America, vol. 106, no. 36, pp. 15430–15435, Sep. 2009, doi: 10.1073/pnas.0904944106.
23. P. Ziccardi et al., "Reduction of inflammatory cytokine concentrations and improvement of endothelial functions in obese women after weight loss over one year," Circulation, vol. 105, no. 7, pp. 804–809, Feb. 2002, doi: 10.1161/hc0702.104279.
24. P. G. Kopelman, "Obesity as a medical problem," Nature, vol. 404, no. 6778. Macmillan Magazines Ltd, pp. 635–643, Apr. 06, 2000, doi: 10.1038/35007508.
25. N. Abate, A. Garg, R. M. Peshock, J. Stray-Gundersen, and S. M. Grundy, "Relationships of generalized and regional adiposity to insulin sensitivity in men," Journal of Clinical Investigation, vol. 96, no. 1, pp. 88–98, 1995, doi: 10.1172/JCI118083.
26. M. Uusitupa, V. Lindi, A. Louheranta, T. Saiopuro, J. Lindström, and J. Tuomilehto, "Long-term improvement in insulin sensitivity by changing lifestyles of people with impaired glucose tolerance: 4-Year results from the Finnish Diabetes Prevention Study," Diabetes, vol. 52, no. 10, pp. 2532–2538, Oct. 2003, doi: 10.2337/diabetes.52.10.2532.
27. V. J. Stevens et al., "Long-term weight loss and changes in blood pressure: Results of the trials of hypertension prevention, phase II," Annals of Internal Medicine, vol. 134, no. 1, pp. 1–11, Jan. 2001, doi: 10.7326/0003-4819-134-1-200101020-00007.
28. S. Y. Giese, E. J. Bulan, G. W. Commons, S. L. Spear, and J. A. Yanovski, "Improvements in cardiovascular risk profile with large-volume liposuction: A pilot study," Plastic and Reconstructive Surgery, vol. 108, no. 2, pp. 510–519, 2001, doi: 10.1097/00006534-200108000-00035.
29. S. Y. Giese, R. Neborsky, E. J. Bulan, S. L. Spear, and J. A. Yanovski, "Improvements in cardiovascular risk profile after large-volume lipoplasty: A 1-year follow-up study," Aesthetic Surgery Journal, vol. 21, no. 6, pp. 527–531, 2001, doi: 10.1067/maj.2001.120434.
30. G. Giugliano et al., "Effect of liposuction on insulin resistance and vascular inflammatory markers in obese women," British Journal of Plastic Surgery, vol. 57, no. 3, pp. 190–194, 2004, doi: 10.1016/j.bjps.2003.12.010.
31. F. Samdal, K. I. Birkeland, L. Ose, and P. F. Amland, "Effect of large-volume liposuction on sex hormones and glucose- and lipid metabolism in females," Aesthetic Plastic Surgery, vol. 19, no. 2, pp. 131–135, Mar. 1995, doi: 10.1007/BF00450248.
32. F. D'Andrea et al., "Changing the metabolic profile by large-volume liposuction: A clinical study conducted with 123 obese women," Aesthetic Plastic Surgery, vol. 29, no. 6, pp. 472–478, Dec. 2005, doi: 10.1007/s00266-005-0089-x.
33. D. A. Davis, D. M. Pellowski, D. A. Davis, and W. T. Donahoo, "Acute and 1-month effect of small-volume suction lipectomy on insulin sensitivity and cardiovascular risk," International Journal of Obesity, vol. 30, no. 8, pp. 1217–1222, Aug. 2006, doi: 10.1038/sj.ijo.0803120.
34. L. Busetto et al., "The effects of the surgical removal of subcutaneous adipose tissue on energy expenditure and adipocytokine concentrations in obese women," Nutrition, Metabolism and Cardiovascular Diseases, vol. 18, no. 2, pp. 112–120, Feb. 2008, doi: 10.1016/j.numecd.2006.09.009.
35. J. Ybarra et al., "The effects of liposuction removal of subcutaneous abdominal fat on lipid metabolism are independent of insulin sensitivity in normal-overweight individuals," Obesity Surgery, vol. 18, no. 4, pp. 408–414, Apr. 2008, doi: 10.1007/s11695-007-9261-5.
36. M. González-Ortiz, J. A. Robles-Cervantes, L. Cárdenas-Camarena, R. Bustos-Saldaña, and E. Martínez-Abundis, "The effects of surgically removing subcutaneous fat on the metabolic profile and insulin sensitivity in obese women after large-volume liposuction treatment," Hormone and Metabolic Research, vol. 34, no. 8, pp. 446–449, Aug. 2002, doi: 10.1055/s-2002-33603.
37. E. Swanson, "Prospective clinical study reveals significant reduction in triglyceride level and white blood cell count after liposuction and abdominoplasty and no change in cholesterol levels," Plastic and Reconstructive Surgery, vol. 128, no. 3, Sep. 2011, doi: 10.1097/PRS.0b013e31822213c6.
38. M. R. Rizzo et al., "Is dermolipectomy effective in improving insulin action and lowering inflammatory markers in obese women?," Clinical Endocrinology, vol. 63, no. 3, pp. 253–258, Sep. 2005, doi: 10.1111/j.1365-2265.2005.02337.x.
39. L. Cazes, M. Deitel, and R. H. Levine, "Effect of abdominal lipectomy on lipid profile, glucose handling and blood-pressure in patients with truncal obesity," Obesity Surgery, vol. 6, no. 2, pp. 159–166, 1996, doi: 10.1381/096089296765557123.
40. S. Danilla et al., "Suction-assisted lipectomy fails to improve cardiovascular metabolic markers of disease: A meta-analysis," Journal of Plastic, Reconstructive and Aesthetic Surgery, vol. 66, no. 11, pp. 1557–1563, Nov. 2013, doi: 10.1016/j.bjps.2013.07.001.

41. A. M. Sailon, J. R. Wasserburg, R. R. Kling, C. M. Pasick, and P. J. Taub, "Influence of Large-Volume Liposuction on Metabolic and Cardiovascular Health: A Systematic Review," Annals of Plastic Surgery, vol. 79, no. 6. Lippincott Williams and Wilkins, pp. 623–630, Dec. 01, 2017, doi: 10.1097/SAP.0000000000001195.
42. K. Seretis, D. G. Goulis, G. Koliakos, and E. Demiri, "The effects of abdominal lipectomy in metabolic syndrome components and insulin sensitivity in females: A systematic review and meta-analysis," Metabolism: Clinical and Experimental, vol. 64, no. 12. W.B. Saunders, pp. 1640–1649, Dec. 01, 2015, doi: 10.1016/j.metabol.2015.09.015.
43. F. Boriani, R. Villani, and P. G. Morselli, "Metabolic Effects of Large-Volume Liposuction for Obese Healthy Women: A Meta-Analysis of Fasting Insulin Levels," Aesthetic Plastic Surgery, vol. 38, no. 5. Springer New York LLC, pp. 1050–1056, Sep. 25, 2014, doi: 10.1007/s00266-014-0386-3.
44. F.-X. Crahay and J. L. Nizet, "Conséquences métaboliques et cardiovasculaires de la lipoaspiration : revue systématique de la littérature," Annales de Chirurgie Plastique Esthétique, vol. 61, no. 4, pp. 270–286, Aug. 2016, doi: 10.1016/j.anplas.2016.03.005.
45. K. Seretis, D. G. Goulis, G. Koliakos, and E. Demiri, "Short- and Long-Term Effects of Abdominal Lipectomy on Weight and Fat Mass in Females: a Systematic Review," Obesity Surgery, vol. 25, no. 10. Springer New York LLC, pp. 1950–1958, Oct. 07, 2015, doi: 10.1007/s11695-015-1797-1.
46. S. Y. Giese, E. J. Bulan, G. W. Commons, S. L. Spear, and J. A. Yanovski, "Improvements in cardiovascular risk profile with large-volume liposuction: A pilot study," Plastic and Reconstructive Surgery, vol. 108, no. 2, pp. 510–519, 2001, doi: 10.1097/00006534-200108000-00035.
47. S. Y. Giese, R. Neborsky, E. J. Bulan, S. L. Spear, and J. A. Yanovski, "Improvements in cardiovascular risk profile after large-volume lipoplasty: A 1-year follow-up study," Aesthetic Surgery Journal, vol. 21, no. 6, pp. 527–531, 2001, doi: 10.1067/maj.2001.120434.
48. G. Giugliano et al., "Effect of liposuction on insulin resistance and vascular inflammatory markers in obese women," British Journal of Plastic Surgery, vol. 57, no. 3, pp. 190–194, 2004, doi: 10.1016/j.bjps.2003.12.010.
49. E. Martínez-Abundis, C. A. Molina-Villa, M. González-Ortiz, J. A. Robles-Cervantes, and J. A. Saucedo-Ortiz, "Effect of surgically removing subcutaneous fat by abdominoplasty on leptin concentrations and insulin sensitivity," Annals of Plastic Surgery, vol. 58, no. 4, pp. 416–419, Apr. 2007, doi: 10.1097/01.sap.0000240033.00047.cc.
50. F. D'Andrea et al., "Changing the metabolic profile by large-volume liposuction: A clinical study conducted with 123 obese women," Aesthetic Plastic Surgery, vol. 29, no. 6, pp. 472–478, Dec. 2005, doi: 10.1007/s00266-005-0089-x.
51. S. E. Pratt-Phillips, R. J. Geor, and L. J. McCutcheon, "Comparison among the euglycemic-hyperinsulinemic clamp, insulin-modified frequently sampled intravenous glucose tolerance test, and oral glucose tolerance test for assessment of insulin sensitivity in healthy Standardbreds," American Journal of Veterinary Research, vol. 76, no. 1, pp. 84–91, 2015, doi: 10.2460/ajvr.76.1.84.
52. S. Danilla et al., "Suction-assisted lipectomy fails to improve cardiovascular metabolic markers of disease: A meta-analysis," Journal of Plastic, Reconstructive and Aesthetic Surgery, vol. 66, no. 11, pp. 1557–1563, Nov. 2013, doi: 10.1016/j.bjps.2013.07.001.
53. Almuraikhy, S., et al., Interleukin-6 induces impairment in human subcutaneous adipogenesis in obesity-associated insulin resistance. Diabetologia, 2016. 59(11): p. 2406-2416.

54. Al Khalaf, M.M., et al., Screening for diabetes in Kuwait and evaluation of risk scores. East Mediterr Health J, 2010. 16(7): p. 725-31.
55. Al-Shoumer, K.A., et al., Serum leptin and its relationship with metabolic variables in Arabs with type 2 diabetes mellitus. Ann Saudi Med, 2008. 28(5): p. 367-70.
56. Aung, E., et al., The impact of concordant and discordant comorbidities on patient-assessed quality of diabetes care. Health Expect, 2015. 18(5): p. 1621-32.
57. Aung, E., et al., Association between patient activation and patient-assessed quality of care in type 2 diabetes: results of a longitudinal study. Health Expect, 2016. 19(2): p. 356-66
58. Aung, E., et al., Joint influence of Patient-Assessed Chronic Illness Care and patient activation on glycaemic control in type 2 diabetes. Int J Qual Health Care, 2015. 27(2): p. 117-24.
59. Aung, E., et al., Influence of patient-assessed quality of chronic illness care and patient activation on health-related quality of life. Int J Qual Health Care, 2016. 28(3): p. 306-10.
60. Aung, E., et al., Patient Assessment of Chronic Illness Care (PACIC) in Type 2 Diabetes: A Longitudinal Study. Eval Health Prof, 2016. 39(2): p. 185-203.

61. Baghdadi, L.R., et al., Impact of obesity on reproductive outcomes after ovarian ablative therapy in PCOS: a collaborative meta-analysis. Reprod Biomed Online, 2012. 25(3): p. 227-41.
62. Behbehani, R., et al., Is cerebrospinal fluid leptin altered in idiopathic intracranial hypertension? Clin Endocrinol (Oxf), 2010. 72(6): p. 851-2.
63. Doi, S.A. and G.M. Ward, Examination of the fasting and 2-h plasma glucose in the light of impairment in beta-cell function: what does the epidemiological data tell us? Endocrine, 2015. 48(1): p. 170-8.
64. Doi, S.A.R., et al., Metformin in pregnancy to avert gestational diabetes in women at high risk: Meta-analysis of randomized controlled trials. Obes Rev, 2020. 21(1): p. e12964.
65. Donald, M., et al., Mental health issues decrease diabetes-specific quality of life independent of glycaemic control and complications: findings from Australia's living with diabetes cohort study. Health Qual Life Outcomes, 2013. 11: p. 170.
66. Fatima, Y., S.A. Doi, and A.A. Mamun, Longitudinal impact of sleep on overweight and obesity in children and adolescents: a systematic review and bias-adjusted meta-analysis. Obes Rev, 2015. 16(2): p. 137-49.
67. Fatima, Y., S.A. Doi, and A.A. Mamun, Sleep quality and obesity in young subjects: a meta-analysis. Obes Rev, 2016. 17(11): p. 1154-1166.
68. Fatima, Y., S.A.R. Doi, and A. Al Mamun, Sleep problems in adolescence and overweight/obesity in young adults: is there a causal link? Sleep Health, 2018. 4(2): p. 154-159.
69. Furuya-Kanamori, L., et al., Comorbidities, Exposure to Medications, and the Risk of Community-Acquired Clostridium difficile Infection: a systematic review and meta-analysis. Infect Control Hosp Epidemiol, 2015. 36(2): p. 132-41.
70. Furuya-Kanamori, L., J.C. Stone, and S.A. Doi, Putting the diabetes risk due to statins in perspective: a re-evaluation using the complementary outcome. Nutr Metab Cardiovasc Dis, 2014. 24(7): p. 705-8.
71. Hasan, S.S., et al., Population impact of depression either as a risk factor or consequence of type 2 diabetes in adults: a meta-analysis of longitudinal studies. Asian J Psychiatr, 2013. 6(6): p. 460-72.
72. Hassanain, M., et al., Trends in brain-dead organ donor characteristics: a 13-year analysis. Can J Surg, 2016. 59(3): p. 154-60.
73. Hoque, M.E., et al., Prevalence of overweight and obesity among children and adolescents of the Indian subcontinent: a meta-analysis. Nutr Rev, 2014. 72(8): p. 541-50.
74. Mamun, A.A., M. Mannan, and S.A. Doi, Gestational weight gain in relation to offspring obesity over the life course: a systematic review and bias-adjusted meta-analysis. Obes Rev, 2014. 15(4): p. 338-47.
75. Mannan, M., S.A. Doi, and A.A. Mamun, Association between weight gain during pregnancy and postpartum weight retention and obesity: a bias-adjusted meta-analysis. Nutr Rev, 2013. 71(6): p. 343-52.
76. Musa, O.A.H., et al., The impact of obesity on the gestational diabetes differential between pregnant women with and without polycystic ovary syndrome. Obes Rev, 2019. 20(11): p. 1665-1666.
77. Onitilo, A.A., et al., Increased risk of colon cancer in men in the pre-diabetes phase. PLoS One, 2013. 8(8): p. e70426.
78. Onitilo, A.A., et al., Prostate cancer risk in pre-diabetic men: a matched cohort study. Clin Med Res, 2013. 11(4): p. 201-9.
79. Onitilo, A.A., et al., Clustering of venous thrombosis events at the start of tamoxifen therapy in breast cancer: a population-based experience. Thromb Res, 2012. 130(1): p. 27-31.
80. Onitilo, A.A., et al., Breast and prostate cancer survivors in a diabetic cohort: results from the Living with Diabetes Study. Clin Med Res, 2013. 11(4): p. 210-8.
81. Onitilo, A.A., et al., Diabetes and cancer I: risk, survival, and implications for screening. Cancer Causes Control, 2012. 23(6): p. 967-81.
82. Onitilo, A.A., et al., Diabetes and cancer II: role of diabetes medications and influence of shared risk factors. Cancer Causes Control, 2012. 23(7): p. 991-1008.
83. Onitilo, A.A., et al., Type 2 diabetes mellitus, glycemic control, and cancer risk. Eur J Cancer Prev, 2014. 23(2): p. 134-40.
84. Onitilo, A.A., et al., Breast cancer incidence before and after diagnosis of type 2 diabetes mellitus in women: increased risk in the prediabetes phase. Eur J Cancer Prev, 2014. 23(2): p. 76-83.
85. Onitilo, A.A., et al., A novel method for studying the temporal relationship between type 2 diabetes mellitus and cancer using the electronic medical record. BMC Med Inform Decis Mak, 2014. 14: p. 38.
86. Parappil, A., S.A. Doi, and K.A. Al-Shoumer, Diagnostic criteria for diabetes revisited: making use of combined criteria. BMC Endocr Disord, 2002. 2(1): p. 1.
87. Rao, C., et al., Mortality from diabetic renal disease: a hidden epidemic. Eur J Public Health, 2012. 22(2): p. 280-4.

88. Rao, C. and S.A. Doi, Measuring population-based diabetes-related mortality: a summary of requirements. J Clin Epidemiol, 2013. 66(2): p. 237-8.
89. Stone, J.C., et al., Was there really any evidence that rosiglitazone increased the risk of myocardial infarction or death from cardiovascular causes? Pharmacoepidemiol Drug Saf, 2015. 24(3): p. 223-7.
90. Sutharsan, R., et al., Caesarean delivery and the risk of offspring overweight and obesity over the life course: a systematic review and bias-adjusted meta-analysis. Clin Obes, 2015. 5(6): p. 293-301.
91. Abou Samra, A.B., et al., Beta-lipotropin and cortisol responses to an intravenous infusion dexamethasone suppression test in Cushing's syndrome and obesity. J Clin Endocrinol Metab, 1985. 61(1): p. 116-9.
92. Al-Khawaga, S., et al., Pathways governing development of stem cell-derived pancreatic beta cells: lessons from embryogenesis. Biol Rev Camb Philos Soc, 2018. 93(1): p. 364-389.
93. Al-Thani, A.A., et al., Knowledge and Perception of Diabetes and Available Services among Diabetic Patients in the State of Qatar. Cent Asian J Glob Health, 2019. 8(1): p. 333.
94. Al-Thani, A.A., et al., Public Awareness and Perceptions about Diabetes in the State of Qatar. Cureus, 2018. 10(5): p. e2671.
95. Araia, M., et al., Prevalence of Diabetes in an Urban Hospital Emergency Room Serving Predominantly Indigenous Population. J Natl Med Assoc, 2015. 107(1): p. 11-6.
96. Arredouani, A., et al., DNAJB3 attenuates metabolic stress and promotes glucose uptake by eliciting Glut4 translocation. Sci Rep, 2019. 9(1): p. 4772.
97. Bashir, M., et al., Metformin-treated-GDM has lower risk of macrosomia compared to diet-treated GDM-A retrospective cohort study. J Matern Fetal Neonatal Med, 2018: p. 1-141.
98. Bashir, M., et al., Pregnancy outcomes of early detected gestational diabetes: a retrospective comparison cohort study, Qatar. BMJ Open, 2019. 9(2): p. e023612.
99. Bashir, M., et al., Type 2 diabetes mellitus in pregnancy: The impact of maternal weight and early glycaemic control on outcomes. Eur J Obstet Gynecol Reprod Biol, 2019. 233: p. 53-57.
100. Bashir, M., et al., A pilot study using flash continuous glucose monitoring in patients with type-2 diabetes on multiple anti-diabetic agents during Ramadan. Diabetes Metab Syndr, 2018. 12(6): p. 965-968.
101. Bashir, M., et al., Prevalence of newly detected diabetes in pregnancy in Qatar, using universal screening. PLoS One, 2018. 13(8): p. e0201247.
102. Bashir, M., et al., Outcomes of type 1 diabetes mellitus in pregnancy; effect of excessive gestational weight gain and hyperglycaemia on fetal growth. Diabetes Metab Syndr, 2019. 13(1): p. 84-88.
103. Berhane, F., et al., Plasma Lactate Levels Increase during Hyperinsulinemic Euglycemic Clamp and Oral Glucose Tolerance Test. J Diabetes Res, 2015. 2015: p. 102054.
104. Butt, A.A., et al., HCV treatment initiation in persons with chronic kidney disease in the directly acting antiviral agents era: Results from ERCHIVES. Liver Int, 2018. 38(8): p. 1411-1417.
105. Butt, A.A., et al., Hepatitis C Virus Treatment with Directly Acting Agents Reduces the Risk of Incident Diabetes - Results from ERCHIVES. Clin Infect Dis, 2019.
106. Caruso, M., et al., Increased interaction with insulin receptor substrate 1, a novel abnormality in insulin resistance and type 2 diabetes. Diabetes, 2014. 63(6): p. 1933-47.
107. Dabbous, Z., et al., Differential effects of gender and patient background diversity on the changes in metabolic and biophysical profiles in people with type-2 diabetes from different ethnicities who fast during Ramadan (H1439); a prospective study from Qatar. Diabetes Res Clin Pract, 2019. 152: p. 171-176.
108. Elhadd, T., et al., Incidence of hypoglycaemia in patients with type-2 diabetes taking multiple glucose lowering therapies during Ramadan: the PROFAST Ramadan Study. J Diabetes Metab Disord, 2018. 17(2): p. 309-314.
109. Fite, A., A.B. Abou-Samra, and B. Seyoum, Macrophages inhibit insulin signalling in adipocytes: role of inducible nitric oxide synthase and nitric oxide. Can J Diabetes, 2015. 39(1): p. 36-43.
110. Fu, Z., A.B. Abou-Samra, and R. Zhang, An explanation for recent discrepancies in levels of human circulating betatrophin. Diabetologia, 2014. 57(10): p. 2232-4.
111. Fu, Z., et al., Elevated circulating lipasin/betatrophin in human type 2 diabetes and obesity. Sci Rep, 2014. 4: p. 5013.
112. Goustin, A.S. and A.B. Abou-Samra, The "thrifty" gene encoding Ahsg/Fetuin-A meets the insulin receptor: Insights into the mechanism of insulin resistance. Cell Signal, 2011. 23(6): p. 980-90.
113. Goustin, A.S., N. Derar, and A.B. Abou-Samra, Ahsg-fetuin blocks the metabolic arm of insulin action through its interaction with the 95-kD beta-subunit of the insulin receptor. Cell Signal, 2013. 25(4): p. 981-8.
114. Halama, A., et al., Measurement of 1,5-anhydroglucitol in blood and saliva: from non-targeted metabolomics to biochemical assay. J Transl Med, 2016. 14(1): p. 140.

