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REVIEW

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Leptin is a potential biomarker of childhood obesity and an indicator of the effectiveness of weight-loss interventions

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Summary

Childhood obesity represents a significant public health concern, imposing a substantial burden on the healthcare system. Furthermore, weight-loss programs often exhibit reduced effectiveness in adults who have a history of childhood obesity. Therefore, early intervention against childhood obesity is imperative. Presently, the primary method for diagnosing childhood obesity relies on body mass index (BMI), yet this approach has inherent limitations. Leptin, a satiety hormone produced by adipocytes, holds promise as a superior tool for predicting both childhood and subsequent adulthood obesity. In this review, we elucidate the tools employed for assessing obesity in children, delve into the biological functions of leptin, and examine the factors governing its expression. Additionally, we discuss maternal and infantile leptin levels as predictors of childhood obesity. By exploring the relationship between leptin levels and weight loss, we present leptin as a potential indicator of the effectiveness of obesity interventions.

KEYWORDS
adipokines, BMI, metabolic disease, obesity, weight loss, weight regain

1 | INTRODUCTION

Obesity represents an escalating global public health concern, manifesting as an epidemic that affects individuals across diverse age groups and ethnic background.[1] It is a multifactorial, chronic disease manifested by the excessive buildup of adipose tissue.[2] According to the World Health Organization (WHO), obesity is often determined by having a body mass index (BMI) of 30 or higher. Over the last few decades, obesity has emerged as a serious global public health challenge, with its prevalence nearly tripling since 1975 and afflicting over 600 million adults worldwide.[3,4] Notably, the surge in obesity is not confined to adults, as childhood obesity has surged at an alarming rate. The WHO reports a surge in the number of overweight children under the age of five, rising from 32 million in 1990 to 41 million in 2016.[5] Similarly, the prevalence of obesity in children and adolescents aged 5–19 years has increased dramatically from 8% to 22% between 1990 and 2022.[6]

Obesity is a complex and multifactorial disease influenced by an interplay of various behavioral, environmental, and genetic factors.[2] The development of childhood obesity is conceptualized by an ecological model that encompasses a complex set of interacting predictors to elevate the child's risk of obesity. These predictors operate at various levels, including the individual child (e.g., behavioral patterns,

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age, gender, and familial predisposition), family (e.g., parental dietary intake and weight status, physical activity, and child feeding practices), and the broader sociodemographic environment (e.g., socioeconomic status, ethnicity, and school physical education and launch programs).[7] Essentially, child risk factors such as poor dietary habits, lack of physical activity, and sedentary lifestyle significantly heighten the risk of childhood obesity. Child characteristics, such as age, gender, and genetic predisposition to weight gain, dynamically interact with these risk factors, influencing their impact on body weight. Furthermore, parental factors play pivotal roles in shaping a child's obesity risk. Maternal obesity, excessive weight gain during pregnancy, and gestational diabetes are linked to higher birth weight. Likewise, suboptimal parenting practices may influence a child's dietary choices and preferences, thereby elevating obesity risk.[8] Environmental factors, such as socioeconomic status, cultural background, and urbanization, have likewise been associated with an increased risk of childhood obesity.[9] These multifaceted factors collectively contribute to the obesogenic environment in children, explaining the rising prevalence of childhood obesity in modern society.[10]

Obesity imposes a substantial disease burden, serving as a prominent risk factor for premature mortality, especially in cases of elevated BMI value.[11] Moreover, it is closely associated with chronic diseases such as cardiovascular disorders, type 2 diabetes, and certain types of cancer, which significantly reduce both life expectancy and quality of life.[12,13] The economic burden of obesity is substantial as well, encompassing expenditures related to healthcare, lost productivity, and disability, amounting to billions of dollars annually.[14]

