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Is there an association between metabolic syndrome and rotator cuff-related shoulder pain? A systematic review

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ABSTRACT

Objectives Rotator cuff-related shoulder pain (RCRSP) is a common upper limb complaint. It has been suggested that this condition is more common among people with cardiometabolic risk factors. This systematic review has synthesised evidence from case–control, cross-sectional and cohort studies on the association between metabolic syndrome (MetS) and RCRSP.

Design and data sources Five medical databases (MEDLINE, EMBASE, SCOPUS, CINAHL and AMED) and reference checking methods were used to identify all relevant English articles that considered MetS and RCRSP. Studies were appraised using the Newcastle-Ottawa Scale (NOS). Two reviewers performed critical appraisal and data extraction. Narrative synthesis was performed via content analysis of statistically significant associations.

Results Three cross-sectional, two case–control and one cohort study met the inclusion criteria, providing a total of 1187 individuals with RCRSP. Heterogeneity in methodology and RCRSP or MetS definition precluded a meaningful meta-analysis. Four of the included studies identified associations between the prevalence of MetS and RCRSP. Studies consistently identified independent cardiometabolic risk factors associated with RCRSP. All studies were level III evidence.

Summary and conclusion The low-moderate quality evidence included in this review suggests an association between MetS and RCRSP. Most studies demonstrated moderate quality on appraisal. The direction of association and cardiometabolic factors influencing should be investigated by longitudinal and treatment studies. These preliminary conclusions and clinical utility should be treated with caution due to limitations of the evidence base.

What is already known on this topic

- The prevalence of metabolic syndrome (MetS) is reported to be 23%–46% in the general population.
- MetS has been associated with depression, cancer risk, low health-related quality of life, musculoskeletal pain (low back, neck and knee osteoarthritis) and all-cause mortality.
- Adipose tissue secretes a variety of bioactive molecules that individually or collectively suppress or enhance inflammation.

What this study adds

- There is low-moderate quality evidence for an association between MetS and rotator cuff-related shoulder pain (RCRSP).
- While causality has not been established, associations between low-grade inflammatory biomarkers and RCRSP have been demonstrated in two included studies.
- It remains to be investigated if the impact of MetS exceeds the sum of all its individual risk factors (central obesity, dyslipidaemia, hypertension and insulin resistance).
- People with MetS are potentially at higher risk of shoulder pain, rotator cuff tears and more severe rotator cuff tears.

INTRODUCTION

Metabolic syndrome (MetS) is a complex disorder with high socioeconomic cost and mortality.[1 2] It is a cluster of interconnected physiological, biochemical and clinical factors that is associated with cardiovascular disease (CVD) and type II diabetes mellitus (DM) risk.[3] MetS has been associated with depression,[4] cancer,[5] health-related quality of life[6] and all-cause mortality.[7] MetS has five primarily components—central obesity, elevated triglycerides, hypertension, low high-density lipoprotein cholesterol (HDL-C) and elevated fasting glucose. This presentation is a manifestation of underlying cellular dysfunction, systemic inflammation and oxidative stress.[8–13]

Chronic low-grade systemic inflammation is associated with MetS risk factors including, hypertension, type II DM, obesity and dyslipidaemia.[8 14–16] Systemic low-grade inflammation has key differences to a classic inflammatory response.[17] Specifically,

low-grade systemic inflammation is characterised by subtly elevated acute phase proteins and elevated levels of active inflammatory cytokines in tissues,[14 18–20] with very low presence of neutrophils associated with acute inflammation.[21]

Excess adiposity is central to MetS. Diagnostic criteria typically mandate the presence of excess adiposity plus two of the other components (elevated triglycerides, hypertension, low HDL-C and elevated fasting glucose).[22] Adipose tissue is metabolically active and secretes proinflammatory cytokines and proteinoids, which individually or collectively interact with various biological processes that suppress or enhance inflammation.[23–25] This contributes to the development of many systemic complications, including abnormal insulin action.[12 26 27] Free fatty acid mobilisation is accelerated in the presence of insulin resistance leading to increased glucose production and dyslipidaemia, which perpetuates the low-grade systemic inflammation.[8]

Concordant with the rise in MetS, there is a global increase in the prevalence of musculoskeletal (MSK) diseases and disorders.[28] Cardiometabolic risk factors and MSK pain are common comorbidities that feasibly share similar aetiology.[29] A recent systematic review identified a relationship between MetS and Achilles tendinopathy.[30] Furthermore, MetS is more prevalent in people with neck pain,[31] low back pain[32 33] and knee osteoarthritis.[34] One study showed that MetS was not associated with adhesive capsulitis, although associations with type II DM and hypertension were identified.[35]

Shoulder pain is a common MSK complaint in clinical practice with point prevalence ranging between 7% and 26%.[36 37] Symptoms associated with the rotator cuff and related tissues have been defined as rotator cuff-related shoulder pain (RCRSP).[38] There is a growing body of research associating RCRSP with cardiometabolic risk factors, such as obesity, body mass index (BMI) and body fat.[39–48] Conversely, other studies have reported no relationship with obesity and RCRSP.[49–52] In a cross-sectional study, Miranda *et al*[53] reported no association with obesity; however, people with type I DM had increased risk of RCRSP (OR 8.8; 95% CI 1.9 to 40.3). A recent meta-analysis reported the prevalence of tendinopathy, and tendon thickness is increased in people with diabetes.[54] Diabetes is associated with an upregulation of proinflammatory cytokines as the anti-inflammatory actions of insulin is impaired, inducing deregulation of the tendon matrix, which may lead to symptoms and functional impairments of the affected tendon.[55] The role of dyslipidaemia association is inconsistent with two cohort studies and one cross-sectional study reporting elevated triglyceride and low HDL-C, impact pain and outcome in rotator cuff tears as compared with control groups.[47 56 57] Conversely, Longo *et al*[58] conducted a case–control study finding no significant difference between total cholesterol and triglyceride concentrations in people with rotator cuff tears and asymptomatic controls. Overall, systemic metabolic stress appears to promote low-grade inflammation, altered lipid metabolism and insulin resistance that may be associated with disease risk and/or progression of RCRSP.[59]