115. Ramanjaneya, M., et al., Mitochondrial-Derived Peptides Are Down Regulated in Diabetes Subjects. Front Endocrinol (Lausanne), 2019. 10: p. 331.
116. Ramanjaneya, M., et al., Lipids and insulin regulate mitochondrial-derived peptide (MOTS-c) in PCOS and healthy subjects. Clin Endocrinol (Oxf), 2019. 91(2): p. 278-287.
117. Samantray, J., et al., Glucose control and lipid metabolism in African American patients with type 2 diabetes mellitus and chronic hepatitis C viral infection. Endocr Pract, 2011. 17(3): p. 363-8.
118. Seyoum, B., A. Fite, and A.B. Abou-Samra, Effects of 3T3 adipocytes on interleukin-6 expression and insulin signaling in L6 skeletal muscle cells. Biochem Biophys Res Commun, 2011. 410(1): p. 13-8.
119. Shi, Z. and A.B. Abou-Samra, Association of low serum magnesium with diabetes and hypertension: Findings from Qatar Biobank study. Diabetes Res Clin Pract, 2019. 158: p. 107903.
120. Taddesse, A., et al., Hypogonadism in patients with sickle cell disease: central or peripheral? Acta Haematol, 2012. 128(2): p. 65-8.
121. Taha, W., et al., Low urine calcium excretion in African American patients with primary hyperparathyroidism. Endocr Pract, 2011. 17(6): p. 867-72.
122. Taheri, S., et al., Diabetes Intervention Accentuating Diet and Enhancing Metabolism (DIADEM-I): a randomised controlled trial to examine the impact of an intensive lifestyle intervention consisting of a low-energy diet and physical activity on body weight and metabolism in early type 2 diabetes mellitus: study protocol for a randomized controlled trial. Trials, 2018. 19(1): p. 284.
123. Zhang, R. and A.B. Abou-Samra, Emerging roles of Lipasin as a critical lipid regulator. Biochem Biophys Res Commun, 2013. 432(3): p. 401-5.
124. Zhang, R. and A.B. Abou-Samra, A dual role of lipasin (betatrophin) in lipid metabolism and glucose homeostasis: consensus and controversy. Cardiovasc Diabetol, 2014. 13: p. 133.
125. Zhang, R., et al., Nrac, a novel nutritionally-regulated adipose and cardiac-enriched gene. PLoS One, 2012. 7(9): p. e46254.
126. Jaganjac, M., et al., Combined metformin and insulin treatment reverses metabolically impaired omental adipogenesis and accumulation of 4-hydroxynonenal in obese diabetic patients. Redox Biol, 2017. 12: p. 483-490.
127. Almuraikhy, S., et al., Interleukin-6 induces impairment in human subcutaneous adipogenesis in obesity-associated insulin resistance. Diabetologia, 2016. 59(11): p. 2406-2416.
128. Al-Sulaiti, H., et al., Metabolic signature of obesity-associated insulin resistance and type 2 diabetes. J Transl Med, 2019. 17(1): p. 348.
129. Sohail, M.U., et al., Profiling the Oral Microbiome and Plasma Biochemistry of Obese Hyperglycemic Subjects in Qatar. Microorganisms, 2019. 7(12).
130. Al-Sulaiti, H., et al., Triglyceride profiling in adipose tissues from obese insulin sensitive, insulin resistant and type 2 diabetes mellitus individuals. J Transl Med, 2018. 16(1): p. 175.
131. Reimann, F., et al., Characterization and functional role of voltage gated cation conductances in the glucagon-like peptide-1 secreting GLUTag cell line. J Physiol, 2005. 563(Pt 1): p. 161-75.
132. Habib, A.M., et al., Co-localisation and secretion of glucagon-like peptide 1 and peptide YY from primary cultured human L cells. Diabetologia, 2013. 56(6): p. 1413-6.
133. Shafi, A.M.A., et al., Coronary artery bypass vs percutaneous coronary intervention in under 50s. J Card Surg, 2020. 35(2): p. 320-327.
134. Rogers, G.J., et al., Electrical activity-triggered glucagon-like peptide-1 secretion from primary murine L-cells. J Physiol, 2011. 589(Pt 5): p. 1081-93.
135. De Marinis, Y.Z., et al., GLP-1 inhibits and adrenaline stimulates glucagon release by differential modulation of N- and L-type Ca2+ channel-dependent exocytosis. Cell Metab, 2010. 11(6): p. 543-553.
136. Tolhurst, G., et al., Glutamine triggers and potentiates glucagon-like peptide-1 secretion by raising cytosolic Ca2+ and cAMP. Endocrinology, 2011. 152(2): p. 405-13.
137. Grosse, J., et al., Insulin-like peptide 5 is an orexigenic gastrointestinal hormone. Proc Natl Acad Sci U S A, 2014. 111(30): p. 11133-8.
138. Ellingsgaard, H., et al., Interleukin-6 enhances insulin secretion by increasing glucagon-like peptide-1 secretion from L cells and alpha cells. Nat Med, 2011. 17(11): p. 1481-9.
139. Greenfield, J.R., et al., Oral glutamine increases circulating glucagon-like peptide 1, glucagon, and insulin concentrations in lean, obese, and type 2 diabetic subjects. Am J Clin Nutr, 2009. 89(1): p. 106-113.
140. Iyasere, O., et al., Quality of life with conservative care compared with assisted peritoneal dialysis and haemodialysis. Clin Kidney J, 2019. 12(2): p. 262-268.
141. Friedlander, R.S., et al., Role of phosphodiesterase and adenylate cyclase isozymes in murine colonic glucagon-like peptide 1 secreting cells. Br J Pharmacol, 2011. 163(2): p. 261-71.

142. Tolhurst, G., et al., Short-chain fatty acids stimulate glucagon-like peptide-1 secretion via the G-protein-coupled receptor FFAR2. Diabetes, 2012. 61(2): p. 364-71.
143. Emery, E.C., et al., Stimulation of GLP-1 secretion downstream of the ligand-gated ion channel TRPA1. Diabetes, 2015. 64(4): p. 1202-10.
144. Willemen, H., et al., Identification of FAM173B as a protein methyltransferase promoting chronic pain. PLoS Biol, 2018. 16(2): p. e2003452.
145. Walters, G., et al., Glomerular T cells are of restricted clonality and express multiple CDR3 motifs across different Vbeta T-cell receptor families in experimental autoimmune glomerulonephritis. Nephron Exp Nephrol, 2004. 98(3): p. e71-81.
146. Vincent, J.L., et al., Sepsis diagnosis and management: work in progress. Minerva Anestesiol, 2006. 72(3): p. 87-96.
147. Svendsen, B., et al., GLP1- and GIP-producing cells rarely overlap and differ by bombesin receptor-2 expression and responsiveness. J Endocrinol, 2016. 228(1): p. 39-48.
148. Supanjani, S., et al., Nod factor enhances calcium uptake by soybean. Plant Physiol Biochem, 2006. 44(11-12): p. 866-72.
149. Simpson, A.K., et al., Cyclic AMP triggers glucagon-like peptide-1 secretion from the GLUTag enteroendocrine cell line. Diabetologia, 2007. 50(10): p. 2181-9.
150. Shams Eldin, S.M., et al., Bioactivity-Guided Isolation of Potential Antidiabetic and Antihyperlipidemic Compounds from Trigonella stellata. J Nat Prod, 2018. 81(5): p. 1154-1161.
151. Saad, M.S., et al., Early Progressive Maxillary Changes with Nasoalveolar Molding: Randomized Controlled Clinical Trial. JDR Clin Trans Res, 2019: p. 2380084419887336.
152. Richards, P., et al., High fat diet impairs the function of glucagon-like peptide-1 producing L-cells. Peptides, 2016. 77: p. 21-7.
153. Ramirez, J.D., et al., Null mutation in SCN9A in which noxious stimuli can be detected in the absence of pain. Neurology, 2014. 83(17): p. 1577-80.
154. Parker, H.E., et al., Nutrient-dependent secretion of glucose-dependent insulinotropic polypeptide from primary murine K cells. Diabetologia, 2009. 52(2): p. 289-298.
155. Moustafa, M.A., et al., Feeding obturator as an airway adjunct during complete unilateral cleft palate repair. Indian J Anaesth, 2018. 62(5): p. 376-380.
156. Moss, C.E., et al., Somatostatin receptor 5 and cannabinoid receptor 1 activation inhibit secretion of glucose-dependent insulinotropic polypeptide from intestinal K cells in rodents. Diabetologia, 2012. 55(11): p. 3094-103.
157. Metwally, A.M., A.M. Habib, and S.M. Khafagy, Sterols and triterpene alcohols from rice bran oil. Planta Med, 1974. 25(1): p. 68-72.
158. Mansfield, N., et al., Prolonged disease-free remission following rituximab and low-dose cyclophosphamide therapy for renal ANCA-associated vasculitis. Nephrol Dial Transplant, 2011. 26(10): p. 3280-6.
159. Mahmood, T., et al., The effect of ovarian steroids on epithelial ciliary beat frequency in the human Fallopian tube. Hum Reprod, 1998. 13(11): p. 2991-4.
160. Koenig, J., et al., Regulation of Nav1.7: A Conserved SCN9A Natural Antisense Transcript Expressed in Dorsal Root Ganglia. PLoS One, 2015. 10(6): p. e0128830.
161. Khaja, M.N., et al., High prevalence of hepatitis C virus infection and genotype distribution among general population, blood donors and risk groups. Infect Genet Evol, 2006. 6(3): p. 198-204.
162. Habib, A.M.G., et al., Clinical outcomes among hospital patients with Middle East respiratory syndrome coronavirus (MERS-CoV) infection. BMC Infect Dis, 2019. 19(1): p. 870.
163. Habib, A.M.A., et al., The effect of paravertebral block on maxillofacial free flap survival. Int J Oral Maxillofac Surg, 2017. 46(6): p. 706-711.
164. Habib, A.M.A. and S.A. Hassan, The feasibility of rib grafts in long span mandibular defects reconstruction: A long term follow up. J Craniomaxillofac Surg, 2019. 47(1): p. 15-22.
165. Habib, A.M., J.N. Wood, and J.J. Cox, Sodium channels and pain. Handb Exp Pharmacol, 2015. 227: p. 39-56.
166. Habib, A.M., et al., Postoperative prophylactic antibiotics for facial fractures: A systematic review and meta-analysis. Laryngoscope, 2019. 129(1): p. 82-95.
167. Habib, A.M., et al., Good's syndrome: Is thymectomy the solution? Case report and literature review. Asian Cardiovasc Thorac Ann, 2016. 24(7): p. 712-4.
168. Habib, A.M., et al., Overlap of endocrine hormone expression in the mouse intestine revealed by transcriptional profiling and flow cytometry. Endocrinology, 2012. 153(7): p. 3054-65.

169. Habib, A.M., et al., New xanthones from Psorospermum febrifugum. J Nat Prod, 1987. 50(2): p. 141-5.
170. Habib, A.M., E. Preston, and A. Davenport, Risk factors for developing encapsulating peritoneal sclerosis in the icodextrin era of peritoneal dialysis prescription. Nephrol Dial Transplant, 2010. 25(5): p. 1633-8.
171. Habib, A.M., et al., Microdeletion in a FAAH pseudogene identified in a patient with high anandamide concentrations and pain insensitivity. Br J Anaesth, 2019. 123(2): p. e249-e253.
172. Habib, A.M., A.Y. Mousa, and Z. Al-Halees, Recombinant activated factor VII for uncontrolled bleeding postcardiac surgery. J Saudi Heart Assoc, 2016. 28(4): p. 222-31.
173. Habib, A.M. and A. Medra, The Feasibility of Buccal Fat Pad Flap in Oral Reconstruction Based on Clinical Experience in a Governmental Hospital, Alexandria, Egypt. Cleft Palate Craniofac J, 2016. 53(6): p. 657-663.
174. Habib, A.M., et al., A novel human pain insensitivity disorder caused by a point mutation in ZFHX2. Brain, 2018. 141(2): p. 365-376.
175. Habib, A.M., et al., Colorectal Cancer Presenting as Single Pulmonary Hilar Lymph Node Metastasis. Case Rep Surg, 2018. 2018: p. 5474919.
176. Habib, A.M., et al., Mining the Proteome of Fusobacterium nucleatum subsp. nucleatum ATCC 25586 for Potential Therapeutics Discovery: An In Silico Approach. Genomics Inform, 2016. 14(4): p. 255-264.
177. Habib, A.M., et al., Changing clinical profiles and in-hospital outcomes of octogenarians undergoing cardiac surgery over 18 years: a single-centre experiencedagger. Interact Cardiovasc Thorac Surg, 2019. 28(4): p. 602-606.
178. Habib, A.M., A.G. Elsherbeny, and R.A. Almehizia, Methylene Blue for Vasoplegic Syndrome Postcardiac Surgery. Indian J Crit Care Med, 2018. 22(3): p. 168-173.
179. Habib, A.M., et al., PERIPHERAL AVASCULAR RETINA WITH DISK ANOMALY AND HIGH MYOPIA: A Novel Association in a Hereditary Isolated Ocular Disorder. Retina, 2016. 36(2): p. 408-14.
180. Habib, A.M., et al., Reply. Retina, 2016. 36(7): p. e68-9.
181. Habib, A.M., et al., The EuroSCORE: a neglected measure of medium-term survival following cardiac surgery. Interact Cardiovasc Thorac Surg, 2015. 21(4): p. 427-34.
182. Habib, A.M. and J.J. Cox, Pain in Fabry disease: Plasma lipids sensitise nociceptors. Neurosci Lett, 2015. 594: p. 161-2.
183. Habib, A.M., et al., Recombinant activated factor VII is associated with postoperative thromboembolic adverse events in bleeding after coronary surgery. Interact Cardiovasc Thorac Surg, 2018. 27(3): p. 350-356.
184. Habib, A.M., et al., Analysis of Helicobacter pylori Prevalence in Chittagong, Bangladesh, Based on PCR and CLO Test. Microbiol Insights, 2016. 9: p. 47-50.
185. Habib, A.M., Comparison of low- and high-dose recombinant activated factor VII for postcardiac surgical bleeding. Indian J Crit Care Med, 2016. 20(9): p. 497-503.
186. Gameiro, A., et al., The neurotransmitters glycine and GABA stimulate glucagon-like peptide-1 release from the GLUTag cell line. J Physiol, 2005. 569(Pt 3): p. 761-72.
187. Emery, E.C., et al., Novel SCN9A mutations underlying extreme pain phenotypes: unexpected electrophysiological and clinical phenotype correlations. J Neurosci, 2015. 35(20): p. 7674-81.
188. El Rayes, E.N., et al., Novel Technique for Treatment of Foveoschisis Associated With Optic Disk Pits: Active Aspiration of Intraretinal Fluid. Retina, 2019.
189. Di Mauro, M., et al., Additive and independent prognostic role of abnormal right ventricle and pulmonary hypertension in mitral-tricuspid surgery. Int J Cardiol, 2018. 252: p. 39-43.
190. Chandra, M., et al., Genotyping of Hepatitis C virus (HCV) in infected patients from South India. Infect Genet Evol, 2007. 7(6): p. 724-30.
191. Calafiore, A.M., et al., Elective Primary or Secondary Delayed Sternal Closure Improves Outcome in Severely Compromised Patients. Thorac Cardiovasc Surg, 2018. 66(6): p. 500-507.
192. Brillet, G., et al., [Renal effects of endothelins]. Nephrologie, 1993. 14(3): p. 129-32.
193. Biswas, P.K., et al., Risk factors for infection with highly pathogenic influenza A virus (H5N1) in commercial chickens in Bangladesh. Vet Rec, 2009. 164(24): p. 743-6.
194. Bangash, M.A., et al., Distinct transcriptional responses of mouse sensory neurons in models of human chronic pain conditions. Wellcome Open Res, 2018. 3: p. 78.
195. Akbar, M.T., et al., An insight into the lignin peroxidase of Macrophomina phaseolina. Bioinformation, 2013. 9(14): p. 730-5.
196. Zakharchenko, O., et al., Meta-data analysis as a strategy to evaluate individual and common features of proteomic changes in breast cancer. Cancer Genomics Proteomics, 2011. 8(1): p. 1-14.

197. Zakharchenko, O., et al., Optimized Protocol for Protein Extraction from the Breast Tissue that is Compatible with Two-Dimensional Gel Electrophoresis. Breast Cancer (Auckl), 2011. 5: p. 37-42.
198. Woksepp, H., et al., Proteomics of transforming growth factor beta1 (TGF beta1) signaling in 184A1 human breast epithelial cells suggests the involvement of casein kinase 2alpha in TGF beta1-dependent p53 phosphorylation at Ser392. Exp Oncol, 2019. 41(4): p. 304-311.
199. Stasyk, T., et al., A new highly toxic protein isolated from the death cap Amanita phalloides is an L-amino acid oxidase. Febs j, 2010. 277(5): p. 1260-9.
200. Stasyk, T., et al., Phosphoproteome profiling of transforming growth factor (TGF)-beta signaling: abrogation of TGFbeta1-dependent phosphorylation of transcription factor-II-I (TFII-I) enhances cooperation of TFII-I and Smad3 in transcription. Mol Biol Cell, 2005. 16(10): p. 4765-80.
201. Souchelnytskyi, S., et al., Proteomics success story. Towards early detection of breast and ovarian cancer: plasma proteomics as a tool to find novel markers. Proteomics, 2006. 6 Suppl 2: p. 65-8.
202. Souchelnytskyi, S. and S. Hanash, Focus on breast cancer proteomics. Proteomics Clin Appl, 2009. 3(1): p. 5.
203. Souchelnytskyi, S. and L. Alldridge, Breast Cancer and Proteomics: The inaugural Mammary Gland Proteome Initiative (MGPI) workshop 12-13 July 2007, Cambridge, UK. Proteomics Clin Appl, 2008. 2(1): p. 8-10.
204. Souchelnytskyi, S., Bridging proteomics and systems biology: what are the roads to be traveled? Proteomics, 2005. 5(16): p. 4123-37.
205. Souchelnytskyi, S., Proteomics of TGF-beta signaling and its impact on breast cancer. Expert Rev Proteomics, 2005. 2(6): p. 925-35.
206. Souchelnytskyi, S., Proteomics in studies of signal transduction in epithelial cells. J Mammary Gland Biol Neoplasia, 2002. 7(4): p. 359-71.
207. Silva, E., et al., Quantitative intact proteomics investigations of alveolar macrophages in sarcoidosis. Eur Respir J, 2013. 41(6): p. 1331-9.
208. Saini, R.K., et al., Proteomics of dedifferentiation of SK-N-BE2 neuroblastoma cells. Biochem Biophys Res Commun, 2014. 454(1): p. 202-9.
209. Okumichi, H., et al., Proteomic analyses of retina of excitatory amino acid carrier 1 deficient mice. Proteome Sci, 2007. 5: p. 13.
210. Mousa, H., et al., Acquisition of Invasiveness by Breast Adenocarcinoma Cells Engages Established Hallmarks and Novel Regulatory Mechanisms. Cancer Genomics Proteomics, 2019. 16(6): p. 505-518.
211. Mizukami, M., et al., Wnt14 inhibits death of retinal precursor cells. Exp Eye Res, 2009. 89(4): p. 462-8.
212. Mizukami, M., et al., Proteome profiling of embryo chick retina. Proteome Sci, 2008. 6: p. 3.
213. Mints, M. and S. Souchelnytskyi, Proteomic strategy for detection of circulating tumor cell surface antigens. Exp Oncol, 2011. 33(3): p. 193-5.
214. Lomnytska, M.I., et al., Diagnostic protein marker patterns in squamous cervical cancer. Proteomics Clin Appl, 2010. 4(1): p. 17-31.
215. Lomnytska, M. and S. Souchelnytskyi, Markers of breast and gynecological malignancies: The clinical approach of proteomics-based studies. Proteomics Clin Appl, 2007. 1(9): p. 1090-101.
216. Lomnytska, M., et al., Transforming growth factor-beta1-regulated proteins in human endothelial cells identified by two-dimensional gel electrophoresis and mass spectrometry. Proteomics, 2004. 4(4): p. 995-1006.
217. Kwiecinska, A., et al., Proteomic Profiling of Diffuse Large B-Cell Lymphomas. Pathobiology, 2018. 85(4): p. 211-219.
218. Kolakowska, J., et al., Proteomic analysis of the endometrium during early pregnancy in the domestic pig. Reprod Fertil Dev, 2017. 29(11): p. 2255-2268.
219. Kanamoto, T., et al., Proteomic study of DBA/2J mice retina: Down-regulation of Integrin beta7 correlated with retinal ganglion cell death. Proteomics, 2009. 9(21): p. 4962-9.
220. Kanamoto, T., et al., Proteomic study of retinal proteins associated with transcorneal electric stimulation in rats. J Ophthalmol, 2015. 2015: p. 492050.
221. Kanamoto, T., N. Souchelnytskyi, and Y. Kiuchi, Functional proteomics of failed filtering blebs. Mol Vis, 2009. 15: p. 2762-70.
222. Kanamoto, T., et al., Functional proteomics of transforming growth factor-beta1-stimulated Mv1Lu epithelial cells: Rad51 as a target of TGFbeta1-dependent regulation of DNA repair. Embo j, 2002. 21(5): p. 1219-30.
223. Jia, M. and S. Souchelnytskyi, Proteome profiling of heat shock of human primary breast epithelial cells, a dataset report. Cell Stress Chaperones, 2011. 16(4): p. 459-67.

224. Jia, M. and S. Souchelnytskyi, Kinase suppressor of Ras 2 is involved in regulation of cell proliferation and is up-regulated in human invasive ductal carcinomas of breast. Exp Oncol, 2010. 32(3): p. 209-12.
225. Jia, M., et al., Proteome profiling of immortalization-to-senescence transition of human breast epithelial cells identified MAP2K3 as a senescence-promoting protein which is downregulated in human breast cancer. Proteomics Clin Appl, 2010. 4(10-11): p. 816-28.
226. Iwahana, H., et al., Glycoproteome profiling of transforming growth factor-beta (TGFbeta) signaling: nonglycosylated cell death-inducing DFF-like effector A inhibits TGFbeta1-dependent apoptosis. Proteomics, 2006. 6(23): p. 6168-80.
227. Hassel, S., et al., Proteins associated with type II bone morphogenetic protein receptor (BMPR-II) and identified by two-dimensional gel electrophoresis and mass spectrometry. Proteomics, 2004. 4(5): p. 1346-58.
228. Grimsby, S., et al., Proteomics-based identification of proteins interacting with Smad3: SREBP-2 forms a complex with Smad3 and inhibits its transcriptional activity. FEBS Lett, 2004. 577(1-2): p. 93-100.
229. Dubrovska, A. and S. Souchelnytskyi, Efficient enrichment of intact phosphorylated proteins by modified immobilized metal-affinity chromatography. Proteomics, 2005. 5(18): p. 4678-83.
230. da Silva Santos, C., et al., Proteome profiling of human cutaneous leishmaniasis lesion. J Invest Dermatol, 2015. 135(2): p. 400-410.
231. Conrotto, P., et al., Interactome of transforming growth factor-beta type I receptor (TbetaRI): inhibition of TGFbeta signaling by Epac1. J Proteome Res, 2007. 6(1): p. 287-97.
232. Conrotto, P. and S. Souchelnytskyi, Proteomic approaches in biological and medical sciences: principles and applications. Exp Oncol, 2008. 30(3): p. 171-80.
233. Bhaskaran, N. and S. Souchelnytskyi, Systemic analysis of TGFbeta proteomics revealed involvement of Plag1/CNK1/RASSF1A/Src network in TGFbeta1-dependent activation of Erk1/2 and cell proliferation. Proteomics, 2008. 8(21): p. 4507-20.
234. Bhaskaran, N., et al., Comparative proteome profiling of MCF10A and 184A1 human breast epithelial cells emphasized involvement of CDK4 and cyclin D3 in cell proliferation. Proteomics Clin Appl, 2009. 3(1): p. 68-77.
235. Attarha, S., et al., Endometrial cancer and application of proteomics. Exp Oncol, 2011. 33(3): p. 174-7.
236. Attarha, S., et al., Individualised proteome profiling of human endometrial tumours improves detection of new prognostic markers. Br J Cancer, 2013. 109(3): p. 704-13.
237. Diboun, I., et al., Metabolomics of dates (Phoenix dactylifera) reveals a highly dynamic ripening process accounting for major variation in fruit composition. BMC Plant Biol, 2015. 15: p. 291.
238. Al-Khelaifi, F., et al., Metabolic profiling of elite athletes with different cardiovascular demand. Scand J Med Sci Sports, 2019. 29(7): p. 933-943.
239. Al-Khelaifi, F., et al., Metabolomics profiling of xenobiotics in elite athletes: relevance to supplement consumption. J Int Soc Sports Nutr, 2018. 15(1): p. 48.
240. Al-Khelaifi, F., et al., A pilot study comparing the metabolic profiles of elite-level athletes from different sporting disciplines. Sports Med Open, 2018. 4(1): p. 2.
241. Al-Khelaifi, F., et al., Metabolic GWAS of elite athletes reveals novel genetically-influenced metabolites associated with athletic performance. Sci Rep, 2019. 9(1): p. 19889.
242. Doi SA, Furuya-Kanamori, L., Toft E et al. , Exercise or lifestyle counselling in pregnancy to avert gestational diabetes
243. in women at high-risk: meta-analysis of randomised controlled trials. J Clin Endocrinol Metab 2020 in process.
244. Furuya-Kanamori, L., et al., P value-driven methods were underpowered to detect publication bias: analysis of Cochrane review meta-analyses. J Clin Epidemiol, 2020. 118: p. 86-92.
245. Doi SA, Furuya.-Kanamori, L., Xu C et al, Questionable utility of the relative risk in clinical research: A call for change to practice. J Clin Epidemiol 2020, in process.
246. Doi, S.A.R. and L. Furuya-Kanamori, Selecting the best meta-analytic estimator for evidence-based practice: a simulation study. Int J Evid Based Healthc, 2019.epub ahead of print.
247. Regan, J.P. and J.T. Casaubon, Abdominoplasty (Tummy Tuck), in StatPearls. 2020, StatPearls Publishing StatPearls Publishing LLC.: Treasure Island (FL).
248. Losco, L., et al., Lower Body Lift After Bariatric Surgery: 323 Consecutive Cases Over 10-Year Experience. Aesthetic Plast Surg, 2019.
249. Schwaiger, K., et al., Thighplasty: improving aesthetics through revival of the medial, horizontal procedure: A safe and scar-saving option. J Plast Reconstr Aesthet Surg, 2018. 71(4): p. 585-589.