Several diagnostic methods have been established to measure obesity-related parameters and provide valuable insights for healthcare professionals. The most widely employed methods are BMI, waist-to-hip (WHR) and waist-to-height ratios, waist circumference (WC), body fat percentage (BFP), and visceral fat area (VFA).[15] While BMI remains the most frequently utilized for obesity classification, it exhibits limitations in accurately assessing excessive body fat accumulation. Advanced techniques, such as magnetic resonance imaging (MRI), offer a more precise evaluation of body fat distribution, but their routine clinical availability remains limited.[16] Biomarkers, including adipokines, have recently gained attention as potential diagnostic tools for obesity.[16] Adipokines are bioactive molecules secreted by adipose tissue, playing a crucial role in energy metabolism and inflammation.[17–19] They have been linked to health outcomes associated with obesity and can serve as indicators of adipose tissue dysfunction.[20] One such adipokine is leptin, a hormone primarily produced by adipose tissue, which plays a vital role in the regulation of energy balance and body weight.[21] It exerts its effects by binding to specific receptors in the hypothalamus, activating signaling pathways that suppress appetite and promote energy expenditure.[22] Leptin levels in circulation are directly proportional to the amount of body fat, with higher levels found in individuals with greater adiposity.[23] The association between leptin levels and obesity suggests the potential utility of leptin as a diagnostic tool for assessing obesity. To our knowledge, only one narrative review addressed the potential predictive value of leptin in childhood obesity.[24] Since then, there has been a proliferation of reports in this area, underscoring the necessity for an updated overview.[25] In this review, we delve into the diagnostic tools available for assessing obesity in children, highlight leptin as a novel diagnostic instrument, and explore the effects of weight-loss interventions on leptin levels.

2 | METHODS

We conducted a comprehensive literature review using the PubMed/MEDLINE, Scopus, and Web of Science databases. The search utilized the following terms: "adipokines," "leptin," "biomarker," "childhood obesity," "pediatric obesity," "obesity," and "children." No restrictions were placed on language or publication year. Abstracts of identified studies were screened to determine eligibility, and the reference lists of included studies were examined to supplement the search strategy.

3 | DIAGNOSIS OF CHILDHOOD OBESITY

According to the WHO, obesity is having excessive fat accumulation that impairs health.[6] Various methods are employed to evaluate obesity, but the BMI is the most commonly used method for screening and diagnosing the condition.[26] Although BMI does not provide a direct measure of BFP, epidemiological studies clearly show that a high BMI is correlated with body fatness and is linked to increased morbidity and mortality.[27] The WHO uses BMI cut-offs of 25 and 30 kg/m^2 to classify adults as overweight and obese, respectively.[28] However, in children, BMI varies significantly due to rapid development, and there is no universal agreement on cut-off values. The WHO, the Centers for Disease Control and Prevention (CDC), and the International Obesity Task Force (IOTF) have proposed three main definitions to assess obesity and overweight, using BMI charts standardized for age and sex.[29] The 2000 CDC growth charts encompass sex-specific BMI-for-age percentile curves tailored for children aged 2–19 years. These charts were constructed based on data collected from a series of cross-sectional studies on the US pediatric population collected between 1963 and 1994.[30] To define overweight and obesity, cut-off points above the 85th and 95th percentiles of BMI for age and sex are employed, respectively.[31] The IOTF approach involves age- and gender-specific BMI centile curves constructed from data sourced from six nationally representative datasets spanning six different regions (Brazil, the United Kingdom, Hong Kong, the Netherlands, Singapore, and the United States). Overweight and obesity for children aged 2–18 years are defined by sex- and age-specific BMI cut-off points, which correspond to BMI of 25 and 30 kg/m^2 at the age of 18, respectively.[32] Furthermore, in 2006, the WHO issued growth standards for children up to 5 years of age, derived from data collected from children raised under optimal conditions. The cut-offs recommended for defining overweight and obesity are 2 and 3 standard deviations above the growth reference median for age and sex, respectively.[33] In 2007, the WHO extended growth references to encompass children aged 5–19 years, defining overweight and obesity

as BMI-for-age greater than 1 and 2 standard deviations above the growth curve median, respectively.[34]

Despite its simplicity and low cost, BMI has some limitations. It incorporates lean body mass, fat mass, and total body water mass, making it difficult to estimate the relative weight attributed to body fatness. As a result, BMI tends to overestimate body fat in muscular athletes.[35] Additionally, its accuracy varies according to the degree of fatness, with good predictive power for obesity in relatively fat children and lower sensitivity in relatively thin children. A potential issue known as normal weight obesity (NWO) syndrome can also arise in children who have normal body weight according to BMI but excess fat mass revealed by other techniques that directly measure body fatness. This can result in moderate sensitivity and failure to identify a proportion of children with excess body fat.[36–39] Moreover, the association between BMI and cardiometabolic risks varies among ethnic groups.[40] For example, when compared with Caucasians, Asian populations are known to exhibit greater body fat for the same BMI, and lower BMI cut-offs must be used in such populations while screening for overweight and obesity.[41] Additionally, BMI fails to predict compartmental body fat distribution, which is crucial given that different distribution patterns pose varying health risks.[28]