As the association between MetS and RCRSP is unclear, the aim of this study is to systematically review case-control, cross-sectional and cohort studies investigating the association between MetS and RCRSP.

METHODS

This review was conducted according to methodology guidelines (Centre for Reviews and Dissemination, 2009), and reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement.[60] The review was based on an a priori protocol, which described the procedures that would be followed (eg, PICO, comprehensive search strategy and a piloted data extraction pro forma).

Eligibility criteria

All observational designs such as cross-sectional studies, case–control studies and cohort studies were included. The inclusion criteria were; (1) human study sample comprised of adult participants (>18 years), (2) study sample presented with signs and symptoms suggestive of RCRSP, (3) radiological findings recorded but not considered diagnostic of RCRSP, (4) MetS was recorded in medical history or met diagnostic criteria of three clinical risk factors and (5) participants recruited from specialist clinics were deemed to have accurate diagnosis of RCRSP or MetS (ie, based on clinical expertise, those participants recruited from a metabolic clinic were deemed to have MetS and participants attending an orthopaedic clinic for RCRSP).

Studies were excluded where a spinal source of pain was likely (eg, manikins indicating symptoms over neck and upper back) or the study sample comprised of participants with other pathologies (eg, fracture, dislocation, osteoarthritis, frozen shoulder, neurological presentations).

Data sources and search strategy

The search strategy and inclusion criteria were specified in advance. Studies were identified by an electronic search of MEDLINE, CINAHL, EMBASE, SCOPUS and AMED from inception to 20 June 2019. Additionally, reference lists of all included manuscripts were searched for relevant studies not identified in search strategy, combined with an unpublished (grey) literature search. Studies that included symptoms suggestive of RCRSP diagnosis and cardiometabolic variables related to MetS criteria were sought. Search terms were informed by a feasibility search and consultation with two health information librarians experienced in systematic review methodology. Example of the search terms and keywords used with MEDLINE (MeSH terms, Medical Subject Headings) are detailed in table 1. Records were imported into referencing software (Endnote X7), and duplicates removed. Based on eligibility criteria, the titles and abstracts were independently

Table 1 MEDLINE search strategy

Search terms	
1. Shoulder pain OR shoulder joint OR shoulder impingement OR subacromial pain syndrome* OR rotator cuff OR rotator cuff disease OR rotator cuff tear.	10. Glycaemic homeostasis OR fasting glucose OR glucose intolerance OR Impaired glucose tolerance OR IGT OR plasma insulin OR hyperinsulinemia OR IFG OR insulin resistance OR pre diabet* OR diabetes OR diabetes mellitus OR DM.
2. Subacromial impingement syndrome*.	11. Blood pressure OR elevated arterial pressure OR hypertension.
3. Supraspinatus tend*.	12. Dyslipidemia OR hyperlipidemia OR dyslipid* OR hyperlipid* OR high density lipoprotein OR HDL* OR low density lipoprotein OR LDL* OR triglycerides OR total cholesterol OR hypertriglyceridemia.
4. Shoulder bursitis*.	13. Microalbuminuria OR albumin OR urine albumin.
5. Shoulder tend*.	14. S8 OR S9 OR S10 OR S11 OR S12 OR S13.
6. Painful arc*.	15. S7 AND S14.
7. S1 OR S2 OR S3 OR S4 OR S5 OR S6.	16. Limit to >18 (adult) and English.
8. Metabolic OR metabolic syndrome OR metabolic syndrome X OR syndrome x OR metabolic syn* OR cardio metabolic syn* OR Insulin resistance syndrome*.	
9. Obesity OR waist circumference OR central obesity OR intra-abdominal fat OR waist circumference OR body mass index OR BMI OR visceral obesity OR abdominal obesity OR overweight OR adiposity OR waist-to-hip ratio.	

*Truncation command

reviewed by one reviewer (GB) and relevant studies were accessed for full text. All potentially relevant studies were reviewed to determine final study selection (GB, MM); the reasons for exclusion at this stage were documented. A third reviewer (JL) was available for consultation and consensus.

Data extraction

Data extraction was performed by one reviewer (GB) and checked for verification and accuracy by a second reviewer (MM) using a predesigned piloted form. Data extraction for each study included: study location, study design, sample characteristics (age, gender), case definition and method of diagnosis for RCRSP, definition used to classify MetS or cardiometabolic risk factors included that met MetS definition within study population. Outcomes in terms of OR (unadjusted or adjusted), 95% CIs and when available significant p values <0.05 were extracted. In circumstances where it was not possible to extract these data from the manuscript, corresponding authors were contacted to seek clarification or request individual patient data.