250. Swift, D.L., et al., Effects of clinically significant weight loss with exercise training on insulin resistance and cardiometabolic adaptations. Obesity (Silver Spring), 2016. 24(4): p. 812-9.

Appendix B: HMC research grant

مؤسسة حمد الطبية
Hamad Medical Corporation
مركز البحوث الطبية
Medical Research Center

HMC RESEARCH PROTOCOL

Study Title:	**Metabolic Changes After Body Contouring Surgeries, a Quasi-experiment with Four-Time Points**
Principal Investigator:	**Dr. Saifeddin Badran, MD, MRCSEd** **Plastic Surgery Resident** **Department of Plastic Surgery** **Hamad General Hospital- HMC**

Contents

MRC-01-20-466 Validity: 25 08 2020 - 24 08 2021 E-stamped 25 Aug 2020

1. Synopsis

Obesity is a prevalent disease among the Qatari population affecting more than half of the adult population, which makes it a national priority. This increase in body weight is a major risk factor leading to the development of insulin resistance, metabolic syndrome, and diabetes mellitus (type 2). Bariatric surgery is currently the most effective treatment for obesity. Because this procedure is freely accessed, there is now an accelerating demand for bariatric surgery, and in many of these patients, body contouring plastic surgery is required to remove the excess peripheral body fat tissue. These interventions have led to a corresponding increase in health cost burden in Qatar.

Although it is well known that excess fat tissue leads towards the development of insulin resistance and its other metabolic sequelae such as diabetes mellitus and cardiovascular disease; what remains unknown however is the transcriptomic, proteomic, metabolomic, lipidomic and clinical biochemistry profile in blood and adipose tissue before and after body contouring surgery. A particular characteristic of these patients is their varying degrees of insulin resistance, coupled with the sudden removal of their excess fat.

Through a study of blood and adipose tissue, this research proposal aims to identify:

1) The clinical improvements in biochemical profiles of patients undergoing excess fat removal as a function of time and its potential associations with the percentage of fat removal and other clinical phenotypes.

2) Novel biomarkers for the varying degrees of insulin resistance observed in these patients for a diabetic and non-diabetic group.

3) Critical underlying mechanisms for clinical benefits observed in patients after the sudden removal of excess body fat.

The resulting data will be processed by applying an extensive epidemiological analysis to understand the change in insulin resistance and glycemic as well as body mass trajectories after surgery. It is anticipated that the results of this proposal will provide critical comprehensive data. This, in turn, will enable us not only to further understand novel pathways through which insulin resistance develops and its clinical consequences in obese patients but will also provide us with data that can be used to develop promising diagnostic and therapeutic tools to tackle these cluster of clinical consequences. As such, it is likely to contribute to improvements in the management of obesity, thereby reducing the national health cost burden. The results from this proposed research project will likely enhance the delivery of vital healthcare services for the Qatari population and will increase Qatar's capacity in this field.

These studies have different objectives to our research. Our main goal is to look at the impact of T2DM and obesity on bariatric surgery-induced changes with or without BCS. None of these previous studies has addressed the issue of biochemical or proteomic changes in adipose tissue post-bariatric surgery or/and BCS.

Furthermore, the specificity, scope and depth of our study proposal are different and therefore original.

1- **Specificity (population)**

The majority of studies on disease have been performed in Europeans; the study by Vries CEE et al. and Klein S et al. in the Netherlands and in the USA, respectively are also likely to be on Europeans (white Caucasians). The problem with this trend is that, it is becoming apparent, for example, emerging data indicates that the weight loss after bariatric surgery shows considerable individual

variation and that race might influence in regaining the weight that was lost soon after the surgery (Laura Boswell et al., International Journal of Obesity, 2018; Michael H Wood et al., JAMA 2019; Haleh Amirina et al., Obes Surg, 2020).

Therefore, in our study, we aim to recruit Qatari patients, and the knowledge gained will be directly relevant to the Qatar population and countries in this region.

2- **Scope (patients groups to include those listed below, g-k**

The study by Klein S et al. was performed on

a) women with a normal digestive tract

b) 8 normal glucose tolerance *vs* 7 T2DM and on which

c) changes were looked at a single time point (3 months, postoperatively) and

d) adipose tissue removed from the abdomen only

On the other hand, the recent retrospective study by de Vries CEE et al. was performed on

f) T2DM patients who underwent RYGB bypass and

g) Adipose tissue was also removed from the abdomen only.

In contrast, our study will look at completely sets of patients:

h) Obese non-diabetic (OND) without bariatric
i) OND with RYGB

j) OND with gastric sleeves

k) Obese diabetic with gastric sleeves

l) Adipose tissue from thighs [(since recent data suggest that adult brown adipose tissue (also present in thigh fat) has been linked in obesity and T2DM (Cypess Am et al., NEJM 2010; Aaron M Cypess and C. Ronal Kahn, Curr Opin Endocrinol Diabetes Obes, 2013; Maria Chondronikola et al., Diabetes 2014)].

Therefore, the scope of our study is different to and much broader than from the studies by Klein S et al. and de Vries CEE et al.

3- **depth (detailed profiling)**

The study by de Vries CEE et al did NOT address the same objectives as our project; however, it is informative in that it suggests that benefits of weight loss / BMI take time to develop but are also lost over time. We have specifically designed our studies to examine the time effects of any gain/loss of benefit through biochemical and proteomic profiling analysis. This will be the foundation for generating evidence-based hypothesis to study the underlying mechanistic changes.

In addition, previous studies that measured the change in insulin sensitivity varied in their results between improvement to no change, and most of the studies were conducted with small sample sizes and minimal expertise in proteomics and biochemistry. The mentioned study that was conducted by Klein et al were conducted on a small sample size (15 patients: 8 normal glucose tolerance, 7 diabetic patients), and it looked at the changes at one time point at 3 months post operatively, additionally recent studies have demonstrated a different in the metabolic effect of the fat tissue based on its location, the fat tissue in the abdomen might have a different metabolic effect than the thigh region. Thus, in our study we are looking into these changes separately in a comparative way.

In our research, we will be measuring the complete hormonal profile to include all the incretin hormones, which are secreted from the GI tract after meals and play a major function in our metabolism. These hormones are secreted from different places of the GI tract, thus different bariatric surgeries might result on different metabolic effect based on this variation. Our main target is to look at the metabolic changes post body contouring surgeries, some of these patient will have undergone different kind of body contouring surgeries, looking into their detailed surgical history might help is to run separate group analysis and see if the metabolic changes is different based on their surgical history or not.

It is still not fully clear why certain patients, have a high BMI but still maintain a lower degree of insulin resistance. This understanding might be achieved through proteomic and metabolomic investigation to know which intermediates might be associated with insulin resistance. Another exciting aim of this research proposal is to examine if some of these metabolites are associated with more improvement in the insulin sensitivity status after the body contouring surgeries.

Our target population are patient who are willing to undergo body contouring surgeries, it's quite difficult to have an exact comparative group and do all the same analysis without doing the surgery for them. Thus, we chose the quasi experimental design, where patient will act as a self-control by comparing their results before and after the surgery.

2. Abbreviations and Acronyms

None.

3. Introduction / Background

About 70% of Qatar's adult population is overweight or obese (as discussed at the Qatar Diabetes Leadership Forum on 13th Feb 2020). Qatar is now ranked fifth globally in terms of incidence of obesity [1], which makes further research focused on the field of obesity and associated metabolic diseases including diabetes as a national priority as indicated in the Qatar National Health Strategy 2018 – 2022. A clinical hallmark often linking obesity and type 2 diabetes is the development of insulin resistance. The term "insulin resistance" refers to the weakened blood-glucose-lowering impact of circulating or injected insulin on blood glucose [2].

Bariatric surgery is currently the most effective treatment, not only in terms of weight loss but also glycemic control and decrease of cardiovascular risk [3-5]. Since the early 2000s, the number of bariatric surgeries has increased exponentially [6]; this is particularly true in Qatar, where this surgery is freely available to Qatari Nationals. Of the different types of surgical techniques available, the two procedures mostly used currently in Qatar are Roux-en-Y gastric bypass (RYGB) and vertical sleeve gastrectomy (SG). Both procedures result in a smaller gastric pouch and hence reduce the size of meal intake; however, in RYGB, the alimentary limb is rearranged such that the endocrine cells, for example, the L-cells get stimulated with high amount of nutrients resulting in elevation of glucagon-like peptide-1 (GLP-1) hormone [7]. Secretion of GLP-1 will trigger insulin release from pancreatic β-cell, increasing glucose uptake by the peripheral tissue [8]. Several other circulating gastrointestinal hormones level also change as a result of RYGB surgeries, including, Ghrelin, peptide tyrosine-tyrosine (PYY), Insulin-like 5 and leptin [9, 10].

The substantial percentage weight loss and reduced plasma glucose after bariatric surgery can also be partly attributed to the loss of body fat, which in turn improves insulin sensitivity [11]. Other health benefits or adverse effects resulting from bariatric surgery and their underlying mechanisms are not fully understood. Interestingly, because of the rapid, massive weight loss following the bariatric surgery, within about two years the patients tend to require body contouring plastic surgery to remove redundant skin and excess body fat [12]. A typical example of these surgeries is the abdominoplasty surgery which removes around 2-3kg of subcutaneous fat tissue from the central abdominal area. The body-contouring surgery also can be done in patients not undergoing bariatric surgery for purely cosmetic purposes. As adipose tissue is known to release hundreds of signaling molecules the precise effects of suddenly removing such an amount of patient body fat on the underlying metabolic consequences, for example, its contribution towards the modulation of insulin resistance, biochemical profile, eating behavior and mental wellbeing are not known.

The dysregulation of glucose homeostasis in insulin resistance arises from the combination of deficiency in glucose clearance with the elevation of glucose production in the liver. The preservation of systemic insulin sensitivity is dependent on healthy adipose; the lack of it, as seen in patients with lipodystrophy, results in a severe form of insulin resistance [13]. However, too much of adipose mass also can result in a similar condition, and in such instances, can lead to insufficient glucose clearance. The primary reasons for the latter form of insulin resistance may be hypoxia in adipose tissue that leads to inflammatory lipo-toxicity [14]. Whether the removal of excess fat through abdominoplasty surgery ameliorates the hypoxia and the resulting inflammation is not known. Indeed, several signaling molecules from adipocytes have been ascribed to have a critical role in energy homeostasis through communicating with organs that maintain systemic metabolic homeostasis such as the liver. Of the adipocyte derived factors, **adiponectin, leptin** and **fatty acids** are among essential mediators. Indeed, adiponectin analogues are now considered one of the promising new therapeutic targets for obesity-linked hyperglycemia as its effects are mediated through enhancing insulin-sensitizing peptide release from adipose tissue [15], similar to insulin-sensitizing actions of leptin [16]. To understand the roles of

adipose derived factors, we will now briefly review their action in glucose homeostasis and insulin sensitivity.

Adiponectin: also known as complement related protein is produced solely from fat cells and is considered to be the most abundant gene transcript in adipocytes. Its size varies between 90KDa and 180KDa. It plays a role in increasing insulin sensitivity on various organs in the body, and also locally on the adipocytes to enhance glucose uptake, adding to euglycemia and advancement of adipose tissue increase. Consistent with this observation, in vitro, lentiviral overexpression of adiponectin in fibroblast cell enhanced glucose uptake [17]. Circulating adiponectin levels is decreased in an obese patient and is linked to the development of heart and peripheral vascular disease such as atherosclerosis. Although the adiponectin receptors at the muscle and liver cells are not clearly identified yet, it's been proven that adiponectin production is mandatory for insulin to act normally, which was reported when studying adiponectin knockout mice who demonstrate an increase in insulin resistance.

Leptin: Leptin is a 16KDa protein, and it is secreted mainly by the adipocytes, but also from the gastric epithelium. Leptin secretion is stimulated after food intake and acts on the hypothalamus to produce satiety. Leptin secretion is augmented by insulin at the gene regulation level, while on the hand, leptin act to suppress insulin transcript and secretion from pancreatic beta cells. The receptors for leptin are highly expressed on the adipocyte. In vitro, studies have shown that leptin inhibits insulin-induced glucose uptake in cultured adipocytes [18], and a high concentration of leptin results in enhanced expression of an inhibitor of the insulin receptor autophosphorylation, SOCS3, indicating that leptin suppresses insulin receptor activation [19].

Fatty acids: many fatty acids released from the adipose tissue mediate signals that modulate energy metabolism. These molecules are structurally diverse and have pleiotropic effects on target tissues. For example, ceramide, synthesized from the long-chain fatty acids can inhibit insulin-induced glucose uptake, the translocation of the glucose transporter-4 to the cell membrane, and/or the synthesis of glycogen [20]. Palmitic-acid-9-hydroxy-steric-acid, also released from adipose tissue, is known to improve insulin sensitivity in humans via a G-protein coupled receptor-120 (GPR-120) [21]. Interestingly, GPR-120 is highly expressed in L-cells in the intestine [22], and the palmitic-acid has been shown to stimulate GLP-1 secretion, leading to improving glucose tolerance.

Patients seeking body contouring surgeries that target the abdomen and thigh regions will have a BMI in the overweight to the obese range with different degrees of insulin resistance. The previous literature has suggested that almost all people start to have insulin resistance when their BMI starts to cross 23. Obesity causes an increase in the efflux of fatty acids from the adipocytes, which will be converted into a triglyceride molecule and this results in the production of many metabolites and intermediates that cause insulin signaling impairment and eventually insulin resistance. The latter, in turn, causes an increase in visceral fat such as omental fat and also results in fatty changes in the liver. Thus, in our study, we will be measuring the changes in insulin resistance after removing an average of 2-3 kg of subcutaneous fat cells, and we will try to understand the mechanism behind the observed differences. Previous studies that measured the change in insulin sensitivity varied in their results between improvement to no change, and most of the studies were conducted with small sample sizes and minimal expertise in proteomics and biochemistry. In our research, we will be measuring the complete hormonal profile to include all the adipocytokines, the incretin hormones, the inflammatory markers, the lipid profile, and liver function tests to understand the mechanism behind any change after these surgeries. Similar studies were done on weight loss surgeries, i.e. bariatric surgeries, and it showed a significant metabolic change and significant clinical effect, including the need for diabetic medications after surgery in a specific group of patients. In this study, rather than gradual loss of body fat, we will focus on a sudden loss of 2-3kg of subcutaneous fat after body contouring plastic surgeries which results in a decrease in numbers of fat cells rather than just decreasing the size of fat cells as happening after weight loss due to bariatric surgeries. Results from this study will, therefore, highlight differential

mechanisms associated with sudden (as in body contouring surgery) vs gradual weight-loss (that occurs post-bariatric surgery).

Furthermore, insulin resistance in overweight and obese patients is modulated by intermediates in lipid metabolism. To understand why certain patients, have a high BMI but still maintain a lower degree of insulin resistance, these intermediates need to be studied. This can be achieved through proteomic and metabolomic investigation to know which intermediates might be associated with insulin resistance. Such information will be of value in providing diagnostic and therapeutic benefit as well as for generating tools for early detection of diabetes and metabolic disorders. Another exciting field of this research proposal is to find if some of these metabolites are associated with more improvement in the insulin sensitivity status after the body contouring surgeries.

4. Objectives

This proposal aims to address the following hypotheses concerning sudden excess fat removal by body contouring surgery in obese patients.

Hypothesis-1. Removal of excess fat during body contouring surgery alone can result in measurable clinical benefit (e.g., Mental wellbeing, eating behavior, OMICS and biochemical indices of insulin resistance and glucose homeostasis).

Hypothesis-2. Bariatric surgery together with surgical removal of excess fat yields significant *added* clinical benefit.

Hypothesis-3. Clinical benefits of excess fat removal with or without bariatric surgery are likely to be greater in obese patients with type 2 diabetes compared to non-diabetic obese.

To address the above hypothesis, we will recruit the following patients' groups:

Obese non-diabetic (OND) groups	Obese with Diabetes (OD) groups
1) OND without bariatric surgery	4) OD without bariatric surgery
2) OND with RYGB	5) OD with RYGB
3) OND with GS	6) OD with GS

Thus, in these patient groups we will address the following previously unaddressed important questions relating to the above hypotheses:

1) Does the sudden excess fat removal by body contouring surgery alone result in clinical benefit?

- Over what time-frames post-surgery does this occur?
- Can these be correlated to the degree of insulin resistance and/or to the percentage of body fat removed?
- If there is clinical benefit, what is the underlying molecular mechanisms?
- Can we identify novel biomarkers through transcriptomic, proteomic, lipidomic and biochemical profiling?

2) Does removing excess fat (body contouring surgery) together with bariatric surgery give *added* clinical benefit?

- Is this influenced by the type of bariatric surgery (RYGB vs SG) and if so, what are the underlying molecular mechanisms?

3) Are the clinical benefits associated with the removal of excess body fat different in non-diabetic obese vs diabetic-obese patients?

In summary, through a study of blood and adipose tissue, this research proposal aims to identify-

1) The clinical improvements in biochemical/OMIC profiles of patients undergoing excess body fat removal as a function of time and its potential correlation with the percentage of fat removed and clinical phenotypes.
2) Novel biomarkers for the varying degrees of insulin resistance observed in these patients for diabetic and non-diabetic groups.
3) Critical underlying mechanisms for clinical benefits observed in patients after the sudden removal of excess body fat.

This project will be conducted with specific aims and will involve mainly primary data collection but also secondary data collection from existing research studies.

Outcomes:

1A. Non-diabetic patients: Glycemia related changes will be assessed using well known baseline measurements (HOMA, HbA1c, relevant hormones (GLP-1, PYY, GIP, insulin-like 5, ghrelin, leptin, adiponectin, vitamin D, midnight salivary cortisol, IL-6 and TNF-alpha), fatty acids and the oral glucose tolerance test (OGTT).
1B. Diabetics: similar measurements as above (excluding the OGTT).
1C. Measure the amount of change in anthropometric measurements (height, weight, BMI, waist circumference) as well as measure the changes in the Mental Health Questionnaire (PHQ-9) [23] for depression, the Appearance Anxiety Inventory Questionnaire for body dysmorphic disorder [24], the Generalized Anxiety Disorder-7 Questionnaire (GAD-7), the Japanese Metabolic Syndrome Risk Score (JAMRISC) questionnaire [25] and the Council of Nutrition Appetite Questionnaire (CNAQ) [26] after 6 months of undergoing body-contouring surgery. As well as clinical data on the frequency and intensity of the patient's physical activity.

2A. Proteomics: From fat tissue lysates and serum: Study the relative expression of proteins, lipids with emphasis on fatty acids and steroids, in adipocytes, by applying chromatography, electrophoresis and mass spectrometry

2B. Metabolomics: From cultured preadipocytes: to measure the adipogenic capacity of isolated preadipocytes, the cytokines/adipokines secreted from expanded preadipocyte cultures as well as evaluation of the oxidative stress and insulin signaling from expanded preadipocytes cultures.

3A+3B. To understand the clinical mechanisms through which the changes observed in objective one are mediated, by applying novel epidemiological methods to analyze data collected through aims 1 & 2

5. Indicate if this is a retrospective data review

- **Retrospective Chart/data Review**
  Not applicable.
- **Provide the date range of the chart review**
  Not applicable.

6. Study Methodology

The methodology in this project will leverage the unique position of Qatar where body contouring surgeries occur almost daily in each governmental and private hospital in Qatar due to the combination of relatively low health care costs and a high socio-economic status of the relevant populations receiving body contouring surgery. The LPI/PhD scholar (Badran) will be involved with all patient surgeries recruited to this study (surgical resident) and will manage the recruitment process for the patients in concert with PI's Hammouda and Al-Basti. Recruitment will happen during the routine preoperative visits, during which the research protocol will be explained, and the patient will be given a copy of the research informed consent. Patient participation will be completely optional and will not affect their care in any way, and withdrawal or continuation within this project will be treated identically.
The research design will be a quasi-experiment with four-time points. This experimental design was chosen because the classical experimental design (randomized controlled trial) is not appropriate for this type of study. In this research design the outcome variables of interest will be measured before and at three time points after the surgical intervention (interrupted time series design; preoperative "baseline phase", immediate postoperative, short term phase and long-term phase) as below:
1- **Preoperative Phase:** one day before the surgery, while the patient is admitted to the hospital for next day elective body contouring surgery.
2- **Immediate Phase:** within the first post-operative week, mostly to be done within the same admission before the patient is discharged home.
3- **Short term Phase:** during the short term follow up clinic visit; between 2-6 weeks after surgery.
4- **Long term phase:** during the long term follow up clinic visit; after 6 months post-surgery.

The patient will come to be admitted one day before the surgery as per our routine protocol for these surgeries, he/she will be contacted and requested to come in the morning with an overnight 8 hours fasting then we will take blood samples to do the oral glucose tolerance test while we do their routine blood tests. The oral glucose tolerance test (OGTT) will include taking blood sample after the 8 hours fasting, then patients will be given 100 gm of sugar to drink, then we will take another 3 sets of blood samples during the 2 hours after the sugar drink. The total amount of blood withdrawn will be around 12 ml. The patient will be pricked once during the first sample while we insert a canula, all the other samples will be taken from the cannula after flushing without any additional pricks.

After surgery and during the same hospital stay, the patient will be asked to fast during the night sleeping hours, to be ready for the test in the morning. During clinic visits; the patient will be contacted one day before and asked to come fasting to the clinic in the morning to be ready for blood sampling. During the preoperative and the postoperative visits, patient blood samples will be taken at the same time that the nurses are taking blood samples for their routine perioperative care to check preoperative and daily postoperative hemoglobin levels to avoid extra pain and invasive testing on the participants. Blood samples will be taken in the four phases above, but the at samples will only be obtained at one time point during surgery. All additional tests mentioned in the protocol will be done on the same blood samples taken from the OGTT.