WC is another anthropometric indicator used for the diagnosis of obesity and correlation with visceral fat.[42] However, its superiority to BMI remains controversial.[43] For children, WC percentiles have been proposed for different countries.[44–46] More importantly, Katzmarzyk et al. developed WC percentiles to predict cardiovascular disease (CVD) risk factors among children between 5 and 15 years of age, and the sensitivity and specificity were comparable to that of BMI among all gender/race groups.[47] Alternatively, visceral obesity can be assessed using waist-to-hip circumference ratio (WHR), and population-based WHR reference percentiles have been developed, although standardization among children is lacking.[48] Moreover, waist circumference-to-height ratio (WC/HT) ≥0.5 has been proposed to be a sensitive tool for the detection of obesity in children.[49]

Measurements of body fat using advanced techniques such as computed tomography (CT) and MRI, dual-energy X-ray absorptiometry (DXA), and bioimpedance analysis (BIA) instruments provide accurate assessments of body composition.[50] The advantage of such techniques is their ability to quantify whole-body adipose tissue and lean tissue. Additionally, some techniques can provide an accurate three-dimensional profiling of body composition, thus allowing for the volumetric distribution of visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) to be obtained for different body compartments.[51] Among these techniques, DXA emerges as a useful tool for pediatric adiposity assessment due to the minimal radiation exposure and the short duration required for the child to remain still. However, DXA lacks the ability to distinguish between visceral and subcutaneous fat.[52] In contrast, MRI and CT allow accurate evaluation of different depots of fat, with CT being unsuitable for routine use in children due to radiation exposure concerns. Although MRI poses no radiation exposure, its requirement for subjects to remain still for prolonged periods poses a significant limitation.[53] Nevertheless, MRI is acknowledged as the gold standard for body composition analysis and differentiation of VAT and SAT.[54] Despite the usefulness of such techniques, they are still far from being applied in routine clinical settings. In fact, most are expensive and more complex to use compared to simple anthropometric measures. Furthermore, no standardized cut-offs have been established that define the amount of fat that is abnormal or pathologic, and it is yet to be determined if this is influenced by gender, age, and ethnicity.[50] Overall, BMI is the prevailing method for evaluating obesity in children, particularly for surveillance. Nevertheless, due to its inadequate diagnostic accuracy in specific clinical contexts, such as in some ethnic populations, novel diagnostic approaches may be needed.[26]

4 | EVALUATION OF SERUM ADIPOKINES IN CLINICAL SETTINGS

The discovery of leptin in the mid-1990s revolutionized the study of adipose tissue, leading to its recognition as an endocrine organ that secretes biologically active molecules known as adipokines. Since then, numerous other bioactive molecules have been isolated from adipose tissue and were shown to exhibit local and systemic effects.[55] In essence, adipokines play a crucial role in regulating glucose and lipid metabolism, energy expenditure, endothelial function, immunity, and cardiovascular health.[20] Changes in the size and number of adipocytes have been linked to alterations in the adipokine secretion profile. Notably, an excess of adipose tissue, as observed in obesity, is associated with an increase in pro-inflammatory adipokines such as resistin, tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) and a decrease in anti-inflammatory adipokines such as adiponectin. This dysregulation in adipokine release creates a state of chronic, low-grade inflammation that contributes significantly to the pathogenesis of obesity-related cardiometabolic complications.[56] Conversely, weight loss is associated with a decrease in pro-inflammatory cytokines, highlighting the dynamic interplay between adipose tissue, adipokines, and metabolic health.[57]

In the quest to identify potential biomarkers for obesity and its associated complications, serum adipokines emerge as promising candidates. Increased adipose tissue mass in individuals with obesity correlates with increased serum concentrations of leptin, potentially contributing to obesity-related metabolic complications. Moreover, higher leptin levels have been identified in various other diseases, such as osteoarthritis,[58] rheumatoid arthritis,[59] Crohn's disease,[60] nonalcoholic fatty liver disease,[61] and multiple sclerosis.[62] Furthermore, osteopontin levels are increased in patients with obesity, hence contributing to heightened inflammation within adipose tissue.[57] Likewise, resistin levels correlate positively with obesity and BMI, with evidence pointing to its involvement in the development of atherosclerotic lesions in patients with type 2 diabetes.[63] Elevated serum resistin levels have also been reported in patients with Crohn's disease,[60] rheumatoid arthritis,[59] and sepsis.[64] Conversely, resistin levels appear to be lower in patients with major depressive disorder.[65] Furthermore, circulating levels of chimerin are increased in patients with obesity and insulin resistance and have been found to positively

correlate with blood pressure and cholesterol levels.[66] Collectively, these findings underscore the potential of serum adipokines as biomarkers for inflammatory diseases, highlighting their role in the diagnosis and management of such conditions.