Data analysis

The included studies were assessed by two reviewers (GB, MM) through examination of the data extraction table. This demonstrated significant heterogeneity of subject characteristics (definition of RCRSP), cointerventions, exposure and criteria for diagnosing MetS, subsequently meta-analysis was precluded. A narrative synthesis with emphasis on study design and quality was undertaken as per the method described by Popay *et al*. Oxford Centre for Evidence-based Medicine (OCEBM) levels of evidence was used as guidance to evaluate selected articles.[61]

Quality appraisal

Quality of the included studies was evaluated using the Newcastle-Ottawa Scale (NOS) for cross-sectional, case–control and cohort studies.[62] This appraisal tool is recommended by the Cochrane Handbook for Systematic Reviews of Interventions.[63] The NOS checklist assesses quality of articles across three domains: selection of the study groups; comparability of the groups and control for cofounding factors; and exposure. The minimum and maximum scores available is 0 and 9, respectively. The studies with score ≥6; ≥3 score <6; and score <3 were considered high quality, moderate quality and low quality, respectively.[64] Two reviewers (GB, MM) independently examined the studies for risk of bias and internal validity (table 2). In order to assess interobserver agreement of the risk of bias, the kappa coefficient (κ) was used.[65]

RESULTS

Search strategy

Figure 1 shows search and study selection process. After exclusions, 36 studies required the full text to be assessed. Out of these, 30 studies were excluded (23 studies had incomplete cardiometabolic details available to establish a MetS definition, 5 studies had no shoulder pain data and 2 studies did not meet participant criteria), resulting in 6 studies[42 43 55 66–68] for inclusion in this review.

Study characteristics

Table 3 presents a summary of characteristics and findings of each included study. Within the construct of RCRSP; four studies examined people diagnosed with symptomatic rotator cuff tendinopathy and two studies examined people with symptomatic rotator cuff tears (partial and full thickness). Four studies were cross-sectional, one case controlled and one retrospective cohort. The total number of individuals across the studies was 8259 (mean age 50.9 years), of which 1187 were people experiencing RCRSP. Five studies recruited participants from health centres or hospitals.[42 43 55 67 68] Applegate *et al*[66]

Table 2 Detailed summary of critical appraisal of included studies using the Newcastle Ottawa Scale (NOS) for assessing the quality of non-randomised control trials (cross-sectional/cohort and case–control studies)

	NOS quality assessment for studies included (cross-sectional studies/cohort studies)									
	Selection				Comparability	Outcome				
Study, country	Representativeness of the sample	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at study start	Comparability of the groups on the basis of design or analysis	Assessment of outcome	Adequacy of follow-up of cohorts	Was follow-up long enough for outcomes to occur	Overall quality assessment score (maximum of 9)	Quality (high, medium, low)
Applegate *et al*[66] USA n=1226	*	*	*		**				5	Medium quality
Rechardt *et al*[42] Finland n=6237	*	*	*		*	*			5	Medium quality
Rechardt *et al*[43] Finland n=163	*	*	*		*	*			5	Medium quality
Judge *et al*[68] France n=147			*						1	Low quality
	NOS quality assessment for studies included (case–control studies)									
	Selection				**Comparability**	**Exposure**				
	Is the case definition adequate?	**Representativeness of the cases**	**Selection of controls**	**Definition of controls**	**Comparability of cases or controls on the basis of design or analysis**	**Ascertainment of exposure**	**Same method of ascertainment for cases and controls**	**Non-Response rate**		
Abate *et al*[55] Italy n=180	*		*	*		*	*	*	6	Medium quality
Djerbi *et al*[67] France n=306	*	*	*	*	**	*	*	*	9	High quality

NOS, The Newcastle Ottawa Scale for assessing the quality of non-randomised control trials (cross-sectional/cohort and case–control studies).
* and ** are the star rating as per NOS with the study satisfying the item. A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two can be given for Comparability.

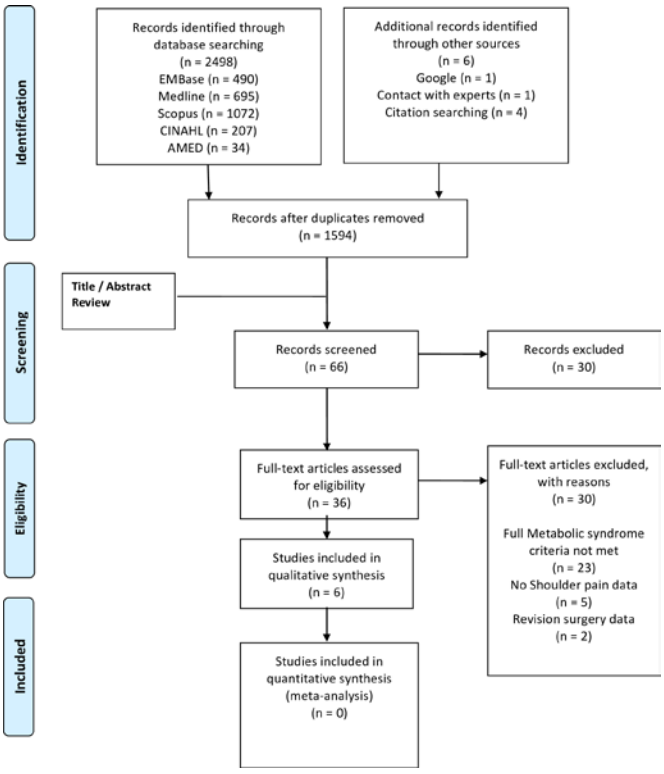

Figure 1 PRISMA flow diagram showing study selection process.[60] PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analysis.

recruited participants from 17 diverse production facilities, including food processing, manufacturing, assembly lines and office jobs.