In the first two phases: the blood sample will be taken by the PI Badran/ Research assistant during the routine blood sample collection by the floor nurse, while during the last two phases; blood samples will be collected by the PI Badran/ Reseach assistant during the routine blood sample collection at Hamad General Hospital as the patient will be followed at the outpatient department rather than admitted as an inpatient. Patient medical history in addition to the questionnaires used in this study which are all freely

available online for routine medical use (JAMRISC, CNAQ, PHQ-9, GAD-7 & body dysmorphism questionnaire) will be assessed before the surgery and 6 months after the surgery. Blood samples collected will be sent to Qatar University laboratory for analysis and the planned profiling. The blood sample that reaches the Qatar University laboratory will be processed and stored at -80 degree Celsius until analysis. 10g of fat, from that removed from the patient during surgery, will be immediately (within 20-30 min) put on dry ice, and sent to the QU Proteomics Core facility to be processed.

Blood samples collection protocol:

To standardize the subjects, they will be refrained from strenuous exercise and alcohol intake for 24 hours prior to the study day. Subject will fast from 12 hours prior to the study but are permitted to drink water.

On each study day, the subject will be acclimatized for minimum 45-60 minutes and three fasting blood baseline blood samples will be taken for glucose and hormone (insulin, GLP1..) analysis at t=-10, -5 and -1 min. Blood sample will be collected into EDTA tubes on ice.

Following collection of the last baseline sample, subjects will drink glucose (75g, 0.42 moles, in 300ml of water) or water (300ml) over approximately 2 minutes (last mouthful at t=0). Blood samples will be collected at t =0, 30, 60 and 120 min) into EDTA tubes. A total of 8ml blood sample will be withdrawn for hormone assay and supplemented with 100ul Aprotinin (50ul/ml blood). 20ul Pefabloc will be added for Acyl-ghrelin hormone blood-sample. For proteomics analysis a total of 4ml blood will be withdrawn. After the collection into EDTA tubes, samples will be placed immediately on ice for transport to Lab. Within 60 minutes of samples withdrawal, the samples will be spinned in a pre-chilled centrifuge at 4C, 1800rpm for 10 minutes. Plasma will be transferred to microtubes, dividing into aliquots. All samples will be at -80C until use.

Aims:

1. To determine if insulin resistance, glycemic status, appetite and mental well-being are modulated by such a sudden change in the non-visceral fat after the body contouring surgeries.
2. To determine using biochemical and OMIC profiling if there could be any novel biomarkers that distinguish between the patients with varying degrees of insulin sensitivity and other clinical phenotypes described above.
3. To understand the mechanisms through which the changes observed in aim one are mediated, thus lending itself as a foundation for further investigation into newer therapeutic approaches for mitigating the development of type 2 diabetes mellitus

Methods for Aim one:

The following approach will be utilized to determine if clinical improvements are modulated by such a change in the non-visceral fat after the body contouring surgeries as below:

1A. Non-diabetic patients: to determine if insulin resistance is modulated by such a change in the non-visceral fat after the body contouring surgeries in the abdomen and thigh regions. This will be ascertained by measuring glycemic changes before and after the surgery over four timelines (pre-operative, immediate post-operative, short term and long-term post-operative). Glycemia related changes will be

assessed using well known baseline measurements (HOMA, HbA1c, relevant hormones (GLP-1, PYY, GIP, insulin-like 5, ghrelin, leptin, adiponectin, vitamin D, midnight salivary cortisol, IL-6 and TNF-alpha), fatty acids and the oral glucose tolerance test (OGTT). The OGTT will use 4 time points (0, 0.5, 1 & 2 hours) with measurement of c-peptide and glucose simultaneously

1B. Diabetics: to determine the impact on glycemic status after such a change in the non-visceral fat, using similar measurements as above (excluding the OGTT).

1C. Measure the amount of change in anthropometric measurements (height, weight, BMI, waist circumference) as well as measure the changes in the Mental Health Questionnaire (PHQ-9) [23] for depression, the Appearance Anxiety Inventory Questionnaire for body dysmorphic disorder [24], the Generalized Anxiety Disorder-7 Questionnaire (GAD-7), the Japanese Metabolic Syndrome Risk Score (JAMRISC) questionnaire [25] and the Council of Nutrition Appetite Questionnaire (CNAQ) [26] after 6 months of undergoing body-contouring surgery.

Methods for Aim Two:

To identify novel biomarkers of changes seen in Aim 1 through epidemiological linkage of clinical data with the signatures derived from proteome, lipidome and steroid hormone profiles of fat tissue and blood of patients with varying degrees of insulin sensitivity. The goal is to translate this profiling into a diagnostic and therapeutic tool for managing insulin resistance among overweight and obese patients. This will be achieved by the following studies on fat tissue and blood samples recruited during and post-surgery (only blood):

2A. Proteomics: From fat tissue lysates and serum

1- Prepare extracts for proteome and lipidome profiling. Fat tissue and serum samples will be extracted to obtain hydrophobic and lipophilic fractions. Extracts will be centrifuged to obtain soluble fractions, which then will be used for a) direct mass spectrometry profiling and/or b) separations by electrophoresis (for proteins) or chromatography (for lipids) followed by mass spectrometry.

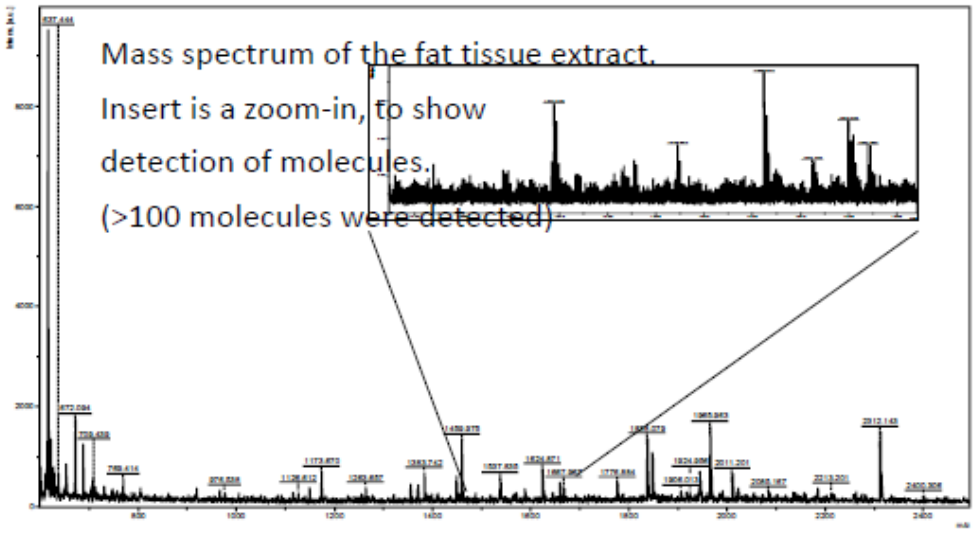
2- Study the relative expression of proteins, lipids with emphasis on fatty acids and steroids, in adipocytes, by applying chromatography, electrophoresis and mass spectrometry. Extracts may contain complex mixtures, and a separation of the mixture components would be required. For proteins, we will use 1D- and 2D-electrophoresis. For lipids, we will use reverse phase (RP) chromatography by using a C18-RP column. Electrophoresis and chromatography allow quantification and measurement of relative quantities of proteins and lipids. For mass spectrometry measurements, we will use relative ion count (for unknown molecules) and comparison with external standards (for known molecules).

3- Generate representative profiles of proteins and lipids for studied clinical conditions. Standardization of extraction, separation and mass spectrometry protocols will allow to generate representative profiles. Profiles of clinical samples will be integrated to obtain representative profiles. For profiles of GLP-1, PYY, GIP, insulin-like 5, ghrelin, leptin, adiponectin, vitamin D, midnight salivary cortisol, IL-6 and TNF-alpha, and c-peptide, external standards will be used to ensure secure identification and relative quantification. External standards will also be used to generate fragmentation spectra with our mass spectrometry instrument (Ultraflextreme).

4- Report systemic analysis of the profiles for correlations with the studied clinical conditions. Representative profiles of medical conditions will be compared to identify unique components and molecules changing levels of expression. Molecules with change in expression for at least 50% of control values will be considered. For integration of data for systemic analysis, we will use open source tools, e.g. Cytoscape, String, FunCoup.

PI Souchelnytskyi and PI Habib will assist with the proteomic analyses. The tissue samples will be extracted with solvents to obtain fractions of proteins (hydrophilic) and lipids (hydrophobic). This extraction protocol will be subjected to quality controls, to ensure high levels of extraction. These

protocols have been developed for solid tumors and cultured cells; we tested these protocols with animal (sheep) fat tissue. Matrix-assisted laser desorption ionization (with a time of flight analyzer; MALDI-ToF) mass spectrometry profiling of the extracts confirmed feasibility of this work. Obtained mass spectra allow us to conclude that the available technologies can deliver informative results.
Our experience of analysis and clinical correlation studies are confirmed in publications [27-67].The figure below depicts that the method has the ability to detect more than 100 molecules in a single mass spectrometry run. This was obtained in a trial run using fat tissue extract (sheep). Note that we will have multiple fractions to run (10-50) per sample which will provide a rich source of detected molecules (proteins, peptides, metabolites).



Separation of proteins will be performed by 2-dimencional gel electrophoresis. To detect 3,000 to 5,000 proteins in a sample and measure differences in their expression which is the routine at the Proteomics Core facility. Differentially expressed proteins will be selected for identification by MALDI TOF/TOF mass spectrometry at Ultraflextreme (Bruker). Peptide mass fingerprinting and fragmentation by post-source decay. Separation of lipids will be by FPLC (Akta). We will optimize the chromatographic matrix, with reverse phase matrix to be the first choice. Chromatographic fractions will be prepared for further mass spectrometry identification, by drying to decrease the volume and quality control of composition. Identification of lipids will be performed by MALDI TOF/TOF mass spectrometry.
For identifications, we will use such databases as NCBInr (for protein ID searches) and primarily METLIN database (http://metlin.scripps.edu) for mass spectrometry spectra matching for metabolites/lipids. For lipids we will also use LipidMaps (http://www.lipidmaps.org/data/index.html), SphinGOMAP (http://sphingomap.org/) and Lipid Bank (http://lipidbank.jp/index00.shtml). Integration of data will be performed with use of such systems biology tools as Cytoscape, FunCoup and KEGG. To evaluate clinical relevance of obtained signatures, we will correlate components of the signatures with available clinical information on pathogenicity, disease-relevance, prognosis, prediction and targeting by drugs, We will use NCBI databases with clinical information, e.g. ClinVar.

2B. Metabolomics: From cultured preadipocytes:

1- Isolate stromal vascular fraction from adipose tissue and expand preadipocytes cultures.

2- Study the adipogenic capacity of isolated preadipocytes.

3- Measure cytokines/adipokines secreted from expanded preadipocyte cultures.

4- Measure oxidative stress and insulin signaling from expanded preadipocytes cultures.

We will isolation of stromal vascular fraction cells from human SC adipose tissue Stromal vascular fraction (SVF) that will be obtained by collagenase digestion, and cell umber will be quantified per gram of tissue. The SVF pellet will be re-suspended in stromal medium (DMEM-F12 containing 10% [vol./vol.] FBS, 100 units/ml penicillin and 0.1 mg/ml streptomycin) and maintained at 37°C with 5% CO2 until confluence, then passaged at 2 × 104 cells/cm2 when necessary.

Viability and differentiation capacity in Insulin Sensitive (IS) vs Insulin Resistance (IR) adipocytes. Total number of nuclei (DAPI positive) and differentiated adipocytes (Lipidtox positive), as well as average sizes of differentiated adipocytes, will be scored in 20 fields per well by ArrayScan XTI (Life Technologies, Grand island, NY, USA) using the automated spot detection module. Cell viability was assessed by comparing the number of cells (stained nuclei) at 1 day post seeding with that scored following completion of differentiation.

Differentiation capacity will be assessed by calculating the number of Lipidtox-positive cells per total number of stained nuclei and presented as a percentage (adipogenic capacity). This will also validated in preadipocytes obtained from a lean individual who showed greater than 80% adipogenic capacity (data not shown). For investigating IL-6-mediated inhibition of differentiation, cells were grown as above, with or without 20 ng/ml IL-6 for the entire differentiation/maintenance periods.

Local cytokine secretion The supernatant media of SC preadipocyte cultures from IS and IR participants will be collected following completion of differentiation. Accumulated levels of secreted IL-6, IL-1β, TNFα and IL-8 in the last 4 days before staining were measured using Inflammatory Cytokine Human Magnetic 5-Plex (Life Technologies) according to manufacturer's instructions and assessed by Luminex Flexmap 3D using xPONENT 4.2 software

Methods for Aim three:

To understand the clinical mechanism through which the changes observed in objective one are mediated, by applying novel epidemiological methods to analyze data collected through aims 1 & 2 thus creating an opportunity for discovery of newer therapeutic approaches for mitigating the development of type 2 diabetes mellitus, and this will be achieved through:

3A- Epidemiological analyses of changes in measured hormones, and profiles (proteomic, metabolomic and gene expression) before and after the surgery (immediate post-operative, short term after 6 weeks and long term after 6 months).

3B- Analytic examination of the magnitude of these changes with the clinical changes described in Aim 1 and the amount of fat tissue removed from the surgery.

Data Analysis:

The members of the research team have a long-standing track record of research collaboration across different teams. Data will be analyzed extensively and collaboratively with the health

system at the Department of Population Medicine at Qatar University. The LPI/PhD scholar (Badran) will work to facilitate the collaboration as he is working as a plastic surgery resident at Hamad General Hospital-HMC and as a PhD scholar in the area of Clinical Epidemiology, at the College of Medicine, Department of Population Medicine at Qatar University. The Department is well positioned to mentor the LPI/PhD scholar (Badran) as it has the requisite analytical and design expertise (LPI Doi, Principal Supervisor) who has not only the relevant expertise but also is the author of several analytic models in Medicine and has written a book on *Methods of Clinical Epidemiology* [68].

In brief, because the data collected over time (four-time points) are correlated, the methods used for longitudinal data analysis will account for the correlated nature of the data. There are many methods through which this can be achieved, but in this study the plan will be to use cluster robust analysis. In this method, we consider statistical inference in regression models where observations can be grouped into clusters, with model errors uncorrelated across clusters but correlated within clusters. The PI Doi has discussed the use of such modeling previously in relation to meta-regression [69] and a variant of this regression approach will be used here. Stata version 15 (College Station, TX, USA) will be used for all analyses. All statistical and epidemiological analyses will be done under oversight from the PI Doi. The LPI/PhD scholar (Badran) will receive research methods training during the period of this project.

7. Study Population and Study Setting/ Location

Study Population and setting:

Patients undergoing body-contouring surgeries at the Department of Plastic Surgery in Hamad General Hospital in the period 2020-2023. Blood and fat samples will be moved to Qatar University for analysis

The blood and fat samples will be collected from patient at Hamad Hospital, the samples will be sent to Qatar University labs at the Faculty of Medicine to run the analysis. The LPI of this project is a PhD scholar at the Faculty of Medicine- QU, where he will get all the needed support for running the required analysis. Support will be provided by two PIs, who are well experienced in biochemistry and proteomics at Qatar University.

Sample Size:

Our primary outcome is the change in insulin resistance after the body contouring surgeries in the abdomen and thigh regions. We consider a minimum clinically significant change in HOMA2 IR to be between 15%-25% [70] from a baseline of 2.0. The variance of HOMA2 IR was derived from a previous study of ours were the HOMA IR was approximately normally distributed in subjects with values < 3.5 with a variance of 0.61[71]. For an alpha of 0.05, we estimate a sample size of 72 (given the conservative difference of 15% in HOMA-IR) will give us 90% power to detect a statistically significant difference should a true difference of this magnitude exist. Given an expected 30% drop out rate, we will recruit 100 subjects or more.

Our primary outcome is the change in insulin resistance after the body contouring surgeries in the abdomen and thigh regions. Thus, we based our sample size calculation on it. The changes of the HOMA level after body contouring surgeries are not consistent, some of the studies are reporting a decrease in the insulin resistance after these surgeries *(Busetto et al. 2006, Andrae et al. 2005)*. While others even have contradicting data *(Yabarra 2007)*. Additionally, we have taken into our account the feasibility of this study and the expected number of recruited patients who will continue to follow through our study.

Inclusion criteria:

- Abdominoplasty surgeries: aims to remove the excess fat and skin from the abdominal area [72].

- Lower Body Lifting Surgeries: aims to remove the excess fat and skin tissue in the lower trunk circumferentially, the gluteal area and the thighs [73].

- Thighplasty: aims to remove excess fat and skin tissue from the thigh region [74].

- BMI 25-32.

- Age 18 - 65y.

Exclusion criteria:

-Patients declining participation in the study or asking to be withdrawn at any time.

-Patients who underwent bariatric surgery less than 18 months before the body contouring surgery.

-co-morbidities (except diabetes).

-Diabetic nephropathy (eGFR <60ml/min).

-Age <18 or >65y.

-Body contouring surgeries outside the abdomen or thigh.

8. Study procedures

Study Duration and Timelines

This study is expected to last for three years (1.9.2020 – 31.8.2023) including patient recruitment, primary data collection from patient, secondary data generation from blood and fat samples analysis, data analysis, manuscript writing and Papers submission.

Procedure and activity

Patient enrollment will be done using the informed consent form signed in clinic after explaining the project and answering the patients questions by the attending physician.

Informed Consent

The local ethics committee approval of the study and patients will be managed according to the Declaration of Helsinki. Consent will be taken at the plastic surgery clinic- Hamad General Hospital by the consultant/ doctor who is taking care of the patient after a full explanation of the study. Subjects will be informed that their data will be used during the entire period of research without any link to their profiles. The informed consent form is going to be given and explained carefully to the patient at the outpatient clinic visit preoperatively. Signing of the consent form will be later on at the admission encounter or the next clinic visit.

a) *How people will be **NOTIFIED OR APPROACHED** to consider being a research subject in this study?*

Patients will be approached by the consulting physician (the attending physician). And once the patient has agreed, they can be directed to the study team for further explanation and obtaining consent.

b) *Describe the CONSENT PROCESS procedures (When, Where, How, by Whom).*

Consenting the patient will be during the preoperative clinic visit, or in the ward preoperatively. The project will be explained fully and all patients' questions will be answered before electively asking the patient if they are interested to participate and sign the informed consent.

c) *Describe HOW LONG potential participants will have to decide on participation.*

The patient in the clinic can sign the informed consent within the same setting after explaining the project and answering their questions, or they can take the consent with them at home and come for another visit to sign it, this is up to the patient decision.

d) *Describe how subjects will be SCREENED FOR ELIGIBILITY for the study.*

Screening will be by the consulting surgeon during the clinic visits.

e) *Describe how subjects will be ENROLLED into the research study below.*

Data Collection, Management & Confidentiality

a) Indicate below HOW study data will be collected for the proposed research.

☐ *Study Forms* X☐ *Study Database* ☐ *Study Web-Based/App* ☐ *Other*

Please detail how study data will be coded:

Patient data will be coded using numbers, the sheet that have the link between the patient daata and the codes will be stored separately in a safe place inside Hamad General Hospital.

b) Describe below WHERE and HOW the study data is physically stored.

All data collected will be coded with links to actual patient information kept confidentially in a secure location at Hamad General Hospital. Data will be de-identified before release to PI's by the PhD Scholar.

c) Describe below WHO controls access to the study data

Only the LPI and PhD Scholar as well as the two surgical consultants will have access to the patient identification details.

d) Describe below WHO has access to the study data.

All PI's of the project will have access to the coded data according to their part within the project.

e) Describe below HOW the study data is accessed.

The study data will be circulated by the LPI to the concerning PI's as needed in an electronic form.

f) Will subject identifiers be shared outside of HMC? If YES describe below WHOM the study data is shared

No.

Outcomes:

Expected Primary Outcomes: one papers on clinical changes, and one paper on relationship between clinical parameters and biochemical / OMICS data.

Expected Secondary Outcomes: *one Conference Presentations+ 1 PhD Thesis for the LPI/PhD scholar (Badran).*

Subject Withdrawal/ Withdrawal of Consent Outcomes:

A subject can withdraw from the study at any time during the study. But their plan of care will follow the hospital protocol and their withdrawal from the study will not affect their plan of care. If patient consented and then asked to be withdrawn from the study after samples have been collected, there is no guarantee that it will be removed. but patient confidentiality will be maintained all the time.

9. Statistical Consideration and Data Analysis

Sample size:

Our primary outcome is the change in insulin resistance after the body contouring surgeries in the abdomen and thigh regions. We consider a minimum clinically significant change in HOMA2 IR to be between 15%-25% [70] from a baseline of 2.0. The variance of HOMA2 IR was derived from a previous study of ours were the HOMA IR was approximately normally distributed in subjects with values < 3.5 with a variance of 0.61[71]. For an alpha of 0.05, we estimate a sample size of 72 (given the conservative difference of 15% in HOMA-IR) will give us 90% power to detect a statistically significant difference should a true difference of this magnitude exist. Given an expected 30% drop out rate, we will recruit 100 subjects.

Data Analysis:

The members of the research team have a long-standing track record of research collaboration across different teams. Data will be analyzed extensively and collaboratively with the health system at the Department of Population Medicine at Qatar University. The LPI/PhD scholar (Badran) will work to facilitate the collaboration as he is working as a plastic surgery resident at Hamad General Hospital-HMC and as a PhD scholar in the area of Clinical Epidemiology, at the College of Medicine, Department of Population Medicine at Qatar University. The Department is well positioned to mentor the LPI/PhD scholar (Badran) as it has the requisite analytical and design expertise (LPI Doi, Principal Supervisor) who has not only the relevant expertise but also is the author of several analytic models in Medicine and has written a book on *Methods of Clinical Epidemiology* [68].

In brief, because the data collected over time (four-time points) are correlated, the methods used for longitudinal data analysis will account for the correlated nature of the data. There are many methods through which this can be achieved, but in this study the plan will be to use cluster robust analysis. In this method, we consider statistical inference in regression models where observations can be grouped into clusters, with model errors uncorrelated across clusters but correlated within clusters. The PI Doi has discussed the use of such modeling previously in relation to meta-regression [69] and a variant of this regression approach will be used here. Stata version 15 (College Station, TX, USA) will be used for all analyses. All statistical and epidemiological analyses will be done under oversight from the PI Doi. The LPI/PhD scholar (Badran) will receive research methods training during the period of this project.

10. Adverse Event Reporting

Risks of the research will be minimal and limited to the very rare skin ecchymosis, small hematoma or dizziness, which will be treated at the time of the event and will be dealt with as per Hamad Medical Corporation's safety protocol for venipuncture sampling. These minor events will be reported to the Medical Research Center on the regular follow up reports. All adverse events will be monitored to ensure that they are consistent with those encountered during usual care. Any serious adverse event will be reported to the Hospital and IRB within 24 hours of our knowledge.

11. Ethical Consideration

Our study will be conducted in full compliance with principles of the "Declaration of Helsinki", Good Clinical Practice (GCP) and within the laws and regulations of the Ministry of Public Health (MOPH) in Qatar. The study will only be conducted after review and approval from the relevant ethics review committees. This project will persue the expedieted IRB approval by Qatar University after obtaining the IRB approval from the performing site at HMC.

12. Sponsor, Funding & Collaborator Information

This project is a collaborative work between Two institutions inside Hamad Medical Corporation (Department of Plastic Surgery & Metabolic Institute) and Qatar University- College of Medicine. And fund have been requested from MRC at HMC.