5 | BIOLOGICAL FUNCTIONS OF LEPTIN

Leptin is a polypeptide hormone that is encoded by the leptin gene (ob gene) located on chromosome 7. It is primarily produced by the adipocytes of white adipose tissue (WAT) in proportion to fat stores.[67] It plays a crucial role in the regulation of food intake and energy expenditure, primarily through its actions on the hypothalamus in the brain. Specifically, leptin has been demonstrated to activate anorexigenic pro-opiomelanocortin (POMC) neurons while inhibiting orexigenic neuropeptide Y and agouti-related protein (NPY/AGRP) neurons in the arcuate nucleus of the hypothalamus (Figure 1).[68] Beyond its central role in appetite regulation, leptin exerts influence over a range of physiological functions, including the regulation of glucose and lipid metabolism, hematopoiesis, neuroprotection, immune responses, and reproductive processes.[69] Notably, in mouse models with leptin deficiency (ob/ob mice) caused by a non-sense mutation in the leptin gene's coding region, a characteristic phenotype has emerged, including hyperphagia, obesity, diabetes, and hypogonadism. Similar observations have been made in extremely rare cases of humans lacking leptin due to genetic mutations, wherein they display hyperphagic obesity and decreased energy expenditure. Importantly, administration of exogenous leptin has been shown to ameliorate the defects observed in leptin-deficient patients.[70]

Leptin receptor (LepR) belongs to the type I cytokine receptor family. Alternative splicing of the LepR primary transcript produces six LepR isoforms, which fall into three categories: short (LepRa, LepRc, LepRd, and LepRf), long (LepRb), and secreted (LepRe) isoforms.[71] All isoforms share a common N-terminal domain that binds to leptin. LepRe serves as the primary leptin-binding protein in the plasma and regulates leptin signaling activity by maintaining equilibrium between free and protein-bound leptin. The short and long isoforms are membrane-bound, differing mainly in their C-terminal intracellular domains. In contrast to the short isoforms, LepRb has an extensive cytoplasmic domain that houses multiple motifs crucial for activating the Janus kinase 2 (JAK2)–signal transducer and activator of transcription (STAT) signaling pathway. This isoform is predominantly expressed in brain regions responsible for regulating energy homeostasis, underscoring its central role in mediating the effects of leptin in the control of body weight and metabolism.[72] In fact, LepRb-deficient db/db mice display a characteristic phenotype similar to that of ob/ob mice.[73] Leptin-responsive neurons in the brain orchestrate leptin's effects by (i) modulating ingestive behavior and promoting satiety and (ii) increasing sympathetic impulses towards WAT, thereby stimulating lipolysis in adipocytes. Furthermore, leptin stimulates the secretion of