Quality assessment

The six included studies were clinical human reports and considered level III evidence in line with OCBEM guidance. The results of the quality appraisal are shown in table 2. According to our definition, 1/6 of the studies were good quality, 4/6 medium quality and 1/6 of low quality. This was due to a number of common deficiencies in the methodological quality of these studies. With the exception of one study,[67] the others did not report a study protocol. Response rates from preliminary sampled subjects were not reported in three studies,[42 43 66] thus substantial selection bias may have occurred. Studies tended to report variables for all their stated aims but did not specify which aims were determined in advance of conducting the study. Study quality as assessed by the NOS varied considerably across the studies ranging from 1/9 to 9/9, the main issues being lack of adequate diagnosis, definition of controls and lack of adjustment for potential cofounders (table 2). Interobserver agreement regarding the risk of bias was considered 'substantial' (κ=0.76) according to the Viera and Garrett[69] kappa interpretation model.

RCRSP diagnosis classification

The six studies had inconsistent diagnostic classification of RCRSP through a mix of self-reported symptoms, clinical findings and radiological imaging (table 3). For example, one study confirmed RCRSP as pain during functional activities (range of motion) and sonographic diagnosis of a partial or full thickness rotator cuff tear.[55] Conversely, one study utilised the international classification of disease (ICD) 10 code[70] and one other study utilised radiography to differentiate primary or centred osteoarthritis.[67]

MetS diagnosis classification

MetS diagnosis was clearly defined within two studies using the National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III).[42 43] The remaining studies did not state which definition criteria was used (table 3). Within data extraction all studies met a definition set by many international expert groups, such as the WHO and the International Diabetes Federation (IDF). There is no currently agreed diagnostic consensus.[8] The variance is attributed to the focus of each definition, from the obesity-centric IDF to a gluco-centric WHO definition and the collection of statistically elevated CVD risk factor by the NCEP ATP III.

Analysis

Of the studies included, four studies reported a positive association between MetS and shoulder pain. Applegate *et al*[66] reported an adjusted OR for glenohumeral joint pain among people with the highest CVD risk score (18+), scaled in accordance with a modified Framingham Heart Study's risk assessment,[71] namely, hypertension, dyslipidaemia and diabetes of 4.55 (95% CI 1.99 to 10.40, p<0.001). Similarly, the adjusted OR for RC tendinopathy in those with the highest CVD risk score was 5.97 (95% CI 2.12 to 16.83, p<0.008). Djerbi *et al*[67] reported an unadjusted OR for symptomatic rotator cuff tears (SCOI 1–3) of OR 2.55 (95% CI 1.4 to 4.58, p=0.0017) for obesity, 2.04 (95% CI 1.18 to 3.52, p=0.0102) for systolic BP and 7.69 (95% CI 3.35 to 17.25, p<0.0001) for dyslipidaemia. Higher grade tears (SCOI 4) were also associated with obesity (OR 2.105, p=0.0117), systolic BP (OR 4.311, p<0.0001) and dyslipidaemia (OR 2.867, p=0.0004). Although, when adjusted, only dyslipidaemia (OR 4.920; 95% CI 2.046 to 11.834, p=0.0004) and systolic BP (OR 3.215; 95% CI 1.67 to 6.19, p=0.0005) were associated. Rechardt *et al*[42] reported an adjusted OR for unilateral glenohumeral joint pain over a 3 month period of 1.7 (95% CI 1.3 to 2.1) for MetS (NCEP ATP II definition) in males. This study found MetS was not associated with rotator cuff tendinopathy (OR 0.7; 95% CI 0.4 to 1.1). Juge *et al* reported a significant difference in the proportion of people with established MetS criteria (obesity, DM, dyslipidaemia, hypertension) between RCRSP (6.5%) and those with osteoarthritis (0%, p=0.03). Two studies reported no association between MetS and RCRSP. Abate *et al*[55] reported no significant difference in rotator cuff tear prevalence in people with cardiometabolic risk factors meeting MetS criteria. Although, this study did report positive power of the predictor coefficient (β) for