13. Dissemination of Results and Publication policy

It is anticipated that one **peer-reviewed articles** outlining the clinically relevant changes in the hormonal profiles and their clinical implications after the body contouring surgeries as well as an understanding of the trajectories of these changes will be published in specialized endocrinology and plastic surgery journals (such as *PRS or Clin Endocrinol*).

Another peer-reviewed article is expected to be published making use of epidemiological linkage of the clinical and proteomic/metabolomic data. These will be planned to be published in high impact endocrinology and metabolism journals (such as *J Clin Endocrinol Metab*).

One conference presentation is expected to be attended by the PhD Scholar for career development (1 national and 1 international).

PhD Thesis to be written and submitted by the LPI/PhD scholar (Badran), based on the research output of this project as a graduation requirement by Qatar University at the College of Medicine.

14. Importance to Qatar & Impact of the study

The surgeries that we are assessing are very frequently performed in Qatar (almost daily across hospitals in the country – public and private) and therefore it is important to document and assess the metabolic consequences of these surgeries. The data on the latter are very minimal and this project will bring conclusiveness to this area. The data collected will guide policy in this area.

Given the position of the PIs (at HMC and QU), and the trans-disciplinary team across three institutions (Qatar University, The Qatar Metabolic Institute and the Department of Plastic Surgery at Hamad Medical Corporation), this proposal will promote a culture of collaborative research work and create a culture of scholarship that will progress the educational agenda of Qatar. Regardless of clinical outcomes, this in itself is a very important outcome for Qatar.

The research papers are expected to generate new knowledge that will have a direct bearing on our understanding of the mechanisms for the development of insulin resistance and subsequent metabolic complications in overweight/obese populations. This is expected to lead to identification of novel methods of early detection for people at risk which aligns with the priorities of the Qatar National Diabetes Research Agenda. The impact on the Qatari population is expected to be significant given that the prevalence of overweight/obesity in this population is about 70% (as discussed at the Qatar Diabetes Leadership Forum on 13th Feb 2020).

15. References

1. Finucane, M.M., et al., *National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants.* Lancet, 2011. **377**(9765): p. 557-67.
2. Czech, M.P., *Insulin action and resistance in obesity and type 2 diabetes.* Nat Med, 2017. **23**(7): p. 804-814.
3. Mingrone, G., et al., *Bariatric-metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 year follow-up of an open-label, single-centre, randomised controlled trial.* Lancet, 2015. **386**(9997): p. 964-73.
4. Schauer, P.R., et al., *Bariatric surgery versus intensive medical therapy for diabetes--3-year outcomes.* N Engl J Med, 2014. **370**(21): p. 2002-13.
5. Sjostrom, L., et al., *Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery.* N Engl J Med, 2004. **351**(26): p. 2683-93.
6. Santry, H.P., D.L. Gillen, and D.S. Lauderdale, *Trends in bariatric surgical procedures.* Jama, 2005. **294**(15): p. 1909-17.
7. Larraufie, P., et al., *Important Role of the GLP-1 Axis for Glucose Homeostasis after Bariatric Surgery.* Cell Rep, 2019. **26**(6): p. 1399-1408.e6.
8. Nauck, M.A. and J.J. Meier, *The incretin effect in healthy individuals and those with type 2 diabetes: physiology, pathophysiology, and response to therapeutic interventions.* Lancet Diabetes Endocrinol, 2016. **4**(6): p. 525-36.

9. de Lartigue, G., C.C. Ronveaux, and H.E. Raybould, *Deletion of leptin signaling in vagal afferent neurons results in hyperphagia and obesity*. Mol Metab, 2014. 3(6): p. 595-607.
10. Beckman, L.M., T.R. Beckman, and C.P. Earthman, *Changes in gastrointestinal hormones and leptin after Roux-en-Y gastric bypass procedure: a review*. J Am Diet Assoc, 2010. **110**(4): p. 571-84.
11. Sjostrom, L., *Review of the key results from the Swedish Obese Subjects (SOS) trial - a prospective controlled intervention study of bariatric surgery*. J Intern Med, 2013. **273**(3): p. 219-34.
12. Kitzinger, H.B., et al., *After massive weight loss: patients' expectations of body contouring surgery*. Obes Surg, 2012. **22**(4): p. 544-8.
13. Kim, J.K., et al., *Mechanism of insulin resistance in A-ZIP/F-1 fatless mice*. J Biol Chem, 2000. **275**(12): p. 8456-60.
14. Kusminski, C.M., et al., *MitoNEET-driven alterations in adipocyte mitochondrial activity reveal a crucial adaptive process that preserves insulin sensitivity in obesity*. Nat Med, 2012. **18**(10): p. 1539-49.
15. Kadowaki, T. and T. Yamauchi, *Adiponectin Receptor Signaling: A New Layer to the Current Model*. Cell Metabolism, 2011. **13**(2): p. 123-124.
16. Chinookoswong, N., J.L. Wang, and Z.Q. Shi, *Leptin restores euglycemia and normalizes glucose turnover in insulin-deficient diabetes in the rat*. Diabetes, 1999. **48**(7): p. 1487.
17. Fu, Y., et al., *Adiponectin promotes adipocyte differentiation, insulin sensitivity, and lipid accumulation*. J Lipid Res, 2005. **46**(7): p. 1369-79.
18. Walder, K., et al., *Leptin inhibits insulin binding in isolated rat adipocytes*. J Endocrinol, 1997. **155**(3): p. R5-7.
19. Perez, M.A., et al., *Motor skill training induces changes in the excitability of the leg cortical area in healthy humans*. Exp Brain Res, 2004. **159**(2): p. 197-205.
20. Nevzorova, J., et al., *Multiple signalling pathways involved in beta2-adrenoceptor-mediated glucose uptake in rat skeletal muscle cells*. Br J Pharmacol, 2006. **147**(4): p. 446-54.
21. Qiu, W.Q., *Amylin and its G-protein-coupled receptor: A probable pathological process and drug target for Alzheimer's disease*. Neuroscience, 2017. **356**: p. 44-51.
22. Regan, J.P. and J.T. Casaubon, *Abdominoplasty (Tummy Tuck)*, in *StatPearls*. 2020, StatPearls Publishing
StatPearls Publishing LLC.: Treasure Island (FL).
23. Losco, L., et al., *Lower Body Lift After Bariatric Surgery: 323 Consecutive Cases Over 10-Year Experience*. Aesthetic Plast Surg, 2019.
24. Schwaiger, K., et al., *Thighplasty: improving aesthetics through revival of the medial, horizontal procedure: A safe and scar-saving option*. J Plast Reconstr Aesthet Surg, 2018. **71**(4): p. 585-589.
25. Swift, D.L., et al., *Effects of clinically significant weight loss with exercise training on insulin resistance and cardiometabolic adaptations*. Obesity (Silver Spring), 2016. **24**(4): p. 812-9.
26. Doi, S.A. and G.M. Ward, *Examination of the fasting and 2-h plasma glucose in the light of impairment in beta-cell function: what does the epidemiological data tell us?* Endocrine, 2015. **48**(1): p. 170-8.

27. *METHODS OF CLINICAL EPIDEMIOLOGY*. 2018, [Place of publication not identified]: SPRINGER INTERNATIONAL PU.
28. Xu, C. and S.A.R. Doi, *The robust error meta-regression method for dose-response meta-analysis*. Int J Evid Based Healthc, 2018. **16**(3): p. 138-144.

16. Appendices

1. Informed Consent.
2. Data Collection sheet
3. Research Questionnaires (PHQ-9, GAD-7, JAMRISC, AAI and CANQ)

1. Finucane, M.M., et al., *National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants*. Lancet, 2011. **377**(9765): p. 557-67.
2. Czech, M.P., *Insulin action and resistance in obesity and type 2 diabetes*. Nat Med, 2017. **23**(7): p. 804-814.
3. Mingrone, G., et al., *Bariatric-metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 year follow-up of an open-label, single-centre, randomised controlled trial*. Lancet, 2015. **386**(9997): p. 964-73.
4. Schauer, P.R., et al., *Bariatric surgery versus intensive medical therapy for diabetes--3-year outcomes*. N Engl J Med, 2014. **370**(21): p. 2002-13.
5. Sjostrom, L., et al., *Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery*. N Engl J Med, 2004. **351**(26): p. 2683-93.
6. Santry, H.P., D.L. Gillen, and D.S. Lauderdale, *Trends in bariatric surgical procedures*. Jama, 2005. **294**(15): p. 1909-17.
7. Larraufie, P., et al., *Important Role of the GLP-1 Axis for Glucose Homeostasis after Bariatric Surgery*. Cell Rep, 2019. **26**(6): p. 1399-1408.e6.
8. Nauck, M.A. and J.J. Meier, *The incretin effect in healthy individuals and those with type 2 diabetes: physiology, pathophysiology, and response to therapeutic interventions*. Lancet Diabetes Endocrinol, 2016. **4**(6): p. 525-36.
9. de Lartigue, G., C.C. Ronveaux, and H.E. Raybould, *Deletion of leptin signaling in vagal afferent neurons results in hyperphagia and obesity*. Mol Metab, 2014. **3**(6): p. 595-607.
10. Beckman, L.M., T.R. Beckman, and C.P. Earthman, *Changes in gastrointestinal hormones and leptin after Roux-en-Y gastric bypass procedure: a review*. J Am Diet Assoc, 2010. **110**(4): p. 571-84.
11. Sjostrom, L., *Review of the key results from the Swedish Obese Subjects (SOS) trial - a prospective controlled intervention study of bariatric surgery*. J Intern Med, 2013. **273**(3): p. 219-34.
12. Kitzinger, H.B., et al., *After massive weight loss: patients' expectations of body contouring surgery*. Obes Surg, 2012. **22**(4): p. 544-8.

13. Kim, J.K., et al., *Mechanism of insulin resistance in A-ZIP/F-1 fatless mice.* J Biol Chem, 2000. **275**(12): p. 8456-60.
14. Kusminski, C.M., et al., *MitoNEET-driven alterations in adipocyte mitochondrial activity reveal a crucial adaptive process that preserves insulin sensitivity in obesity.* Nat Med, 2012. **18**(10): p. 1539-49.
15. Kadowaki, T. and T. Yamauchi, *Adiponectin Receptor Signaling: A New Layer to the Current Model.* Cell Metabolism, 2011. **13**(2): p. 123-124.
16. Chinookoswong, N., J.L. Wang, and Z.Q. Shi, *Leptin restores euglycemia and normalizes glucose turnover in insulin-deficient diabetes in the rat.* Diabetes, 1999. **48**(7): p. 1487.
17. Fu, Y., et al., *Adiponectin promotes adipocyte differentiation, insulin sensitivity, and lipid accumulation.* J Lipid Res, 2005. **46**(7): p. 1369-79.
18. Walder, K., et al., *Leptin inhibits insulin binding in isolated rat adipocytes.* J Endocrinol, 1997. **155**(3): p. R5-7.
19. Perez, M.A., et al., *Motor skill training induces changes in the excitability of the leg cortical area in healthy humans.* Exp Brain Res, 2004. **159**(2): p. 197-205.
20. Nevzorova, J., et al., *Multiple signalling pathways involved in beta2-adrenoceptor-mediated glucose uptake in rat skeletal muscle cells.* Br J Pharmacol, 2006. **147**(4): p. 446-54.
21. Qiu, W.Q., *Amylin and its G-protein-coupled receptor: A probable pathological process and drug target for Alzheimer's disease.* Neuroscience, 2017. **356**: p. 44-51.
22. Reimann, F., et al., *Glucose sensing in L cells: a primary cell study.* Cell Metab, 2008. **8**(6): p. 532-9.
23. Kroenke, K., R.L. Spitzer, and J.B. Williams, *The PHQ-9: validity of a brief depression severity measure.* Journal of general internal medicine, 2001. **16**(9): p. 606-613.
24. Veale, D., et al., *The Appearance Anxiety Inventory: validation of a process measure in the treatment of body dysmorphic disorder.* Behav Cogn Psychother, 2014. **42**(5): p. 605-16.
25. Tan, C., et al., *Evaluation of the Japanese Metabolic Syndrome Risk Score (JAMRISC): a newly developed questionnaire used as a screening tool for diagnosing metabolic syndrome and insulin resistance in Japan.* Environmental health and preventive medicine, 2016. **21**(6): p. 470-479.
26. Tokudome, Y., et al., *Development of the Japanese version of the Council on Nutrition Appetite Questionnaire and its simplified versions, and evaluation of their reliability, validity, and reproducibility.* Journal of epidemiology, 2017. **27**(11): p. 524-530.
27. Zakharchenko, O., et al., *Meta-data analysis as a strategy to evaluate individual and common features of proteomic changes in breast cancer.* Cancer Genomics Proteomics, 2011. **8**(1): p. 1-14.
28. Zakharchenko, O., et al., *Optimized Protocol for Protein Extraction from the Breast Tissue that is Compatible with Two-Dimensional Gel Electrophoresis.* Breast Cancer (Auckl), 2011. **5**: p. 37-42.
29. Woksepp, H., et al., *Proteomics of transforming growth factor beta1 (TGF beta1) signaling in 184A1 human breast epithelial cells suggests the involvement of casein kinase 2alpha in TGF beta1-dependent p53 phosphorylation at Ser392.* Exp Oncol, 2019. **41**(4): p. 304-311.

30. Stasyk, T., et al., *A new highly toxic protein isolated from the death cap Amanita phalloides is an L-amino acid oxidase.* Febs j, 2010. **277**(5): p. 1260-9.
31. Stasyk, T., et al., *Phosphoproteome profiling of transforming growth factor (TGF)-beta signaling: abrogation of TGFbeta1-dependent phosphorylation of transcription factor-II-I (TFII-I) enhances cooperation of TFII-I and Smad3 in transcription.* Mol Biol Cell, 2005. **16**(10): p. 4765-80.
32. Souchelnytskyi, S., et al., *Proteomics success story. Towards early detection of breast and ovarian cancer: plasma proteomics as a tool to find novel markers.* Proteomics, 2006. **6 Suppl 2**: p. 65-8.
33. Souchelnytskyi, S. and S. Hanash, *Focus on breast cancer proteomics.* Proteomics Clin Appl, 2009. 3(1): p. 5.
34. Souchelnytskyi, S. and L. Alldridge, *Breast Cancer and Proteomics: The inaugural Mammary Gland Proteome Initiative (MGPI) workshop 12-13 July 2007, Cambridge, UK.* Proteomics Clin Appl, 2008. **2**(1): p. 8-10.
35. Souchelnytskyi, S., *Bridging proteomics and systems biology: what are the roads to be traveled?* Proteomics, 2005. 5(16): p. 4123-37.
36. Souchelnytskyi, S., *Proteomics of TGF-beta signaling and its impact on breast cancer.* Expert Rev Proteomics, 2005. **2**(6): p. 925-35.
37. Souchelnytskyi, S., *Proteomics in studies of signal transduction in epithelial cells.* J Mammary Gland Biol Neoplasia, 2002. 7(4): p. 359-71.
38. Silva, E., et al., *Quantitative intact proteomics investigations of alveolar macrophages in sarcoidosis.* Eur Respir J, 2013. **41**(6): p. 1331-9.
39. Saini, R.K., et al., *Proteomics of dedifferentiation of SK-N-BE2 neuroblastoma cells.* Biochem Biophys Res Commun, 2014. **454**(1): p. 202-9.
40. Okumichi, H., et al., *Proteomic analyses of retina of excitatory amino acid carrier 1 deficient mice.* Proteome Sci, 2007. **5**: p. 13.
41. Mousa, H., et al., *Acquisition of Invasiveness by Breast Adenocarcinoma Cells Engages Established Hallmarks and Novel Regulatory Mechanisms.* Cancer Genomics Proteomics, 2019. **16**(6): p. 505-518.
42. Mizukami, M., et al., *Wnt14 inhibits death of retinal precursor cells.* Exp Eye Res, 2009. **89**(4): p. 462-8.
43. Mizukami, M., et al., *Proteome profiling of embryo chick retina.* Proteome Sci, 2008. 6: p. 3.
44. Mints, M. and S. Souchelnytskyi, *Proteomic strategy for detection of circulating tumor cell surface antigens.* Exp Oncol, 2011. 33(3): p. 193-5.
45. Lomnytska, M.I., et al., *Diagnostic protein marker patterns in squamous cervical cancer.* Proteomics Clin Appl, 2010. **4**(1): p. 17-31.
46. Lomnytska, M. and S. Souchelnytskyi, *Markers of breast and gynecological malignancies: The clinical approach of proteomics-based studies.* Proteomics Clin Appl, 2007. **1**(9): p. 1090-101.
47. Lomnytska, M., et al., *Transforming growth factor-beta1-regulated proteins in human endothelial cells identified by two-dimensional gel electrophoresis and mass spectrometry.* Proteomics, 2004. **4**(4): p. 995-1006.
48. Kwiecinska, A., et al., *Proteomic Profiling of Diffuse Large B-Cell Lymphomas.* Pathobiology, 2018. 85(4): p. 211-219.

49. Kolakowska, J., et al., *Proteomic analysis of the endometrium during early pregnancy in the domestic pig.* Reprod Fertil Dev, 2017. **29**(11): p. 2255-2268.
50. Kanamoto, T., et al., *Proteomic study of DBA/2J mice retina: Down-regulation of Integrin beta7 correlated with retinal ganglion cell death.* Proteomics, 2009. 9(21): p. 4962-9.
51. Kanamoto, T., et al., *Proteomic study of retinal proteins associated with transcorneal electric stimulation in rats.* J Ophthalmol, 2015. **2015**: p. 492050.
52. Kanamoto, T., N. Souchelnytskyi, and Y. Kiuchi, *Functional proteomics of failed filtering blebs.* Mol Vis, 2009. **15**: p. 2762-70.
53. Kanamoto, T., et al., *Functional proteomics of transforming growth factor-beta1-stimulated Mv1Lu epithelial cells: Rad51 as a target of TGFbeta1-dependent regulation of DNA repair.* Embo j, 2002. **21**(5): p. 1219-30.
54. Jia, M. and S. Souchelnytskyi, *Proteome profiling of heat shock of human primary breast epithelial cells, a dataset report.* Cell Stress Chaperones, 2011. **16**(4): p. 459-67.
55. Jia, M. and S. Souchelnytskyi, *Kinase suppressor of Ras 2 is involved in regulation of cell proliferation and is up-regulated in human invasive ductal carcinomas of breast.* Exp Oncol, 2010. **32**(3): p. 209-12.
56. Jia, M., et al., *Proteome profiling of immortalization-to-senescence transition of human breast epithelial cells identified MAP2K3 as a senescence-promoting protein which is downregulated in human breast cancer.* Proteomics Clin Appl, 2010. **4**(10-11): p. 816-28.
57. Iwahana, H., et al., *Glycoproteome profiling of transforming growth factor-beta (TGFbeta) signaling: nonglycosylated cell death-inducing DFF-like effector A inhibits TGFbeta1-dependent apoptosis.* Proteomics, 2006. **6**(23): p. 6168-80.
58. Hassel, S., et al., *Proteins associated with type II bone morphogenetic protein receptor (BMPR-II) and identified by two-dimensional gel electrophoresis and mass spectrometry.* Proteomics, 2004. **4**(5): p. 1346-58.
59. Grimsby, S., et al., *Proteomics-based identification of proteins interacting with Smad3: SREBP-2 forms a complex with Smad3 and inhibits its transcriptional activity.* FEBS Lett, 2004. **577**(1-2): p. 93-100.
60. Dubrovska, A. and S. Souchelnytskyi, *Efficient enrichment of intact phosphorylated proteins by modified immobilized metal-affinity chromatography.* Proteomics, 2005. **5**(18): p. 4678-83.
61. da Silva Santos, C., et al., *Proteome profiling of human cutaneous leishmaniasis lesion.* J Invest Dermatol, 2015. **135**(2): p. 400-410.
62. Conrotto, P., et al., *Interactome of transforming growth factor-beta type I receptor (TbetaRI): inhibition of TGFbeta signaling by Epac1.* J Proteome Res, 2007. 6(1): p. 287-97.
63. Conrotto, P. and S. Souchelnytskyi, *Proteomic approaches in biological and medical sciences: principles and applications.* Exp Oncol, 2008. **30**(3): p. 171-80.
64. Bhaskaran, N. and S. Souchelnytskyi, *Systemic analysis of TGFbeta proteomics revealed involvement of Plag1/CNK1/RASSF1A/Src network in TGFbeta1-dependent activation of Erk1/2 and cell proliferation.* Proteomics, 2008. **8**(21): p. 4507-20.
65. Bhaskaran, N., et al., *Comparative proteome profiling of MCF10A and 184A1 human breast epithelial cells emphasized involvement of CDK4 and cyclin D3 in cell proliferation.* Proteomics Clin Appl, 2009. **3**(1): p. 68-77.

66. Attarha, S., et al., *Endometrial cancer and application of proteomics.* Exp Oncol, 2011. **33**(3): p. 174-7.
67. Attarha, S., et al., *Individualised proteome profiling of human endometrial tumours improves detection of new prognostic markers.* Br J Cancer, 2013. **109**(3): p. 704-13.
68. *METHODS OF CLINICAL EPIDEMIOLOGY*. 2018, [Place of publication not identified]: SPRINGER INTERNATIONAL PU.
69. Xu, C. and S.A.R. Doi, *The robust error meta-regression method for dose-response meta-analysis.* Int J Evid Based Healthc, 2018. **16**(3): p. 138-144.
70. Swift, D.L., et al., *Effects of clinically significant weight loss with exercise training on insulin resistance and cardiometabolic adaptations.* Obesity (Silver Spring), 2016. **24**(4): p. 812-9.
71. Doi, S.A. and G.M. Ward, *Examination of the fasting and 2-h plasma glucose in the light of impairment in beta-cell function: what does the epidemiological data tell us?* Endocrine, 2015. **48**(1): p. 170-8.
72. Regan, J.P. and J.T. Casaubon, *Abdominoplasty (Tummy Tuck)*, in *StatPearls*. 2020, StatPearls Publishing
StatPearls Publishing LLC.: Treasure Island (FL).
73. Losco, L., et al., *Lower Body Lift After Bariatric Surgery: 323 Consecutive Cases Over 10-Year Experience*. Aesthetic Plast Surg, 2019.
74. Schwaiger, K., et al., *Thighplasty: improving aesthetics through revival of the medial, horizontal procedure: A safe and scar-saving option.* J Plast Reconstr Aesthet Surg, 2018. **71**(4): p. 585-589.