Table 3 Summary of study characteristics and findings of included studies

Study, country	Study design, level of evidence	Cohort characteristics	No individuals with RCRSP/ study sample size	Case definition of RCRSP, pathology reported and duration	Criteria used to classify MetS or cardiometabolic risk factors included	Prevalence of MetS within population (%)	Adjustments for other covariates	Summary: Findings (OR with 95% CI) or p value	Summary: Positive direction of association by UVA or MVA results
Abate *et al*[55] Italy	Case–control study, level III	Age: 59.2 (±7.1) Gender: M (n=65, 36.1%), F (n=115, 63.9%)	180/180	Unilateral shoulder pain with functional limitations, ultrasound examination RCT (full or partial thickness) Unknown duration	No recorded criteria but MetS risk factors meeting definition by WHO: ▶ Obesity (BMI kg/m^2 calculation). ▶ Dyslipidaemia (diagnosis, drugs assumptions and recent blood biomarkers). ▶ DM (diagnosis, drugs assumptions and recent blood biomarkers). ▶ BP (diagnosis and current systolic reading).	Unable to extract	Age, heavy repetitive work, diabetes	Metabolic risk factors Independently associated in the presence of bilateral tears UVA: ▶ Obesity (p=0.017). ▶ DM (p=0.004). MVA: ▶ BMI (p=0.047). ▶ DM (p=0.029).	For RCT ▶ MVA, BMI.* ▶ MVA, DM.*
Applegate *et al*[66] USA	Cross-sectional, level III	Age: 42.1 (±11.4) Gender: M (n=421, 34.3%), F (n=805, 65.7%)	RC tendon pain 156/1226 GHJT pain 386/1226	Questionnaire and manikin followed by standardised physical examination (palpation, ROM and positive impingement sign) RC tendinopathy Any pain within last 1 month	No recorded criteria but MetS risk factors meeting definition by WHO: ▶ Obesity (BMI >30 kg/m^2). ▶ Dyslipidaemia (>200 mg/dL). ▶ DM (diagnosis). ▶ BP (diagnosis and current systolic reading).	Unable to extract	Only adjusted for multiple CVD risk factors (gender, BMI, job satisfaction and family problems)	Metabolic risk factors Independently associated in the presence of RC tendinopathy UVA: ▶ Higher systolic BP (OR 1.01; 95% CI 1.00 to 1.02, p<0.05). MVA: ▶ Multiple CVD risk scores (18+) for RC tendinopathy (OR 5.97; 95% CI 2.12 to 16.83, p<0.008) namely (age, gender, BP, cholesterol and DM). Metabolic risk factors Independently associated in the presence of GHJT pain UVA: ▶ DM (OR 1.76; 95% CI 1.07 to 2.91, p<0.05). ▶ Hypercholesterolemia (OR 1.45; 95% CI 1.07 to 1.96, p<0.05). ▶ Higher systolic BP (OR 1.01; 95% CI 1.00 to 1.02, p<0.05). MVA: ▶ Multiple CVD risk scores (18+) for GHJT pain (OR 4.55; 95% CI 1.99 to 10.40, p<0.001) namely (age, gender, BP, cholesterol and DM).	For RC tendinopathy ▶ UVA, BP.* ▶ MVA, CVD risk score.* For GHJT pain ▶ UVA, DM.* ▶ UVA, BP. ▶ UVA, hypercholesterolemia.* ▶ MVA, CVD risk score.†

Continued

Table 3 Continued

Study, country	Study design, level of evidence	Cohort characteristics	No individuals with RCRSP/ study sample size	Case definition of RCRSP, pathology reported and duration	Criteria used to classify MetS or cardiometabolic risk factors included	Prevalence of MetS within population (%)	Adjustments for other covariates	Summary	
								Findings (OR with 95% CI) or p value	Positive direction of association by UVA or MVA results
Djerbi *et al*[67] France	Case–control study, level III	Age: 57.8 Gender: M (n=124, 60%), F (n=82, 40%)	206/306	Undergoing shoulder surgery for RCRSP (preoperative clinical exam, CT arthrography and arthroscopy) RCT Unknown duration	No recorded criteria but MetS risk factors meeting definition by WHO: ▶ BP (diagnosis or 140/90 mm Hg). ▶ Obesity (BMI >30 kg/m^2). ▶ DM (FBG >1.26 g/L or if patient treated for type I/II DM). ▶ Dyslipidaemia (LDL-C >1.60 g/L, TG >1.50 g/L, HDL-C >0.40 g/L or if taking cholesterol lowering medication).	Unable to extract	No mention	Metabolic risk factors Independently associated in the presence of RCT SCOI 1–3 UVA: ▶ Obesity (OR 2.55; 95% CI 1.4 to 4.58, p=0.0017). ▶ Higher systolic BP (OR 2.04; 95% CI 1.18 to 3.52, p=0.0102). ▶ Dyslipidaemia (OR 7.69; 95% CI 3.35 to 17.25, p<0.0001). RCT SCOI 4 UVA: ▶ Obesity (OR 2.105, p=0.0117) ▶ Higher systolic BP (OR 4.311, p<0.0001) ▶ Dyslipidaemia (OR 2.867, p=0.0004). RCT SCOI 1–3 MVA: ▶ Dyslipidaemia (OR 4.920; 95% CI 2.046 to 11.834, p=0.0004). RCT SCOI 4 MVA: ▶ Dyslipidaemia (OR 4.920; 95% CI 2.046 to 11.834, p=0.0004). ▶ Higher systolic BP (OR 3.215; 95% CI 1.67 to 6.19, p=0.0005).	For RCT SCOI 1–4 ▶ UVA, obesity.* ▶ UVA, BP.* ▶ UVA and MVA, dyslipidaemia.† For RCT SCOI stage 4 (severe) only ▶ UVA, dyslipidaemia.* ▶ UVA, obesity.* ▶ MVA, BP.

Continued

Table 3 Continued

Study, country	Study design, level of evidence	Cohort characteristics	No individuals with RCRSP/ study sample size	Case definition of RCRSP, pathology reported and duration	Criteria used to classify MetS or cardiometabolic risk factors included	Prevalence of MetS within population (%)	Adjustments for other covariates	Summary: Findings (OR with 95% CI) or p value	Summary: Positive direction of association by UVA or MVA results
Rechardt *et al*[42] Finland	Cross-sectional, level III	Age: 57.8 Gender: M (n=124, 60%), F (n=82, 40%)	175/6237	Physical examination, painful arc, shoulder pain provoked with resistance, manikin GHJT pain and RC tendinopathy >3 months	NCEP ATP III classification: ▶ Central obesity (waist circumference >102 cm in males, >88 cm in females). ▶ FBG (>110 mg/L). ▶ LHDL-C (<40 mg/dL in men and <50 mg/dL in women). ▶ BP (diagnosis, 130/85 mm Hg).	Total: 30.2% (n=1884)	Age, sex, residential district and language	Metabolic risk factors Independently associated in the presence of GHJT pain MVA: ▶ Central obesity unilateral association in men (BMI >30 kg/m^2, OR 1.6; 95% CI 1.1 to 2.3; waist circumference >102 cm OR 2.0; 95% CI 1.5 to 2.8; WHR 'high' OR 3.0; 95% CI 1.7 to 5.3). ▶ MetS (OR 1.7; 95% CI 1.3 to 2.1). ▶ Type II DM (OR 2.2; 95% CI 1.3 to 3.5) was associated with unilateral shoulder pain in men. ▶ Central obesity stronger association for women with bilateral shoulder pain (BMI >30 kg/m^2, OR 2.2; 95% CI 1.5 to 3.4; waist circumference >88 cm OR 4.2; 95% CI 2.8 to 6.4; WHR high OR 3.6; 95% CI 2.2 to 5.9). Metabolic risk factors Independently associated in the presence of RCT tendinopathy MVA: ▶ Obesity (WHR high OR 3.6; 95% CI 2.2 to 5.9) and type I DM (OR 4.1; 95% CI 0.98 to 16.8) was associated with chronic RC tendinopathy in men. ▶ Obesity (WHR high OR 2.3; 95% CI 1.2 to 4.3) was associated with chronic RC tendinopathy in women.	For GHJT pain ▶ MVA, MetS.* ▶ MVA, DM.* ▶ MVA, obesity.* For RC tendinopathy ▶ MVA, obesity.* ▶ MVA, DM.*
Rechardt *et al*[43] Finland	Cross-sectional, level III	Age: 45.0 (±9.8) Gender: M (n=23, 14%), F (n=140, 86%)	36/163	Physical examination and clinical tests, pain intensity scale (0–100), RC tendinopathy <1 month	NCEP ATP III classification: ▶ Central obesity (waist circumference >102 cm in males, >88 cm in females). ▶ FBG (>110 mg/L). ▶ Low HDL-C (<40 mg/dL in men and <50 mg/dL in women). ▶ BP (diagnosis, 130/85 mm Hg).	Total: 18% (n=29)	Age, sex	Metabolic risk factors Independently associated in the presence of RC tendinopathy among UESTD MVA: ▶ Central obesity (BMI >30 kg/m^2, OR 2.1; 95% CI 0.8 to 5.4; WHR >0.9, OR 3.3; 95% CI 1.3 to 8.6; waist circumference OR 3.2; 95% CI 1.4 to 7.4). ▶ Dyslipidaemia (low (<1.48 mmol/L) HDL-C (OR 2.7; 95% CI 1.2 to 6.3)>1.08 mmol/L) TG (OR 2.8; 95% CI 1.2 to 6.6).	For UESTD ▶ MVA, obesity.* ▶ MVA, dyslipidaemia.*

Continued

Table 3 Continued

Study, country	Study design, level of evidence	Cohort characteristics	No individuals with RCRSP/ study sample size	Case definition of RCRSP, pathology reported and duration	Criteria used to classify MetS or cardiometabolic risk factors included	Prevalence of MetS within population (%)	Adjustments for other covariates	Summary: Findings (OR with 95% CI) or p value	Summary: Positive direction of association by UVA or MVA results
Juge *et al*[68] France	Cohort study, level III	Age: 72.4 (±11) Gender: M (n=17, 35.4%), F (n=31, 64.6%)	48/147	Undergoing shoulder surgery for RCRSP shoulder pain, standard radiography RCRSP Unknown duration	No recorded criteria but MetS risk factors meeting definition by WHO: ▲▲▲ Obesity (BMI kg/m^2 calculation). Dyslipidaemia (diagnosed/use of lipid lowering medication or abnormal dosage TG). ▲ Hypertension (diagnosed or use of antihypertensive agents). ▲ Type II DM (diagnosed status or use of antidiabetic medication).	Total: 12.9% (n=19)	Age, CVD, hypothyroidism	Metabolic risk factors Independently associated in the presence of RCRSP MVA: ▲ 4 MetS criteria (obesity, dyslipidaemia, hypertension and type II DM) than in shoulder osteoarthritis patients (p=0.03). 2 or 3 criteria no association when compared with shoulder osteoarthritis (p=0.14).	For RCRSP ▲ MVA, MetS criteria (4/5).*

*P<0.05
†P<0.01
DM diabetes mellitus; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; FBG, fasting blood glucose; GHJT, glenohumeral joint; HDL-C, high density lipoprotein cholesterol; NCEP ATP III, National Cholesterol Education Programme (NCEP) Adult Treatment Panel III (ATP III) devised definition for the metabolic syndrome; LDL-C, low density lipoprotein cholesterol;MetS, metabolic syndrome; MVA, multivariate analysis; NOS, Newcastle-Ottawa score; RC, rotator cuff;RCRSP, rotator cuff-related shoulder pain; ROT, rotator cuff tear; ROC, receiver operating characteristic; ROM, range of motion; SCOI, Southern California Orthopaedic Institute - Rotator cuff *tear* classification system; TG, triglycerides; UESTD, upper extremity soft tissue disorders; UVA, univariate analysis; WHR, waist-to-hip ratio.

cardiometabolic risk factors of BMI (β=0.32, p=0.047) and DM (β=1.01, p=0.029).[55] Indicating higher values of BMI and DM are related to a higher probability to detect rotator cuff tears. Similarly, Rechardt *et al*[43] reported no association with pain intensity in RCRSP and MetS, however, did report central obesity (waist-to-hip ratio >0.9, OR 3.3; 95% CI 1.3 to 8.6; waist circumference OR 3.2; 95% CI 1.4 to 7.4) and dyslipidaemia (OR 2.7; 95% CI 1.2 to 6.3) were positively associated when adjusting for age and sex.