Appendix C. QU research grant

Qatar University
Office of Research Support (ORS)

Student Grant Application College of Medicine

Cycle (1)
2020

By Lead Principle Investigator (LPI)
Name: Suhail A. R. Doi
Date of Submission: 25-04-2020

For Office of Research Support Use only			
Project ID		Project Number	
Start date		End Date	
Requested Amount (QR)		Approved Amount (QR)	

Project Title			
Metabolic Changes After Body Contouring Surgeries			
Linked Course			
	Yes, Course number		**No, please specify**
Is this project linked to course?	Yes. The Project is a part the student's PhD thesis.		
Compliance and Ethical Considerations			
Will the project involve using any of the following:	**No**	**Yes, approval pending**	**Yes, approval granted**
Human subjects?	Not applicable		
Animal subjects?	Not applicable		
Hazardous materials?	Not applicable		
Lead Principle Investigator (LPI) information			
Name	Suhail A.R. Doi *MBBS, MMed, MClinEpid, PhD, FRCP*		
Position Title	Head, Department of Population Medicine, College of Medicine, Qatar University		
Department, Research Center, laboratory or equivalent	Department of Population Medicine		
E-mail Address	sdoi@qu.edu.qa		
Phone/mobile			
Students Information (please, attach copy of valid QU student-ID)			
	Student#1		
Name	Saifeddin Moh'd Badran		
Current Standing (Graduate/ Undergraduate)	PhD scholar		
College, Dept.	College of Medicine, Department of Population Medicine		
Expected Graduate Semester	Spring, 2022		
Email address	Sb1901114@qu.edu.qa		
Phone/mobile	55726648		

List of Student Tasks			
	Task	**Expected Time to Finish**	**Outcomes**
1.	building the search strategy and retrieving all relevant publications (1 month).	August, 2020	One publication submitted to a journal
2.	screening and selection of publications (1 month).	September, 2020	
3.	data extraction and analysis (1 month).	October, 2020	
4.	write-up and submission of the manuscript to a journal (2 months).	December, 2020	

Current and Previous Research Grants Held by the Applicant				
Project ID	**Project Title**	**Source of Grant Funding**	**Start/end date**	**Grant Amount (QR)**
NPRP 10-0129-170274	Translating research evidence into practice for gestational diabetes and refining tools for meta-analytic research synthesis	QNRF	Jan 2018-Dec 2020	1,559,000 QR
Research Project Plan and Expected Outcomes (Not to exceed 3 pages), please describe the project background/literature survey, and then list project objectives/significance, methods and time lines, and expected outcomes:				

Background

About 70% of Qatar's adult population is overweight or obese (as discussed at the Qatar Diabetes Leadership Forum on 13th Feb 2020). Qatar is now ranked fifth globally in terms of incidence of obesity [1], which makes further research focused on the field of obesity and associated metabolic diseases including diabetes as a national priority as indicated in the Qatar National Health Strategy 2018 – 2022. A clinical hallmark often linking obesity and type 2 diabetes is the development of insulin resistance. The term "insulin resistance" refers to the weakened blood-glucose-lowering impact of circulating or injected insulin on blood glucose [2].

Several signaling molecules from adipocytes have been ascribed to have a critical role in energy homeostasis through communicating with organs that maintain systemic metabolic homeostasis such as the liver. Of the adipocyte derived factors, adiponectin, leptin and fatty acids are among essential mediators [3, 4].

Patients seeking body contouring plastic surgeries that target the abdomen and thigh regions, to remove excess subcutaneous fat tissue to gain a cosmetic benefit, will have a BMI in the overweight to the obese range with different degrees of insulin resistance. The previous literature has suggested that almost all people start to have insulin resistance when their BMI starts to cross 23. Obesity causes an increase in the efflux of fatty acids from the adipocytes, which will be converted into a triglyceride molecule and this results in the production of many metabolites and intermediates that cause insulin signaling impairment and eventually insulin resistance. The latter, in turn, causes an increase in visceral fat such as omental fat and also results in fatty changes in the liver.

Previous studies that measured the change in insulin sensitivity varied in their results between improvement to no change, and most of the studies were conducted with small sample sizes and minimal expertise in proteomics and biochemistry. Similar studies were done on weight loss surgeries, i.e. bariatric surgeries, and it showed a significant metabolic change and significant clinical effect, including the need

for diabetic medications after surgery in a specific group of patients. In this study, rather than gradual loss of body fat, we will focus on a sudden loss of 2-3kg of subcutaneous fat after body contouring plastic surgeries which results in a decrease in numbers of fat cells rather than just decreasing the size of fat cells as happening after weight loss due to bariatric surgeries. Results from this study will, therefore, highlight differential mechanisms associated with sudden (as in body contouring surgery) vs gradual weight-loss (that occurs post-bariatric surgery).

Hypothesis: Removal of excess fat during body contouring surgery alone can result in measurable clinical benefit (e.g. biochemical indices of insulin resistance and glucose homeostasis).

Aim: To determine if insulin resistance, glycemic status and appetite are modulated by such a sudden change in the non-visceral fat after the body contouring surgeries.

Objective: To compare using a systematic review and meta-analysis, the changes in insulin resistance and glycemic status in:

A) Patients before and after body contouring surgery (abdomen & thigh)

B) Patients before and after bariatric surgery

Research Methods and Timeline

One systematic review and meta-analyses will be conducted to achieve the above objective.

The tasks involved include:

1. building the search strategy and retrieving all relevant publications (1 month).
2. screening and selection of publications (1 month).

2. data extraction and analysis (1 month).
4. write-up and submission of the manuscript to a journal (2 months).

Expected Outcomes (Training Skills, Research output)

1. It is anticipated that at least 1 peer-reviewed meta-analysis with targeted clinical impact will be published. Given the relevance of the results and the impact that these will have on clinical decision making and public health policies, high impact medical journals (e.g., *BMJ, Lancet*) will be targeted.
2. This project aims to provide the PhD scholar Badran with the needed skills to conduct a systematic review and meta-analysis, that include a step by step approach starting from the literature review up to the data analysis phase using the STATA software.

References

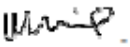
1. Finucane, M.M., et al., *National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants.* Lancet, 2011. **377**(9765): p. 557-67.
2. Czech, M.P., *Insulin action and resistance in obesity and type 2 diabetes.* Nat Med, 2017. **23**(7): p. 804-814.
3. Kadowaki, T. and T. Yamauchi, *Adiponectin Receptor Signaling: A New Layer to the Current Model.* Cell Metabolism, 2011. **13**(2): p. 123-124.

Budget Breakdown (Before including any software, equipment or book, please make sure it is not available in or not supported by QU)			
Description	**QTY**	**Unit Price**	**Total (QR)**
A. Software Packages: STATA software	1	2000	2000
B. Material, Supplies and Equipment: **Laptop for data collection and analysis**	1	5000	5000
C. Publication fees:	1	5000	5000
D. Travel Expenses: **International Conference Presentation**	1	6000	6000
E. Miscellaneous: Research Assistant (RA): 7 days	1	2000	2000
		Total (QR)	**20,000**

Signatures:

We the undersigned, certify that to the best of our knowledge all the information provided in this application are correct. If the research proposal is approved for funding, we will be bounded by all rules of the Qatar University in spending the allocated research grant.

Lead Principal Investigator (LPI):

Signature:  Date: 25/04/2020

Appendix D. HMC IRB approvals

مؤسسة حمد الطبية
Hamad Medical Corporation

INSTITUTIONAL REVIEW BOARD

HAMAD MEDICAL CORPORATION
DOHA-QATAR

Saifeddin Mohd Ahmad Badran **Medical Resident, Medical Education** **Hamad Medical Corporation** **Doha-Qatar**	**Email: irb@hamad.qa Tel: 00974-40256410** **HMC-IRB Registration: MoPH-HMC-IRB-020** **IRB-MoPH Assurance: IRB-A-HMC-2019-0014**

APPROVAL NOTICE

Protocol No. :	MRC-01-20-466
Protocol Title :	**Metabolic changes after body contouring surgeries, a quasi-experiment with four time points**
QNRF/Other Reference Number :	NA
Date of HMC-IRB Approval :	25 August 2020
Date of Letter Issued :	25 August 2020
Review Type :	Expedited
Decision :	Approved
Approved HMC Enrollment :	**100 (Enrollment), 200 (Screening)**
NPRP Grant Holder :	NA

The IRB has reviewed the submitted documents of the above titled research and approval for the study has been granted. The list of approved document(s) is attached.

IRB oversight expires 12 months from the date of approval indicated above. It is the responsibility of the Investigator to ensure timely renewal of study oversight. Progress reports for continuing review must be approved prior to expiration date therefore, submissions must be received by the IRB 60 to 90 days prior to the expiration date.

Requested Resolutions: None

Any resolutions submitted must include a letter indicating that the submission is a follow up request by the IRB; this will ensure that resolutions are processed appropriately and in a timely manner.

Please note; this approval only covers HMC, you may also need approvals from other institutions involved in your study. You should not start your study until all of these have been obtained.

If you have any questions or need additional information, please contact IRB at the above mentioned email address or telephone number.

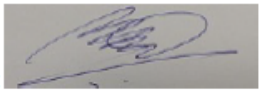
As part of PI`s responsibilities, all research activities must be recorded in Cerner`s medical records per visit for each subject involved in the study.

Important Note: The list of your responsibilities as Principal Investigator is attached to this letter.

مؤسسة حمد الطبية
Hamad Medical Corporation

Sincerely,

Deputy Chairman of Institutional Review Board: _____

Signature: 

Date: _____

List of Approved Documents:

S.No	DOCUMENTTYPE	DOCUMENTNAME	LANGUAGE	NOOFPAGES	VERSIONNO
1	Research Protocol	MRC-01-20-466_ResearchProtocol_V1.0_25-AUG-20_26Pages_1760570.8_25-AUG-20_26Pages_1760570.pdf	English	26	V1.0
2	Data Collection Sheet	MRC-01-20-466_DataCollectionSheet_Eng_25-AUG-20_1Pages_1770112.pdf	English	1	V1.0
3	Questionnaire/ Survey	MRC-01-20-466_Questionnaire/Survey_Eng_V1.0_25-AUG-20_5Pages_1770792.3_25-AUG-20_5Pages_1770792.pdf	English	5	V1.0
4	Research Consent Form	MRC-01-20-466_ResearchConsentForm_Eng_V1.0_25-AUG-20_5Pages_1787079.5_25-AUG-20_5Pages_1787079.pdf	English	5	V1.0
5	Research Consent Form	MRC-01-20-466_ResearchConsentForm_Ara_V1.0_25-AUG-20_5Pages_1823053.1_25-AUG-20_5Pages_1823053.pdf	Arabic	5	V1.0

مؤسسة حمد الطبية
Hamad Medical Corporation

Hamad Medical Corporation
Institutional Review Board

Email: irb@hamad.qa Tel: 00974-40256410

HMC-IRB Registration: MoPH-HMC-IRB-020

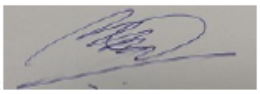
IRB-MoPH Assurance: IRB-A-HMC-2019-0014

Responsibilities of the Principal Investigator:

As the Principal Investigator of this research project, you are ultimately responsible for:

- Protecting the rights, safety and welfare of research subjects
- Following the IRB-approved protocol (application and any materials submitted with it; e.g. only research team members designated to obtain consent on the scheme of delegation should only do so and no other personnel)
- Ensuring that the inclusion and exclusion criteria are adhered to before enrolling participants in research studies
- Maintaining confidentiality of the subjects by not sharing Patient Identifiable Information outside HMC Facility
- Maintaining privacy of the subjects by performing research related procedures on subjects in private settings
- Reporting serious adverse events and serious unanticipated problems to the HMC-IRB and the other relevant compliance entities of HMC within 24 Hours of knowing about it
    - "Serious Adverse Event" (SAE) is any adverse event temporally associated with the subject's participation in research (whether or not considered related to the subject's participation in the research) that meets any of the following criteria:
    - results in death;
    - is life-threatening (places the subject at immediate risk of death from the event as it occurred);
    - requires inpatient hospitalization or prolongation of existing hospitalization;
    - results in a persistent or significant disability/incapacity;
    - results in a congenital anomaly/birth defect; or
    - any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition
- Keeping the source documents (i.e. Cerner's medical records) updated regarding the enrollment of the patient , the MRC study number and study related procedures for each subject involved in the study
- Using only HMC-IRB stamped documents at HMC facilities while conducting the research. Those documents might have other institution's IRB stamp if applicable
- Following the requirements of HMC HRP policies, especially with regard to obtaining prior approval of changes to the research, reporting events or new information, progress reports before the expiry of the IRB approval by 60-90 days and final reports.
- Making sure that no study procedures should be conducted after the expiry date of the ethical (IRB) approval
- The conduct of the study team with regards to all of the above

Sincerely,

Signature: 

Dr. Naseer Ahmad Masoodi

Deputy Chairman Institutional Review Board

Hamad Medical Corporation

مؤسسة حمد الطبية
Hamad Medical Corporation

INSTITUTIONAL REVIEW BOARD

HAMAD MEDICAL CORPORATION
DOHA-QATAR

Dr. Saifeddin Mohd Ahmad Badran **Medical Resident, Medical Education** **Hamad Medical Corporation** **Doha-Qatar**	**Email: irb@hamad.qa Tel: 00974-40256410** **HMC-IRB Registration: IRB-HMC-2021-011** **IRB-MoPH Assurance: IRB-A-HMC-2019-0014**

Continuing Review Approval Notice

Protocol Title :	Metabolic changes after body contouring surgeries, a quasi-experiment with four time points
Study Number :	MRC-01-20-466
QNRF Number:	NA
HMC Principal Investigator:	Dr. Saifeddin Mohd Ahmad Badran
Date of HMC-IRB Approval :	11 August 2021
Review Type :	Expedited
Decision :	Approved for Renewal
Approved HMC Enrollment:	**100 (Enrollment), 200 (Screening)**

The IRB has reviewed the submitted documents of the above titled research and approval to continue the study has been granted. The list of approved document(s) is attached.

IRB oversight expires 12 months from the date of the current expiry date - as indicated in the stamp at the bottom of the approved documents.

It is the responsibility of the Investigator to ensure timely renewal of study oversight. Progress reports for continuing review must be approved prior to expiration date; therefore submissions must be received by the IRB 60 to 90 days prior to the expiration date.

Requested Resolutions: **PI to ensure that the private identifiable must not leave the HMC facility in order to maintain the confidentiality of the research participants.**

Any resolutions submitted must include a letter indicating that the submission is a follow up request by the IRB; this will ensure that resolutions are processed appropriately and in a timely manner.

Please note; this approval only covers HMC, you may also need approvals from other institutions involved in your study. You should not continue your study until all of these have been obtained

If you have any questions or need additional information, Please contact IRB at the above mentioned email address or telephone number.

As part of PI's responsibilities, all research activities must be recorded in Cerner's medical records per visit for each subject involved in the study.

Important Note: The list of your responsibilities as Principal Investigator is attached to this letter.

Sincerely,

Dr. Mohammed Bashir

Acting Chairman of Institutional Review Board:

Hamad Medical Corporation

Date: 15th August 2021

Signature:

Dr. Mohammed Bashir
Sr. Consultant, Endocrine & Diabetes Medicine - HMC
038537

List of Approved Documents:

S.No	DOCUMENTTYPE	DOCUMENTNAME	LANGUAGE	NOOFPAGES	VERSIONNO
1	Research Consent Form	MRC-01-20-466_ResearchConsentForm_Eng_V1.0_15-AUG-21_5Pages_1906317.5_18-JAN-21_5Pages_1906317.5_25-AUG-20.pdf	English	5	V1.0
2	Questionnaire/ Survey	MRC-01-20-466_Questionnaire/Survey_Eng_V1.0_15-AUG-21_5Pages_1906318.3_18-JAN-21_5Pages_1906318.3_25-AUG-20.pdf	English	5	V1.0
3	Research Consent Form	MRC-01-20-466_ResearchConsentForm_Ara_V1.0_15-AUG-21_5Pages_1906370.1_18-JAN-21_5Pages_1906370.1_25-AUG-20.pdf	Arabic	5	V1.0
4	Data Collection Sheet	MRC-01-20-466_DataCollectionSheet_Eng_15-AUG-21_25Pages_1910218.pdf	English	25	V1.0
5	Research Protocol	MRC-01-20-466_ResearchProtocol_V1.0_15-AUG-21_16Pages_1910287.2_11-APR-21_16Pages_1910287.pdf	English	16	V1.0

مؤسسة حمد الطبية
Hamad Medical Corporation

INSTITUTIONAL REVIEW BOARD

HAMAD MEDICAL CORPORATION
DOHA-QATAR

Email: Irb@hamad.qa Tel: 00974-40256410
HMC-IRB Registration: IRB-HMC-2021-011
IRB-MoPH Assurance: IRB-A-HMC-2019-0014

Responsibilities of the Principal Investigator (PI)

As the Principal Investigator of this research project, you are ultimately responsible for:

- Protecting the rights, safety and welfare of research subjects
- Following the IRB-approved protocol (application and any materials submitted with it; e.g. only research team members designated to obtain consent on the scheme of delegation should only do so and no other personnel)
- Maintaining confidentiality of the subjects by not sharing Patient Identifiable Information outside HMC Facility
- Maintaining privacy of the subjects by performing research related procedures on subjects in private settings
- Reporting serious adverse events and serious unanticipated problems to the HMC-IRB and the other relevant compliance entities of HMC within 24 hours of knowing about it
    - ?Serious Adverse Event? (SAE) is any adverse event temporally associated with the subject's participation in research (whether or not considered related to the subject's participation in the research) that meets any of the following criteria:
        - results in death;
        - is life-threatening (places the subject at immediate risk of death from the event as it occurred);
        - requires inpatient hospitalization or prolongation of existing hospitalization;
        - results in a persistent or significant disability/incapacity;
        - results in a congenital anomaly/birth defect; or
        - any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition
- Keeping the source documents (i.e. Cerner's medical records) updated regarding the enrollment of the patient , the MRC study number and study related procedures for each subject involved in the study
- Using only HMC-IRB stamped documents at HMC facilities while conducting the research. Those documents might have other institution's IRB stamp if applicable
- Enrolling only the approved sample size which will include all the withdrawn and lost to follow up subjects. Over recruitment, without prior approval is considered as protocol deviation.
- Following the requirements of HMC HRP policies, especially with regard to obtaining prior approval of changes to the research, reporting events or new information, progress reports before the expiry of the IRB approval by 60-90 days and final reports.
- Making sure that no study procedures should be conducted after the expiry date of the ethical (IRB) approval
- The conduct of the study team with regards to all of the above.

Sincerely,

Signature:

Dr. Mohammed Bashir

Acting Chairman Institutional Review Board

Appendix E: QU IRB approvals

جامعة قطر
QATAR UNIVERSITY

Qatar University Institutional Review Board **QU-IRB**
QU-IRB Registration: IRB-QU-2020-006, QU-IRB, Assurance: IRB-A-QU-2019-0009

November 1st, 2020

Dr. Suhail Doi
College of Medicine
Qatar University
Phone: +974 4403 7854
Email: sdoi@qu.edu.qa

Dear Dr. Suhail Doi,

Sub.: Research Ethics Expedited Approval
Ref.: Student, Saifeddin Badran / e-mail: sb1901114@student.qu.edu.qa
Project Title: "Metabolic Changes after Body Contouring Surgeries: A Quasi-experiment with Four-Time Points"

We would like to inform you that your application along with the supporting documents provided for the above project, has been reviewed by the QU-IRB, and having met all the requirements, has been granted research ethics **Expedited Approval** based on the following category(ies) listed in the Policies, Regulations and Guidelines provided by MOPH for Research Involving Human Subjects. Your approval is for one year effective from November 1st, 2020 till October 31st, 2021.

1) Present no more than minimal risk to human subject, and
2) Involve only procedures listed in the following category(ies).
Category 2: Collection of blood samples by finger stick, heel stick, ear stick, or vein puncture.
Category 4: Collection of data through noninvasive procedures.
Category 5: Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes.

Documents Reviewed: signed application (v2), checklist, 3- approved protocol, 2- HMC IRB approval, 4- consent English, 5- consent Arabic, 6- data collection form, 7- questionnaires, IBC Approval Letter - 2020-066, QU-IRB Review Forms, responses to IRB queries and updated documents.

Please note that expedited approvals are valid for a period of **one year** and renewal should be sought one month prior to the expiry date to ensure timely processing and continuity. Moreover, any changes/modifications to the original submitted protocol should be reported to the committee to seek approval prior to continuation.

Your Research Ethics Expedited Approval Number is: **QU-IRB 1412-EA/20**. Kindly state this number in all your future correspondence to us pertaining to this project. In addition, please submit a closure report to the QU-IRB upon completion of the project.

Best wishes,
Dr. Ahmed Awaisu
Chair, QU-IRB

جامعة قطر
Institutional Review Board
(IRB)
Office Of Academic Research

DATE:	September 22, 2021
TO:	SUHAIL DOI, MD, PhD
FROM:	Qatar University Institutional Review Board (QU-IRB)
PROJECT TITLE:	1808662-1 "Metabolic Changes after Body Contouring Surgeries: A Quasi-experiment with Four-Time Points"
QU-IRB REFERENCE #:	QU-IRB 1412-EA/20
SUBMISSION TYPE:	Continuing Review/Progress Report
ACTION:	APPROVED
REVIEW TYPE:	Expedited Review
DECISION DATE:	October 30, 2021

Thank you for your submission of Continuing Review/Progress Report materials for this project. The Qatar University Institutional Review Board (QU-IRB) has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a project design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

This submission has received Expedited Review according to Qatar Ministry of Public Health (MoPH) regulations. This project has been determined to be a MINIMAL RISK project.

Please remember that informed consent is a process beginning with a description of the project and insurance of participant understanding followed by a signed consent form. Informed consent must continue throughout the project via a dialogue between the researcher and research participant. Qatar MoPH regulations require that each participant receives a copy of the consent document.

Please note that the first renewal of the above proposal is approved and it is renewed for a further period of one year effective from October 30, 2021 untill October 29, 2022. Please note that Expedited Review approvals are valid for a period of one year and renewal should be sought prior to September 29, 2022 to ensure timely processing and continuity. Moreover, any changes/modifications to the original submitted protocol should be reported to the committee to seek approval prior to continuation.

All UNANTICIPATED PROBLEMS involving risks to subjects or others (UPIRSOs) and SERIOUS and UNEXPECTED adverse events must be reported promptly to this office. Please use the appropriate reporting forms for this procedure.

All NON-COMPLIANCE issues or COMPLAINTS regarding this project must be reported promptly to this office.

Please note that all research records must be retained for a minimum of three years after the completion of the project.

Documents Reviewed:

- Application Form - Reviewed & Approved Documents.pdf (UPLOADED: 09/4/2021)
- Consent Form - consent.pdf (UPLOADED: 09/4/2021)
- Consent Form - consent - english.pdf (UPLOADED: 09/4/2021)
- Consent Form - consent arabic.pdf (UPLOADED: 09/4/2021)

- Consent Waiver - consent english.pdf (UPLOADED: 09/4/2021)
- Continuing Review/Progress Report - QU IRB renewal request .docx (UPLOADED: 09/4/2021)
- Letter - HMC IRB approval renewal.pdf (UPLOADED: 09/4/2021)
- Letter - IBC Approval Letter - 2020-066.pdf (UPLOADED: 09/4/2021)
- Letter - QU-IRB 1412EA-2020- Dr. Suhail Doi + Saifeddin Badran_Signed AA.pdf (UPLOADED: 09/4/2021)

If you have any questions, please contact QU-IRB at 4403 5307 or qu-irb@qu.edu.qa. Please include your project title and reference number in all correspondence with this committee.

Best wishes,

Dr. Mohamed Emara
Chairperson, QU-IRB

جامعة قطر
QATAR UNIVERSITY
Institutional Review Board
(IRB)
Office Of Academic Research

This letter has been issued in accordance with all applicable regulations, and a copy is retained within Qatar University's records.

Appendix F: QU IBC approvals

جامعة قطر
QATAR UNIVERSITY

Qatar University
Institutional Bio-safety Committee

To: Dr. Suhail A. R. Doi
Population Medicine
Qatar University

30th September 2020

Ref: Project Titled "Metabolic Changes After Body Contouring Surgeries, a Quasi-experiment with Four-Time Points"
Grant: MRC-01-20-466

Dear Dr. Suhail,
We would like to inform you that your application along with supporting documents provided for the above proposal have been reviewed by QU-IBC, and having met all the requirements, has been granted approval. The approval is for a period of one year and renewable for each year thereafter, should be sought and approved by QU-IBC period to continue.