DISCUSSION

The low-moderate quality evidence included in this review suggests an association between MetS and RCRSP. From the six studies included (one good quality, one low quality and four medium quality) it appears there is an association between MetS (and its constituent factors) and RCRSP. Two medium quality studies reported no association with MetS, but reported associations between cardiometabolic risk factors (BMI, DM and dyslipidaemia) and painful shoulders with identifiable unilateral rotator cuff tears and with RCRSP. In addition, populations with independent cardiometabolic risk factors associated with RCRSP were identified across all studies (table 3); age >45 years, obesity (notably central adiposity), DM, hypertension and dyslipidaemia.

Obesity, DM, hypertension and dyslipidaemia are components of MetS and are also interrelated. It is therefore difficult to separate the individual versus combined effect of these factors. Previous research on RCRSP has identified relationships with independent cardiometabolic risk factors including adiposity,[41 45 46] diabetes,[54 72] dyslipidaemia[57] and hypertension.[73] For example, an 11-year nation-wide, longitudinal follow-up study of 498 678 people of whom 26 664 developed RCRSP showed a diagnosis of diabetes had a hazard ratio (HR) of 1.47 (95% CI 1.41 to 1.54; p<0.0001) for RCRSP and hyperlipidaemia had a HR of 1.48 (95% CI 1.42 to 1.55; p<0.0001) for RCRSP.[74] Similarly, a 4-year, longitudinal follow-up of 10 044 people with clustered back, neck and/or shoulder pain showing a diagnosis of diabetes had a relative risk of 1.64 (95% CI 1.23 to 2.18) for shoulder pain in males and hyperlipidaemia had a relative risk of 1.19 (95% CI 0.98 to 1.44) for shoulder pain in males.[75] Furthermore, a large case–control study of 5000 patients with RCRSP identified that increased BMI (BMI between 25.1 and 30) was independently associated (OR 1.15; 95% CI 1.02 to 1.31) with RCRSP.[76] Given these associations, RCRSP and cardiometabolic risk factors may share a common aetiology. As yet it is unclear whether the impact of MetS of RCRSP exceeds the sum of all its individual factors. More studies are required to assess the independent contribution of MetS; however, the above aggregative risk factors suggest MetS may play a role in RCRSP.

The postulated pathophysiological mechanisms cannot be fully understood on the basis of available studies. While causality has not been established, associations between low-grade inflammatory biomarkers and RCRSP have been shown. Excess central adiposity is key

constituent of MetS and adipose tissue is a rich source of circulating proinflammatory cytokines; collectively referred to as adipocytokines, including, tumour necrosis factor alpha (TNF-α), IL-1β, IL-1, IL-6, adiponectin, leptin and restinin. Increased cytokine expression has been observed in the subacromial bursa (IL-1 and IL-6) and partial thickness rotator cuff tear tissue (IL-6) from subjects undergoing rotator cuff surgery.[77–79] Also, increased expression serum levels of TNF-α within subacromial bursa specimens have been retrieved during symptomatic rotator cuff tendon surgery.[80] In parallel, reduced level of IL-10 is detected in patients with obesity, dyslipidaemia and insulin resistance.[81] IL-10 is an anti-inflammatory cytokine that modulates the immune system by antagonising the activities of proinflammatory cytokines.[12] It is possible that the resultant increased proinflammatory adipocytokine expression and anti-inflammatory adipocytokine suppression is a risk factor for developing RCRSP.[43]

Dysregulation of adipokines resulting from central obesity contributes to DM.[82] Type I and type II DM has been associated with increased risk of chronic RCRSP.[23 54] Hyperglycaemia has vasodilatory and proinflammatory actions mediated by cytokine suppression. [83] Increased glucose availability had direct effects on tendons of the rotator cuff and can alter the physiological behaviour of tendons.[84] The low-grade, subclinical, but persistent inflammation in DM has been shown to affect collagen crosslinking, proteoglycan content, cytokine activity, which can lead to tendon thickening and matrix degeneration.[23 54 85]

Multifunctional (proinflammatory or anti-inflammatory) proteins such as leptin, adiponectin, resitin and vistafin have been discovered within the adipocytokine family. These are involved with the low-grade inflammation encountered in obese and diabetic subjects linked to the pathogenesis of MetS.[86 87] Little is known about their role within MSK disorders. An association has been reported between increased proinflammatory leptin and pain related to arthrosis of the shoulder.[88] Decreased anti-inflammatory adiponectin levels have been associated to pathological conditions of diabetes and MetS[89] and found to be lower within the synovial fluid of people with shoulder pain.[88] Although little is known about the role of these proteins they may have a role within shoulder pain and metabolic disorders.

There is inconsistency regarding the link between hypercholesterolemia and RCRSP. Longo *et al*[58] found no association between elevated total cholesterol and rotator cuff injury; however, the mean triglyceride concentration was below the threshold 1.7 mmol/L for 62.5% (mean 1.49 mmol/L) to meet the diagnostic criteria required for MetS. In contrast, Abboud *et al*[57] did find a correlation between rotator cuff tears and increased cholesterol levels, specifically with elevated low-density lipoprotein cholesterol (LDL-C) and low HDL-C levels. The mechanism by which dyslipidaemia affects shoulder pain is also unknown. It is hypothesised that due to catabolism of HDL-C increased LDL-C could initiate and maintain, low-grade persistent inflammation within the rotator cuff tendon, as shown in vivo studies on rotator cuff tendon in mice.[23 90] There may also be direct cholesterol deposition within tendon.[91–95] Dyslipidaemia is a known precursor for hypertension and CVD.[96] This may also contribute to RCRSP, as subsequent endothelial damage caused by hypertension and deregulated lipid metabolism has been associated with tissues damage in tendons.[97] This is supported by Gumina *et al*[73] who noted hypertension was associated with a twofold increase of a large rotator cuff tear (OR 2.09; 95% CI 1.39 to 3.16) and fourfold increase of massive rotator cuff tear (OR 4.30; 95% CI 2.44 to 7.58). However, the study was not able to adjust for the range of antihypertensive medication drugs, thus not possible to define this influence on tear dimensions. This tissue damage in the presence of hypertension has been linked to hypovascularity and hypoxia, ultimately depriving tissues of appropriate nutrient exchange.[98] This triggered deregulation of the tendon matrix may lead to symptoms and functional impairments of the affected tendon in RCRSP.[55]

These findings should be viewed with some caution as biological measures do not work in isolation but rather interact with an array of complex systems and consideration of a composite of measures reflecting system functioning.[99] No study has reported biomarkers that might represent potential mediators between MetS and RCRSP.[100] Furthermore, the evidence supporting the influence of postulated MetS-induced inflammatory biomarkers and its association with symptoms in either the acute or chronic stage of RCRSP is lacking.[100] RCRSP has a multifactorial aetiology. It is recommended these findings be considered within a wider management of RCRSP including recognition of increased excitability of the peripheral and central neuraxis or decreased inhibition,[101] psychosocial and work-related factors.[101–103] Clinicians should, however, remain cognisant of cardiometabolic status throughout rehabilitation, particularly in respect to how metabolic stress may precipitate low-grade systemic inflammation[17] and it's purported deleterious impact in RCRSP.

Limitations

This review summarises the potential association between MetS and RCRSP, the basis of which are limited to the outcomes used by the original studies. With no clear consensus across the included literature, the clinical utility of identifying MetS in patients with RCRSP may be questioned.

The diagnostic criteria for RCRSP varied considerably across studies. Including a combination of participant self-reported symptoms, clinical assessment testing and varied radiological imaging techniques, which may impact the reliability and external validity of findings. Furthermore, four studies included an assembled MetS profile, with only two studies stated predetermined criteria used to define MetS. Currently, no universally agreed diagnostic

criteria for MetS or RCRSP exists, which can be used as a comparative within both clinical and research fields. It is recognised that the classification of the NOS scoring criteria ('high', 'moderate' and 'low') adopted in this review is novel and has limited evidence. However, this method of 'grading' can provide context when applying our findings to future research and clinical practice. The standardisation of MetS and RCRSP diagnosis criteria is essential for clinicians and researchers alike to generate research. This allows results to be compared and pooled to make meaningful conclusions regarding metabolic factors in MSK shoulder pain. It is important to consider methodological quality of the included studies as the majority were cross-sectional in which selection bias cannot be avoided. For example, associations maybe accentuated because the investigators accessed pools of RCRSP patients from specialist health centres with access to pools of MetS subjects. Furthermore, it cannot be determined that exposure predetermined disease since data were ascertained at the same time. Overall, the available evidence was of relatively low-moderate quality, specifically, all studies were of level III evidence. With evident methodological concerns, as described above, it is likely the findings from this review will evolve as high-quality studies become available.

Future research

Questions remain on the direction of RCRSP association and therefore on the possibility of an effective management of MetS and vice versa. Initially, researchers should address the need for harmonising the diagnostic criteria for MetS, including the definition of optimal metabolic biomarkers and normative age-related values. The consistency of RCRSP diagnostic criteria also needs to be established in future studies; this will enhance the analysis of results when this review is updated. Cross-sectional design limits causal inference. Well-controlled prospective large-scale studies will be an important next step to examining the relationship between MetS and RCRSP. This should include examining changes in pain, cofounders, health behaviours and biological measures in order to better appreciate potential causal direction. When sufficient homogenous representative samples are available, a repeated systematic review with meta-analysis should be considered to pool data of an adequate sample size to quantify the strength of the association. This may then allow investigations into the effects comorbidity management could influence RCRSP associated symptoms and through which biological pathway they act. Furthermore, this may propose a subcategory of metabolic shoulder pain introducing new ideas of management and prognosis.

CONCLUSIONS

The results of this review suggest a positive association between MetS and RCRSP in six low-moderate quality studies. Specifically, patients with MetS are potentially at higher risk of shoulder pain, rotator cuff tears and more severe rotator cuff tears. While causality has not been established, two studies included in this review have associations between low-grade inflammatory biomarkers and RCRSP.

These preliminary conclusions should be treated with caution due to significant methodological limitations and concerns regarding their validity. It is likely that future high-quality primary studies may challenge these preliminary conclusions.

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