Please note that QU-IBC approval is contingent upon your adherence to the following QU-IBC Guidelines:

- Ensuring compliance with QU Safety Plans and applicable national and international regulations.
- Ensuring experiments that require prior IBC approval are not conducted until IBC approval is obtained and making initial determination of containment levels required for experiments.
- Notifying the IBC of any changes to other hazardous material experiments previously approved by the IBC.
- Reporting any significant problems, violations of QU Safety Plans and applicable regulations/guidelines, or any significant research-related accidents and illnesses to the QU-IBC. Also, ensuring personnel receive appropriate orientation and specific training for the safe performance of the work.

Your research approval No. is: QU-IBC-2020/066. Please refer to this approval number in all your future correspondence pertaining to this research.

Best wishes,

Hadi M. Yassine, M.Sc., Ph.D
Chairperson, QU-IBC
Section Head of Research
Associate Professor of Infectious Diseases
Qatar University, Doha, Qatar.
Tel: +974 4403-6819
E-mail: hyassine@qu.edu.qa

Institutional Bio-safety Committee
(IBC)
Office Of Academic Research

جامعة قطر
QATAR UNIVERSITY

Qatar University
Institutional Bio-safety Committee

To: SUHAIL DOI, PhD
Qatar University

November 18, 2021

Ref: Project Titled Metabolic Changes After Body Contouring Surgeries, a Quasi- experiment with Four-Time Points
Grant: MRC-01-20-466

Dear Dr. SUHAIL DOI, PhD,
We would like to inform you that your application along with supporting documents provided for the above proposal have been reviewed by QU-IBC, and having met all the requirements, has been granted approval. The approval is for a period of one year and renewable for each year thereafter, should be sought and approved by QU-IBC period to continue.

Please note that QU-IBC approval is contingent upon your adherence to the following QU-IBC Guidelines:

- Ensuring compliance with QU Safety Plans and applicable national and international regulations.
- Ensuring experiments that require prior IBC approval are not conducted until IBC approval is obtained and making initial determination of containment levels required for experiments.
- Notifying the IBC of any changes to other hazardous material experiments previously approved by the IBC.
- Reporting any significant problems, violations of QU Safety Plans and applicable regulations/ guidelines, or any significant research-related accidents and illnesses to the QU-IBC. Also, ensuring personnel receive appropriate orientation and specific training for the safe performance of the work.

Your research approval No. is: **QU-IBC-2020/066-REN1**. Please refer to this approval number in all your future correspondence pertaining to this research.

Best wishes,
Chairperson, QU-IBC

Institutional Bio-safety Committee
(IBC)
Office Of Academic Research

Appendix G. Research consents forms

RESEARCH CONSENT FORM

مؤسسة حمد الطبية
Hamad Medical Corporation
HEALTH · EDUCATION · RESEARCH صحة · تعليم · بحوث

1. Title of research

Metabolic Changes After Body Contouring Surgeries, a Quasi-experiment with Four-Time Points

2. Principal Investigator

Dr. Saifeddin Badran, MD, MRCSEd
Plastic Surgery Resident
Department of Plastic Surgery
Hamad General Hospital- HMC

3. Why are we inviting you to join this research?

The investigator and colleagues at Hamad Medical Corporation (HMC) and Qatar University (QU are conducting this research. We are inviting you to join because you are planning to undergo body-contouring surgeries at the Department of Plastic Surgery in Hamad General Hospital in the period 2020-2023.

4. What should you know about this research?

- We will explain the research to you
- Whether or not you join is your decision (you can accept or refuse no matter who is inviting you to participate)
- Please feel free to ask questions or mention concerns before deciding, or during or after the research
- You can say yes but change your mind later
- We will not hold your decision against you

5. Who can you talk to?

If you have questions or concerns, or if you think the research has hurt you, talk to the research team at:
e-mail: sbadran@hamad.qa, or phone: 55726648.
If you have questions about your rights as a volunteer, or you want to talk to someone outside the research team, please contact:

- HMC Institutional Review Board (HMC-IRB) Chair at 5554 6316
- HMC-IRB Office at 4025 6410 (from Sunday to Thursday between 7:00am-3:00pm) or email at irb@hamad.qa

6. Why are we doing the research?

This research is aiming to examine if these plastic surgeries can have health related implication, in regard to your hormones and metabolic status. We are planning to study how this increase in the weight cause these diseases in order to reach more promising therapies in the future that can help the population of Qatar and the patients worldwide.

MRC-01-20-466 Validity: 25 08 2021 - 24 08 2022 E-stamped 15 Aug 2021

10. Could the research be bad for you?

Risks associated are minimal and limited to taking an additional blood sample from the patient using the same puncture site for the routine blood workup, this causes very rarely: minor bruising, small hematoma, diaphoresis, and hypotension. To minimize these risks, Hamad Medical Corporation policies will be used during blood sampling.

11. Could the research be good for you?

We cannot promise any benefit to you or to others from you joining this research. However, possible benefits include a comprehensive metabolic check-up investigation to your health status that will be updated to you by your primary physician during the clinical encounters, in addition to further clinical advised and educations that will be helpful for your health status.

12. What happens to information about you?

We will make efforts to secure information about you. This includes using a code to identify you in our records instead of using your name. We will not identify you personally in any reports or publications about this research.

We cannot guarantee complete secrecy, but we will limit access to information about you. Only people who have a need to review information will have access. These people might include:

- Members of the research team and other representatives whose work is related to the research or to protecting your rights and safety
- Representatives of the Ministry of Public Health Qatar, HMC and Qatar University who make sure the study is done properly and that your rights and safety are protected
- Your doctors and nurses.

We plan to use data from this study in other projects in the future. This might include sharing the data with other researchers. Before we store the data for future use, we will destroy all links between your identity and the data about you.

During the study, your samples will be kept and used in Qatar only. We would like to keep any samples left over at the end of the study for 10 years for future research.

We will store these leftover samples without a link to your identity. Leftover samples might be shared with researchers who were not part of this study. Your leftover samples will be used for research into any condition.

You can change your mind and withdraw your samples from the study by contacting us before taking them. After that, we will not know which samples belong to you and we will not be able to remove them from the study.

If you do not wish to allow this future use, we cannot include you in this study.

13. What if you don't want to join?

You can say no and we will not hold it against you.

14. What if you join but change your mind?
You can stop participating at any time and we will not hold it against you. If you stop early, please contact us and we will take the suitable actions immediately. If you stop participating, we might be unable to delete information that we have already collected about you.
15. What else should you know?
This research is funded by Hamad Medical Corporation. If you are injured as a direct result of research procedures, contact the investigator and appropriate care will be made available at HMC. If you seek care outside of HMC, such care will be at your expense. Compensation is not available in case of injury. Your specimens might help in the development of commercial products, such as new treatments or diagnostic tests. You will not receive any financial compensation for commercial products.
16. Additional Choices
Please be informed that your clinical information blood and tissue samples might be used in the future for further studies if needed without any linkage to your personal information. This is optional, meaning that you can participate in the study even if you do not allow your samples to be used for future research. Please indicate your choice by initialing the appropriate line below: _____I AGREE that my samples can be used for future studies. _____I DO NOT AGREE for use of my samples to be used for future studies.

Signature Page for Capable Adult
Volunteer
I voluntarily agree to join the research described in this form. Printed Name of Volunteer Signature of Volunteer Date
Person Obtaining Consent
I document that: • I (or another member of the research team) have fully explained this research to the volunteer. • I have personally evaluated the volunteer's understanding of the research and obtained their voluntary agreement. Printed Name of Person Obtaining Consent Signature of Person Obtaining Consent Date
Witness (if applicable)
I document that the information in this form (and any other written information) was accurately explained to the volunteer, who appears to have understood and freely given Consent to join the research. Printed Name of Witness Signature of Witness Date

نموذج الموافقة على المشاركة في بحث طبي

1. عنوان البحث

التغييرات الأيضية بعد جراحات نحت الجسم. شبه تجربة ذات نقاط على أربع مرات.

2. الباحث الأساسي

د. سيف الدين بدران، طبيب، عضو الكلية الملكية للجراحين في أدنبرة
طبيب مقيم بقسم جراحة التجميل
قسم جراحة التجميل
مستشفى حمد العام- مؤسسة حمد الطبية

3. لماذا ندعوك للانضمام إلى هذا البحث؟

يجري الباحث وزملاؤه في مؤسسة حمد الطبية وجامعة قطر هذا البحث. ندعوك للمشاركة لأنك تخطط للخضوع لعمليات نحت الجسم في قسم جراحة التجميل في مستشفى حمد العام في الفترة من 2020 إلى 2023.

4. ما الذي يجب أن تعرفه عن هذا البحث؟

- سنشرح لك البحث شرحًا وافيًا.
- قرار مشاركتك في البحث أو عدم مشاركتك يرجع لك وحدك (يمكنك قبول الدعوة أو رفضها بغض النظر عن الجهة التي تدعوك للمشاركة).
- لك مطلق الحرية في طرح أية استفسارات أو ذكر المخاوف قبل اتخاذ قرارك أو أثناء أو بعد المشاركة في البحث.
- يمكنك الموافقة ثم تغيير رأيك في وقت لاحق
- لن يكون قرارك سببًا في تعرضك لأي تحامل من جانبنا بأي حال من الأحوال.

5. ما هي الجهة التي يمكنك مراجعتها؟

إذا كان لديك أية استفسارات أو مخاوف أو إذا ارتأيت أن هذا البحث قد تسبب لك في أي إيذاء، يمكنك مراجعة فريق البحث:
بريد إلكتروني: sbadran@hamad.qa، أو هاتف: 55726648.
وإذا كان لديك أية استفسارات عن حقوقك كمتطوعة أو كانت لديك رغبة في محادثة شخص لا ينتمي لفريق البحث، يرجى مراجعة:

- رئيس لجنة مراجعة البحوث التابعة لمؤسسة حمد الطبية على الرقم 55546316
- مكتب لجنة مراجعة البحوث التابعة لمؤسسة حمد الطبية على الرقم 40256410 (من الأحد إلى الخميس من الساعة 7:00 صباحا إلى 3:00 مساء) أو عبر البريد الإلكتروني: irb@hamad.qa

6. ما هي الأسباب التي استدعت إجراء البحث؟

يهدف هذا البحث إلى دراسة ما إذا كان هذا النوع من جراحات التجميل يمكن أن يكون لها آثار صحية متعلقة بالهرمونات وحالة التمثيل الغذائي. إننا نخطط لدراسة كيف أن هذه الزيادة في الوزن تسبب هذه الأمراض من أجل الوصول إلى المزيد من العلاجات المستهدفة في

المستقبل التي يمكن أن تساعد سكان قطر والمرضى في جميع أنحاء العالم.

7. ما هي المدة التي سيستغرقها البحث؟

تعتقد أنك ستبقى مشاركًا في البحث حتى نهاية زيارات المتابعة الروتينية مع قسم جراحة التجميل، والتي عادة ما تستمر حتى 6 أشهر. بعد الموافقة، ستكون مشاركتك في الدراسة حتى 6 أشهر بعد الجراحة.

8. كم عدد الأشخاص الذين سيشاركون في هذا البحث؟

نخطط لدراسة 100 شخصًا.

9. ماذا سيترتب على مشاركتك في البحث؟

إذا وافقت على المشاركة، سنطلب منك القيام بما يلي:

سيتم تقييم تاريخك الطبي بالإضافة إلى الاستبيانات المستخدمة في هذه الدراسة قبل الجراحة وبعد 6 أشهر من الجراحة.

خلال زيارات ما قبل الجراحة وبعدها، سيتم وخزك مرة واحدة فقط أثناء أخذ عينات الفحص الروتيني. في هذا الوقت سنقوم بإدخال قُنَيْةٌ، وسيتم أخذ أي عينة دم إضافية من هذه القنية بعد التنظيف لتجنب أي ألم إضافي من الوخز .

سيتم قبولك قبل الجراحة بيوم واحد وفقًا لبروتوكولنا الروتيني لهذه العمليات الجراحية، وسيتم الاتصال بك وطلب الحضور في الصباح صائمًا لمدة 8 ساعات طوال الليل، ثم سنأخذ عينات دم لإجراء اختبار تحمل الجلوكوز الفموي (OGTT) أثناء قيامنا باختبارات الدم الروتينية.

سيشمل اختبار تحمل الجلوكوز عن طريق الفم سحب الدم بعد 8 ساعات من الصيام، ثم سيتم إعطاؤك 100 جرام من السكر للشرب، ثم سنأخذ 3 مجموعات أخرى من عينات الدم خلال ساعتين بعد تناول السكر. سيكون إجمالي الدم المأخوذ حوالي 12 مل.

بعد الجراحة وأثناء الإقامة نفسها بالمستشفى، سيُطلب منك الصيام أثناء ساعات النوم ليلاً، لتكون مستعدًا لنفس الاختبار في الصباح. خلال زيارات العيادة سيتم الاتصال بك قبل يوم واحد وسيُطلب منك الحضور صائمًا إلى العيادة في الصباح لتكون جاهزًا لتكرار الاختبار نفسه.

سيتم أيضًا أخذ عينة من الأنسجة الدهنية التي تمت إزالتها أثناء الجراحة (حوالي 10 جرام) لتحليلها. سيتم إرسال جميع عينات الدم والدهون إلى جامعة قطر لتحليلها. سيتم إجراء أي فحص دم إضافي باستخدام نفس الدم المسحوب من اختبار تحمل الجلوكوز الفموي OGTT.

10. هل يمكن أن يسبب هذا البحث لك أي ضرر؟

المخاطر المرتبطة قليلة ومحدودة لأخذ عينة دم إضافية من المريض باستخدام نفس مكان البزل لفحص الدم الروتيني. وهذا يسبب نادرًا جدًا: كدمات طفيفة، ورم دموي صغير، تعرق، وانخفاض ضغط الدم. لتقليل هذه المخاطر، سيتم استخدام سياسات مؤسسة حمد الطبية أثناء أخذ عينات الدم.

11. هل يمكن أن تستفيد من هذا البحث؟

لا يمكننا أن نعد بأي فائدة لك أو للآخرين من انضمامك إلى هذا البحث. ومع ذلك، تشمل الفوائد المحتملة إجراء فحص أيضي شامل لحالتك الصحية سيتم إبلاغه لك من قبل طبيبك الأساسي أثناء اللقاءات السريرية. بالإضافة إلى المزيد من النصائح السريرية والتعليمات التي ستكون مفيدة لحالتك الصحية.

12. ما هي أوجه استخدام المعلومات الخاصة بك؟

سنبذل جهودًا لتأمين معلوماتك. يتضمن هذا استخدام رمز لتحديد هويتك في سجلاتنا بدلاً من استخدام اسمك. لن نتعرف عليك شخصيًا في أي تقارير أو منشورات حول هذا البحث.

لا يمكننا ضمان السرية التامة. لكننا سنحد من الوصول إلى المعلومات الخاصة بك. لن يتمكن من الوصول إلى المعلومات إلا الأشخاص الذين يحتاجون إلى مراجعة المعلومات. قد يشمل هؤلاء الأشخاص:

- أعضاء فريق البحث والممثلين الآخرين الذين يرتبط عملهم بالبحث أو بحماية حقوقك وسلامتك
- ممثلو وزارة الصحة العامة، ومؤسسة حمد الطبية وجامعة قطر لذين يتأكدون من أن الدراسة قد تمت بشكل صحيح وأن حقوقك وسلامتك محمية
- الأطباء والممرضات.

نخطط لاستخدام بيانات من هذه الدراسة في مشاريع أخرى في المستقبل. قد يشمل ذلك مشاركة البيانات مع باحثين آخرين. قبل أن نقوم بتخزين البيانات للاستخدام المستقبلي، سنقوم بإتلاف جميع الروابط بين هويتك والبيانات الخاصة بك.

أثناء الدراسة، سيتم الاحتفاظ بعيناتك واستخدامها في قطر فقط. نود الاحتفاظ بأي عينات متبقية في نهاية الدراسة لمدة 10 سنوات للبحث في المستقبل.

سنقوم بتخزين هذه العينات المتبقية دون ارتباط بهويتك. يمكن مشاركة العينات المتبقية مع باحثين لم يكونوا جزءًا من هذه الدراسة. سيتم استخدام عيناتك المتبقية للبحث في أي حالة.

يمكنك تغيير رأيك وسحب عيناتك من الدراسة عن طريق الاتصال بنا قبل أخذها. بعد ذلك، لن نعرف العينات التي تخصك ولن نتمكن من إزالتها من الدراسة.

إذا كنت لا ترغب في السماح بهذا الاستخدام المستقبلي، فلا يمكننا تضمينك في هذه الدراسة.

13. ماذا لو كنت لا تريد المشاركة؟

يمكنك رفض المشاركة دون أن يعرضك ذلك لأي تحامل من جانبنا.

14. ماذا لو شاركت في البحث ولكن غيرت رأيك لاحقاً؟

يمكنك التوقف عن المشاركة في أي وقت دون أن يعرضك ذلك لأي تحامل من جانبنا.

إذا توقفت مبكرًا، يرجى الاتصال بنا وسنتخذ الإجراءات المناسبة على الفور.

إذا توقفت عن المشاركة، فقد لا نتمكن من حذف المعلومات التي جمعناها بالفعل عنك.

15. ما هي المعلومات الإضافية التي يجب أن تعرفها؟

تم تمويل هذا البحث من قبل مؤسسة حمد الطبية. إذا تعرضت للإصابة كنتيجة مباشرة لإجراءات البحث، فاتصل بالباحث وسيتم توفير الرعاية المناسبة في مؤسسة حمد الطبية. إذا طلبت الرعاية خارج مؤسسة حمد الطبية، فستكون هذه الرعاية على نفقتك الخاصة. التعويض غير متوفر في حالة الإصابة.

قد تساعد عيناتك في تطوير منتجات تجارية، مثل العلاجات الجديدة أو الاختبارات التشخيصية. لن تتلقى أي تعويض مالي مقابل المنتجات التجارية.

نموذج الموافقة على المشاركة في بحث طبي

16. الخيارات الإضافية
يرجى العلم أنه قد يتم استخدام عينات الدم والأنسجة الخاصة بالمعلومات السريرية الخاصة بك في المستقبل لإجراء مزيد من الدراسات إذا لزم الأمر دون أي ربط بمعلوماتك الشخصية. هذا اختياري، مما يعني أنه يمكنك المشاركة في الدراسة حتى لو لم تسمح باستخدام عيناتك للبحث في المستقبل. يرجى تحديد اختيارك عن طريق التوقيع بجوار السطر المناسب أدناه: _____ أوافق على استخدام عيناتي للدراسات المستقبلية. _____ لا أوافق على استخدام عيناتي للدراسات المستقبلية.

نموذج الموافقة على المشاركة في بحث طبي

صفحة توقيع المشارك البالغ ذي الأهلية
المتطوع
أوافق بمحض إرادتي على الانضمام الى البحث المشروح في هذا النموذج الاسم الكامل للمتطوع توقيع المتطوع التاريخ
الشخص الحاصل على المو فقة
أقر بما يلي: • لقد قمت (أنا أو عضو آخر من فريق البحث) بشرح هذا البحث للمتطوع شرحًا وافيًا. • لقد قمت شخصيًا بتقييم فهم المتطوع للبحث والحصول على موافقته الاسم الكامل للشخص الحاصل على الموافقة التوقيع التاريخ
الشاهد (عند الضرورة)
أشهد بأن المعلومات الواردة في هذا النموذج (وأية معلومات أخرى مكتوبة) قد شرحت بدقة للمتطوع وقد بدى أنه قد فهم البحث ومنح موافقته على المشاركة بمحض إرادته. الاسم الكامل للشاهد التوقيع التاريخ

Patient number: ( ) Preoperative: (A)	
Clinical Data	
1. Age (yrs.)	
2. Gender (m=0, f=1)	
3. Marital status (0= Single, 1= married)	
4. Nationality (0= Qatari, 1= Arab, 2= others)	
5. Education (0= Primary school, 1= secondary, 2= university).	
6. Occupation (0= unemployed, 1= unskilled, 2= skilled, 3= professional)	
7. Smoking (0,1)	
8. Diabetic (0,1)	
9. DM medications (0= metformin,1= insulin, 2= sulfonylureas, 3= others)	
10. Hypertension (0,1)	
11. Coronary artery disease (0,1)	
12. Peripheral vascular disease (0,1)	
13. Dyslipidemia (0,1)	
14. History of childhood obesity (0,1)	
15. Other comorbidities (0,1)	
16. Family hx of DM (0,1)	
17. Family hx of HTN (0,1)	
18. Family hx of CAD/PVD/ Stroke (0,1)	
19. Family hx of Dyslipidemia (0,1)	
20. Sleeve (LSG) surgery (0,1)	
21. Sleeve date (dd,mm,yyyy)	
22. Weight before sleeve (at surgery) (kg)	
23. Weight after sleeve (lowest weight) (kg)	
24. Gastric bypass (RYGB) (0,1)	
25. Gastric bypass date (dd,mm,yyyy)	
26. Weight before RYGB (kg)	
27. Weight after RYGB (lowest) (kg)	
28. Previous abdominoplasty (0,1)	
29. Previous liposuction abdomen (0,1)	
30. Previous thighplasty (0,1)	

Patient number: ( ) Preoperative: (A)	
Appetite Questionnaires	
38. My appetite is	1. Very poor 2. Poor 3. Average 4. Good 5. Very good
39.When I eat, I feel full after	1. Eating only a few mouthfuls 2. Eating about a third of a plate/meal 3. Eating over half of a plate/meal 4. Eating most of the food 5. Hardly ever
40. I feel hungry	1. Never 2. Occasionally 3. Some of the time 4. Most of the time 5. All of the time
41. Food tastes	1. Very bad 2. Bad 3. Average 4. Good 5. Very good
42. Compared to when I was younger, food tastes	1. Much worse 2. Worse 3. Just as good 4. Better 5. Much better
43. Normally, I eat (including snacks)	1. Less than one regular meal a day 2. One meal a day 3. Two meals a day 4. Three meals a day 5. More than three meals aday
44. Most of the time my mood is	1. Very sad 2. Sad 3. Neither sad nor happy 4. Happy 5. Very happy
45. Do you drink (0,1)	
46. Do you eat in excess (0,1)	
47. Do you fast rapidly (0,1)	
48. Do you often skin breakfast (0,1)	
49. Do you enjoy eating salty food (0,1)	
50. Do you enjoy strong tasting food (0,1)	
51. Do you exercise < **2 hours**/ week ☹ (0,1)	

Patient number: ( )

Preoperative: (A)	
Depression Questionnaires	
52. Over the last two weeks, how often have you been bothered by any of the following problems?	
53. Little interest or pleasure in doing things?	1. Not at all 2. Several days 3. > half of the days 4. Almost everyday
54. Feeling down, depressed, or hopeless?	1. Not at all 2. Several days 3. > half of the days 4. Almost everyday
55. Trouble falling or staying asleep, or sleeping too much?	1. Not at all 2. Several days 3. > half of the days 4. Almost everyday
56. Feeling tired or having little energy?	1. Not at all 2. Several days 3. > half of the days 4. Almost everyday
57. Poor appetite or overeating?	1. Not at all 2. Several days 3. > half of the days 4. Almost everyday
58. Feeling bad about yourself - or that you are a failure or have let yourself or your family down?	1. Not at all 2. Several days 3. > half of the days 4. Almost everyday
59. Trouble concentrating on things, such as reading the newspaper or watching television?	1. Not at all 2. Several days 3. > half of the days 4. Almost everyday
60. Moving or speaking so slowly that other people could have noticed? Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual?	1. Not at all 2. Several days 3. > half of the days 4. Almost everyday
61. Thoughts that you would be better off dead, or of hurting yourself in some way?	1. Not at all 2. Several days 3. > half of the days 4. Almost everyday
62. If you checked off any problem, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?	1. Not difficult at all 2. Somewhat difficult 3. Very difficult 4. Extremely difficult

Patient number: ( ) Preoperative: (A)	
APPEARANCE ANXIETY Questionnaires	
OVER THE PAST **WEEK**, INCLUDING TODAY:	
63. I compare aspects of my appearance to others	0. Not at all 1. A little 2. Often 3. A lot 4. All the time
64. I check my appearance (e.g. in mirrors, by touching with my fingers, or by taking photos of myself)	0. Not at all 1. A little 2. Often 3. A lot 4. All the time
65. I avoid situations or people because of my appearance	0. Not at all 1. A little 2. Often 3. A lot 4. All the time
66. I brood about past events or reasons to explain why I look the way I do	0. Not at all 1. A little 2. Often 3. A lot 4. All the time
67. I THINK about how to camouflage or alter my appearance	0. Not at all 1. A little 2. Often 3. A lot 4. All the time
68. I am focussed on how I feel I look, rather than on my surroundings	0. Not at all 1. A little 2. Often 3. A lot 4. All the time
69. I avoid reflective surfaces, photos, or videos of myself	0. Not at all 1. A little 2. Often 3. A lot 4. All the time
70. I discuss my appearance with others or question them about it	0. Not at all 1. A little 2. Often 3. A lot 4. All the time
71. I try to camouflage or alter aspects of my appearance	0. Not at all 1. A little 2. Often 3. A lot 4. All the time
72. I try to prevent people from seeing aspects of my appearance within particular situations (e.g., by changing my posture, avoiding bright lights)	0. Not at all 1. A little 2. Often 3. A lot 4. All the time

Patient number: ( ) Preoperative: (A)	
GENERALIZED ANXIETY Questionnaires	
OVER THE PAST **2 WEEK**, how often have you been bothered by any of the following problems?	
73. Feeling nervous, anxious or on edge?	1. Not at all 2. Several days 3. > half of the days 4. Almost everyday
74. Not being able to stop or control worrying?	1. Not at all 2. Several days 3. > half of the days 4. Almost everyday
75. Worrying too much about different things?	1. Not at all 2. Several days 3. > half of the days 4. Almost everyday
76. Trouble relaxing?	1. Not at all 2. Several days 3. > half of the days 4. Almost everyday
77. Being so restless that it is hard to sit still?	1. Not at all 2. Several days 3. > half of the days 4. Almost everyday
78. Becoming easily annoyed or irritable?	1. Not at all 2. Several days 3. > half of the days 4. Almost everyday
79. Feeling afraid as if something awful might happen?	1. Not at all 2. Several days 3. > half of the days 4. Almost everyday

Patient number: ( ) Preoperative: (B)	
Pre op tests from Cerner	
80. WBC	
81. RBC	
82. Hb	
83. RDW-CV	
8.4 Urea	
85. Creatinine	
86. Sodium	
87. Potassium	
88. Calcium	
89. Adjusted Calcium	
90. Bilirubin total	
91. Total Protein	
92. Albumin	
93. Uric Acid	
94. Alk Phos	
95. ALT	
96. AST	
97. Cholesterol	
98. Triglyceride	
99. HDL	
100. LDL	
101. Iron	
102. TIBC	
103. Transferrin	
104. Fe % saturation	
105. Glucose	
106. Hb A1C	
107. Glucose fasting (OGTT)	
108. Glucose 2h (OGTT)	
109. C-peptide	
110. Vitamin D	
111. Ferritin	
112. TSH	
113. FT4	
114. Insulin	
115. Vitamin B12	
116. IL-6	

TANITA preop

HT(CM)	
CLOTHES WEIGHT(KG)	
WT(KG)	
FAT%	
FAT MASS(KG)	
FFM(KG)	
MUSCLE MASS(KG)	
TBW(KG)	
TBW%	
BONE MASS(KG)	
BMR(KJ)	
BMR(K CAL)	
METABLIC AGE	
VISCERAL FAT RATING	
BMI	
IDEAL BODY WEIGHT (KG)	
DEGREE OF OBESITY (%)	
DESIRABLE RANGER	
FAT%	
FAT MASS Kg	

Patient number: ( )	
Intra operative: (C)	
Surgery details	
117. Abdominoplasty (0,1)	
118. Weight removed **(grams)**	
119. Lower Body lift (0,1)	
120. Weight removed **(grams)**	
121. Liposuction Abdomen (0,1)	
122. Weight removed **(cc)**	
123. Thighplasty (0,1)	
124. Weight removed **(grams)**	
125. Liposuction Thighs (0,1)	
126. Weight removed **(cc)**	
127. Length of stay (days)	
128. Total bloody drain output (ml)	
129. Blood transfusion (0,1)	
130. Another surgery for complication (0,1)	
131. Need for ICU admission (0,1)	

Patient number: ( ) 1 W post OP : (D)	
1 week Post op tests from Cerner	
132. Glucose fasting (OGTT)	
133. Glucose 2h (OGTT)	
134. C-peptide	
135. Ferritin	
136. Insulin	
137, IL-6	

MRC-01-20-466 Validity: 25 08 2021 - 24 08 2022 E-stamped 15 Aug 2021

TANITA 1 week post op

HT(CM)	
CLOTHES WEIGHT(KG)	
WT(KG)	
FAT%	
FAT MASS(KG)	
FFM(KG)	
MUSCLE MASS(KG)	
TBW(KG)	
TBW%	
BONE MASS(KG)	
BMR(KJ)	
BMR(K CAL)	
METABLIC AGE	
VISCERAL FAT RATING	
BMI	
IDEAL BODY WEIGHT (KG)	
DEGREE OF OBESITY (%)	
DESIRABLE RANGER	
FAT%	
FAT MASS Kg	

Patient number: ( ) 6 Weeks Post Op: (E)	
Appetite Questionnaires	
138. My appetite is	1. Very poor 2. Poor 3. Average 4. Good 5. Very good
139. When I eat, **I feel full after**	1. Eating only a few mouthfuls 2. Eating about a third of a plate/meal 3. Eating over half of a plate/meal 4. Eating most of the food 5. Hardly ever
140. I feel hungry	1. Never 2. Occasionally 3. Some of the time 4. Most of the time 5. All of the time
141. Food tastes	1. Very bad 2. Bad 3. Average 4. Good 5. Very good
142. Compared to when I was younger, food tastes	1. Much worse 2. Worse 3. Just as good 4. Better 5. Much better
143. Normally, **I eat** (including snacks)	1. Less than one regular meal a day 2. One meal a day 3. Two meals a day 4. Three meals a day 5. More than three meals aday
144. Most of the time my mood is	1. Very sad 2. Sad 3. Neither sad nor happy 4. Happy 5. Very happy

145. Any family history of DM/ MI/ Stroke (0,1)	
146. Have you ever been found to have high BP	
147. Have you ever been found to have high Sugar in your blood/ urine	
148. Do you smoke (0,1)	
149. Do you drink (0,1)	
150. Do you eat in excess (0,1)	
151. Do you fast rapidly (0,1)	
152. Do you often skin breakfast (0,1)	
153. Do you enjoy eating salty food (0,1)	
154. Do you enjoy strong tasting food (0,1)	
155. Do you exercise < **2 hours**/ week ☹ (0,1)	

Patient number: ( ) 6 Weeks Post Op: (E) **Depression Questionnaires**	
Over the last two weeks, how often have you been bothered by any of the following problems?	
156. Little interest or pleasure in doing things?	5. Not at all 6. Several days 7. > half of the days 8. Almost everyday
157. Feeling down, depressed, or hopeless?	5. Not at all 6. Several days 7. > half of the days 8. Almost everyday
158. Trouble falling or staying asleep, or sleeping too much?	5. Not at all 6. Several days 7. > half of the days 8. Almost everyday
159. Feeling tired or having little energy?	5. Not at all 6. Several days 7. > half of the days 8. Almost everyday
160. Poor appetite or overeating?	5. Not at all 6. Several days 7. > half of the days 8. Almost everyday
161. Feeling bad about yourself - or that you are a failure or have let yourself or your family down?	5. Not at all 6. Several days 7. > half of the days 8. Almost everyday
162. Trouble concentrating on things, such as reading the newspaper or watching television?	5. Not at all 6. Several days 7. > half of the days 8. Almost everyday
163. Moving or speaking so slowly that other people could have noticed? Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual?	5. Not at all 6. Several days 7. > half of the days 8. Almost everyday
164. Thoughts that you would be better off dead, or of hurting yourself in some way?	5. Not at all 6. Several days 7. > half of the days 8. Almost everyday
165. If you checked off any problem, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?	5. Not difficult at all 6. Somewhat difficult 7. Very difficult 8. Extremely difficult

Patient number: ( ) 6 Weeks Post Op: (E)	
APPEARACNE ANXIETY Questionnaires	
OVER THE PAST WEEK, INCLUDING TODAY:	
166. I compare aspects of my appearance to others	5. Not at all 6. A little 7. Often 8. A lot 9. All the time
167. I check my appearance (e.g. in mirrors, by touching with my fingers, or by taking photos of myself)	5. Not at all 6. A little 7. Often 8. A lot 9. All the time
168. I avoid situations or people because of my appearance	5. Not at all 6. A little 7. Often 8. A lot 9. All the time
169. I brood about past events or reasons to explain why I look the way I do	5. Not at all 6. A little 7. Often 8. A lot 9. All the time
170. I THINK about how to camouflage or alter my appearance	5. Not at all 6. A little 7. Often 8. A lot 9. All the time
171. I am focussed on how I feel I look, rather than on my surroundings	5. Not at all 6. A little 7. Often 8. A lot 9. All the time
172. I avoid reflective surfaces, photos, or videos of myself	5. Not at all 6. A little 7. Often 8. A lot 9. All the time
173. I discuss my appearance with others or question them about it	5. Not at all 6. A little 7. Often 8. A lot 9. All the time
174. I try to camouflage or alter aspects of my appearance	5. Not at all 6. A little 7. Often 8. A lot 9. All the time
175. I try to prevent people from seeing aspects of my appearance within particular situations (e.g., by changing my posture, avoiding bright lights)	5. Not at all 6. A little 7. Often 8. A lot 9. All the time

Patient number: ( ) 6 Weeks Post Op: (E) **GENERALIZED ANXIETY Questionnaires**	
OVER THE PAST **2 WEEK**, how often have you been bothered by any of the following problems?	
176. Feeling nervous, anxious or on edge?	5. Not at all 6. Several days 7. > half of the days 8. Almost everyday
177. Not being able to stop or control worrying?	5. Not at all 6. Several days 7. > half of the days 8. Almost everyday
178. Worrying too much about different things?	5. Not at all 6. Several days 7. > half of the days 8. Almost everyday
179. Trouble relaxing?	5. Not at all 6. Several days 7. > half of the days 8. Almost everyday
180. Being so restless that it is hard to sit still?	5. Not at all 6. Several days 7. > half of the days 8. Almost everyday
181. Becoming easily annoyed or irritable?	5. Not at all 6. Several days 7. > half of the days 8. Almost everyday
182. Feeling afraid as if something awful might happen?	77. Not at all 78. Several days 79. > half of the days 80. Almost everyday

Patient number: ( ) 6 weeks post op : (F)	
6 WEEKS post op tests from Cerner	
183. WBC	
184. RBC	
185. Hb	
186. RDW-CV	
187. Urea	
188. Creatinine	
189. Sodium	
190. Potassium	
191. Calcium	
192. Adjusted Calcium	
193. Bilirubin total	
194. Total Protein	
195. Albumin	
196. Uric Acid	
197. Alk Phos	
198. ALT	
199. AST	
200. Cholesterol	
201. Triglyceride	
202. HDL	
203. LDL	
204. Iron	
205. TIBC	
206. Transferrin	
207. Fe % saturation	
208. Glucose	
209. Hb A1C	
210. Glucose fasting (OGTT)	
211. Glucose 2h (OGTT)	
212. C-peptide	
213. Vitamin D	
214. Ferritin	
215. TSH	
216. FT4	
217. Insulin	
218. Vitamin B12	
219. IL-6	

TANITA 6 week post op

HT(CM)	
CLOTHES WEIGHT(KG)	
WT(KG)	
FAT%	
FAT MASS(KG)	
FFM(KG)	
MUSCLE MASS(KG)	
TBW(KG)	
TBW%	
BONE MASS(KG)	
BMR(KJ)	
BMR(K CAL)	
METABLIC AGE	
VISCERAL FAT RATING	
BMI	
IDEAL BODY WEIGHT (KG)	
DEGREE OF OBESITY (%)	
DESIRABLE RANGER	
FAT%	
FAT MASS Kg	

Patient number: ( ) 6 Months Post Op: (J)	
Appetite Questionnaires	
My appetite is	1. Very poor 2. Poor 3. Average 4. Good 5. Very good
220. When I eat, 221. I feel full after	1. Eating only a few mouthfuls 2. Eating about a third of a plate/meal 3. Eating over half of a plate/meal 4. Eating most of the food 5. Hardly ever
222. I feel hungry	1. Never 2. Occasionally 3. Some of the time 4. Most of the time 5. All of the time
223. Food tastes	1. Very bad 2. Bad 3. Average 4. Good 5. Very good
224. Compared to when I was younger, food tastes	1. Much worse 2. Worse 3. Just as good 4. Better 5. Much better
225. Normally, I eat (including snacks)	1. Less than one regular meal a day 2. One meal a day 3. Two meals a day 4. Three meals a day 5. More than three meals aday
226. Most of the time my mood is	1. Very sad 2. Sad 3. Neither sad nor happy 4. Happy 5. Very happy

227. Any family history of DM/ MI/ Stroke (0,1)	
228. Have you ever been found to have high BP	
229. Have you ever been found to have high Sugar in your blood/ urine	
230. Do you smoke (0,1)	
231. Do you drink (0,1)	
232. Do you eat in excess (0,1)	
233. Do you fast rapidly (0,1)	
234. Do you often skin breakfast (0,1)	
235. Do you enjoy eating salty food (0,1)	
236. Do you enjoy strong tasting food (0,1)	

237. Do you exercise < **2 hours**/ week ☹ (0,1)	

Patient number: ( ) 6 Months Post Op: (J) **Depression Questionnaires**	
Over the last two weeks, how often have you been bothered by any of the following problems?	
238. Little interest or pleasure in doing things?	9. Not at all 10. Several days 11. > half of the days 12. Almost everyday
239. Feeling down, depressed, or hopeless?	9. Not at all 10. Several days 11. > half of the days 12. Almost everyday
240. Trouble falling or staying asleep, or sleeping too much?	9. Not at all 10. Several days 11. > half of the days 12. Almost everyday
241. Feeling tired or having little energy?	9. Not at all 10. Several days 11. > half of the days 12. Almost everyday
242. Poor appetite or overeating?	9. Not at all 10. Several days 11. > half of the days 12. Almost everyday
243. Feeling bad about yourself - or that you are a failure or have let yourself or your family down?	9. Not at all 10. Several days 11. > half of the days 12. Almost everyday
244. Trouble concentrating on things, such as reading the newspaper or watching television?	9. Not at all 10. Several days 11. > half of the days 12. Almost everyday
245. Moving or speaking so slowly that other people could have noticed? Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual?	9. Not at all 10. Several days 11. > half of the days 12. Almost everyday
246. Thoughts that you would be better off dead, or of hurting yourself in some way?	9. Not at all 10. Several days 11. > half of the days 12. Almost everyday
247. If you checked off any problem, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?	9. Not difficult at all 10. Somewhat difficult 11. Very difficult 12. Extremely difficult

Patient number: ( ) 6 Months Post Op: (J) **APPEARACNE ANXIETY Questionnaires**	
OVER THE PAST **WEEK**, INCLUDING TODAY:	
248. I compare aspects of my appearance to others	10. Not at all 11. A little 12. Often 13. A lot 14. All the time
249. I check my appearance (e.g. in mirrors, by touching with my fingers, or by taking photos of myself)	10. Not at all 11. A little 12. Often 13. A lot 14. All the time
250. I avoid situations or people because of my appearance	10. Not at all 11. A little 12. Often 13. A lot 14. All the time
251. I brood about past events or reasons to explain why I look the way I do	10. Not at all 11. A little 12. Often 13. A lot 14. All the time
252. I THINK about how to camouflage or alter my appearance	10. Not at all 11. A little 12. Often 13. A lot 14. All the time
253. I am focussed on how I feel I look, rather than on my surroundings	10. Not at all 11. A little 12. Often 13. A lot 14. All the time
254. I avoid reflective surfaces, photos, or videos of myself	10. Not at all 11. A little 12. Often 13. A lot 14. All the time
255. I discuss my appearance with others or question them about it	10. Not at all 11. A little 12. Often 13. A lot 14. All the time
256. I try to camouflage or alter aspects of my appearance	10. Not at all 11. A little 12. Often 13. A lot 14. All the time
257. I try to prevent people from seeing aspects of my appearance within particular situations (e.g., by changing my posture, avoiding bright lights)	10. Not at all 11. A little 12. Often 13. A lot 14. All the time

Patient number: ( ) 6 Months Post Op: (J) **GENERALIZED ANXIETY Questionnaires**	
OVER THE PAST **2 WEEK**, how often have you been bothered by any of the following problems?	
258. Feeling nervous, anxious or on edge?	9. Not at all 10. Several days 11. > half of the days 12. Almost everyday
259. Not being able to stop or control worrying?	9. Not at all 10. Several days 11. > half of the days 12. Almost everyday
260. Worrying too much about different things?	9. Not at all 10. Several days 11. > half of the days 12. Almost everyday
261. Trouble relaxing?	9. Not at all 10. Several days 11. > half of the days 12. Almost everyday
262. Being so restless that it is hard to sit still?	9. Not at all 10. Several days 11. > half of the days 12. Almost everyday
263. Becoming easily annoyed or irritable?	9. Not at all 10. Several days 11. > half of the days 12. Almost everyday
264. Feeling afraid as if something awful might happen?	81. Not at all 82. Several days 83. > half of the days 84. Almost everyday

Patient number: ( ) Preoperative: (H)	
6 months post op tests from Cerner	
265. WBC	
266. RBC	
267. Hb	
268. RDW-CV	
269. Urea	
270. Creatinine	
271. Sodium	
272. Potassium	
273. Calcium	
274. Adjusted Calcium	
275. Bilirubin total	
276. Total Protein	
277. Albumin	
278. Uric Acid	
279. Alk Phos	
280. ALT	
281. AST	
282. Cholesterol	
283. Triglyceride	
284. HDL	
285. LDL	
286. Iron	
287. TIBC	
288. Transferrin	
289. Fe % saturation	
290. Glucose	
291. Hb A1C	
292. Glucose fasting (OGTT)	
293. Glucose 2h (OGTT)	
294. C-peptide	
295. Vitamin D	
296. Ferritin	
297. TSH	
298. FT4	
299. Insulin	
300. Vitamin B12	
301. IL-6	

TANITA 6 months post op

HT(CM)	
CLOTHES WEIGHT(KG)	
WT(KG)	
FAT%	
FAT MASS(KG)	
FFM(KG)	
MUSCLE MASS(KG)	
TBW(KG)	
TBW%	
BONE MASS(KG)	
BMR(KJ)	
BMR(K CAL)	
METABLIC AGE	
VISCERAL FAT RATING	
BMI	
IDEAL BODY WEIGHT (KG)	
DEGREE OF OBESITY (%)	
DESIRABLE RANGER	
FAT%	
FAT MASS Kg	

1- Japanese Metabolic Syndrome Risk Score Questionaire

Questionnaire (JAMRISC)

[redacted]
Date of birth

Sex (Male • Female)

Height( ) cm、 Weight( ) kg、 Abdominal circumference ( ) cm
(self-reported measurement)

Please check yes (O) or no (×) to the following questions.

- Has any member of your family (immediate or extended) been diagnosed with diabetes, acute myocardial infarction or cerebral infarction ? ( )
- Have you ever been found to have high blood pressure ? ( )
- Have you ever been found to have high blood glucose or sugar in your urine ? ( )
- Do you smoke ? ( )
- Do you drink over 540ml of sake a week ? ( )
- Please make a circle (O) to any question that applies to your dietary habits .
  - * Do you eat in excess ? ( )
  - * Do you fast rapidly ? ( )
  - * Do you often skip breakfast ? ( )
  - * Do you enjoy eating salty foods ? ( )
  - * Do you enjoy strong tasting foods ? ( )
- Do you perform light exercise for less than 2 hours a week ? ( )

* Please refer to the following conversion formula for alcohol.
(Sake 180ml = Beer 500ml = Shochu 80ml = Whisky 60ml = Wine 240ml)

2- Council of Nutrition Appetite Questionnaire

Answers scored based on the following numerical scale: a = 1; b = 2; c = 3; d = 4; e = 5. The sum of the scores for all individual items constitutes the CNAQ score. The sum of the scores for the individual items marked ** constitutes the SNAQ score.

1. **My appetite is ****
   a. Very poor
   b. Poor
   c. Average
   d. Good
   e. Very good

2. **When I eat ****
   a. I feel full after eating only a few mouthfuls
   b. I feel full after eating about a third of a meal
   c. I feel full after eating over half a meal
   d. I feel full after eating most of the meal
   e. I hardly ever feel full

3. **I feel hungry**
   a. Rarely
   b. Occasionally
   c. Some of the time
   d. Most of the time
   e. All of the time

4. **Food tastes ****
   a. Very bad
   b. Bad
   c. Average
   d. Good
   e. Very good

5. **Compared to when I was younger, food tastes**
   a. Much worse
   b. Worse
   c. Just as good
   d. Better
   e. Much better

6. **Normally I eat ****
   a. Less than one meal a day
   b. One meal a day
   c. Two meals a day
   d. Three meals a day
   e. More than three meals a day

7. **I feel sick of nauseated when I eat**
   a. Most times
   b. Often
   c. Sometimes
   d. Rarely
   e. Never

8. **Most of the time my mood is**
   a. Very sad
   b. Sad
   c. Neither sad nor happy
   d. Happy
   e. Very happy

3- Patient Health Questionnaire-9
For Depression disorder screening

PATIENT HEALTH QUESTIONNAIRE-9

Over the last 2 weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING

__0__ + _____ + _____ + _____

=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

4- Appearance Anxiety Inventory
For Body Dysmorphic Disorder screening

Appearance Anxiety Inventory (AAI)

Instructions:

Please check the box that best describes the way you have felt about your appearance or a specific feature OVER THE PAST WEEK, INCLUDING TODAY.

		Not at all	A little	Often	A lot	All the time
1	I compare aspects of my appearance to others	0	1	2	3	4
2	I check my appearance (e.g. in mirrors, by touching with my fingers, or by taking photos of myself)	0	1	2	3	4
3	I avoid situations or people because of my appearance	0	1	2	3	4
4	I brood about past events or reasons to explain why I look the way I do	0	1	2	3	4
5	I THINK about how to camouflage or alter my appearance	0	1	2	3	4
6	I am focussed on how I feel I look, rather than on my surroundings	0	1	2	3	4
7	I avoid reflective surfaces, photos, or videos of myself	0	1	2	3	4
8	I discuss my appearance with others or question them about it	0	1	2	3	4
9	I try to camouflage or alter aspects of my appearance	0	1	2	3	4
10	I try to prevent people from seeing aspects of my appearance within particular situations (e.g., by changing my posture, avoiding bright lights)	0	1	2	3	4

5- Generalized Anxiety Disorder-7 Questionnaire

GAD-7

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

Total Score ___ = Add Columns ___ + ___ + ___

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