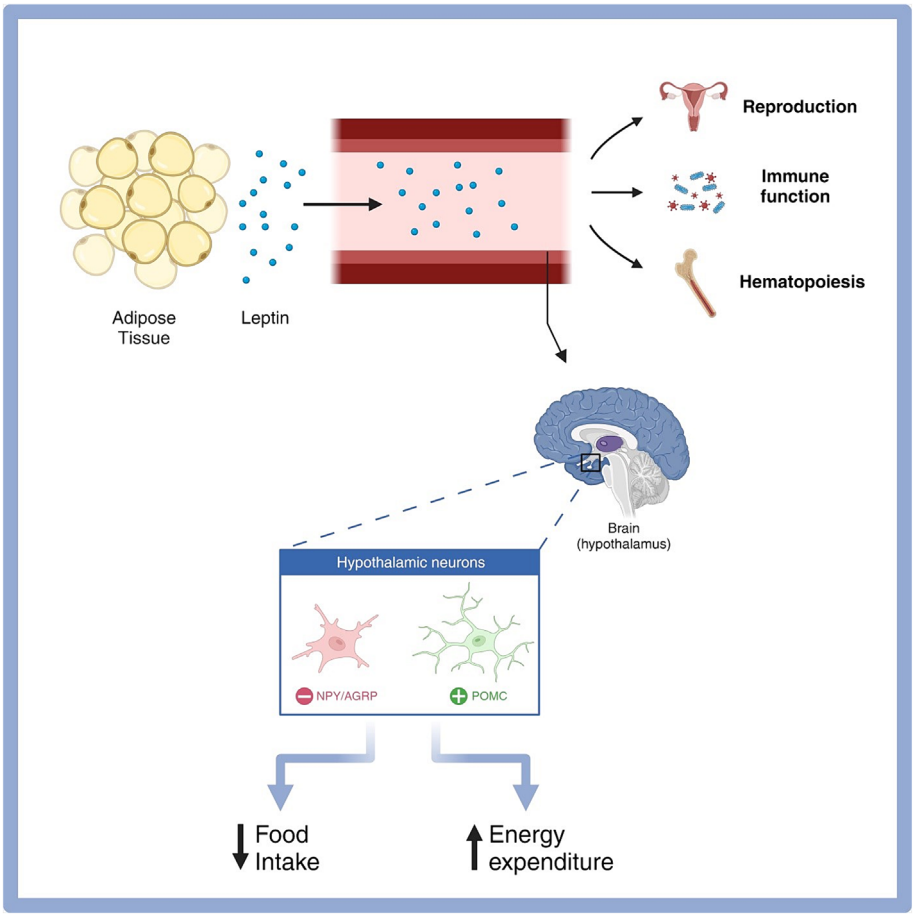

FIGURE 1 Leptin's function in the body. Leptin is primarily produced by adipocytes in white adipose tissue, and its secretion is proportional to the amount of fat stores. It exerts its effects over a range of biologic functions, including the regulation of pubertal development and reproduction, immune responses, and hematopoiesis. Furthermore, leptin modulates energy balance by acting on the brain's hypothalamus. When leptin reaches the brain and binds to its receptor (LepRb) in the arcuate nucleus of the hypothalamus, it activates pro-opiomelanocortin (POMC) neurons while simultaneously inhibiting neuropeptide Y and agouti-related protein (NPY/AGRP) neurons. This leads to increased energy expenditure and reduced food intake.

thyrotropin-releasing hormone (TRH), thus enhancing energy expenditure through the hypothalamic–pituitary–thyroid axis.[74] Surprisingly, humans with obesity and diet-induced obese animals demonstrate higher levels of circulating leptin and a diminished response to exogenous hormone treatment. This diminished ability of leptin to induce satiety and provoke weight loss in subjects with obesity has given rise to the concept of leptin resistance.[75] Several mechanisms have been put forth to explain leptin resistance, including impairment in the transport of leptin across the blood–brain barrier (BBB), hypothalamic inflammation, and endoplasmic reticulum stress.[76] However, impaired leptin signaling remains a hallmark of leptin resistance in individuals with obesity. Leptin–LepRb signaling leads to the activation of STAT3, which translocates to the nucleus and drives the expression of target genes, including suppressor of cytokine signaling 3 (SOCS3), a negative feedback regulator of leptin signaling. During obesity, elevated leptin levels result in the overexpression of SOCS3, which blunts LepRb signaling and contributes to leptin resistance (Figure 2).[77] Furthermore, overexpression of SOCS3 is associated with the development of metabolic disorders, such as insulin resistance and glucose intolerance.[78] Additionally, obesity-associated hyperleptinemia has been shown to promote monocyte proliferation and recruitment, macrophage activation, and the release of pro-inflammatory cytokines such as IL-6, TNF-α, and interleukin-12 (IL-12). In this context, the elevated leptin levels associated with obesity appear to play a pivotal role in linking obesity, insulin resistance, and related metabolic disorders.[79]

6 | REGULATION OF LEPTIN EXPRESSION

The leptin gene is predominantly expressed in WAT, the most abundant form of adipose tissue in humans. WAT serves as a long-term fuel reserve, which is released during periods of food deprivation, and it also functions as an endocrine organ by releasing adipokines.[80] While WAT is the primary source of leptin synthesis, other tissues also produce this hormone in lower quantities. These tissues include skeletal muscle, placenta, brain, pituitary gland, and mammary epithelium.[81–83] The concentration of leptin in the bloodstream directly correlates with the percentage of body fat. Notably, increased adiposity is associated with elevated leptin levels, indicating a positive association between leptin and adipose tissue.[84] Furthermore, the levels of leptin mRNA are positively correlated with adipocyte size, with hypertrophic adipocytes displaying increased leptin expression compared to smaller adipocytes within the same subject.[85] Moreover, leptin expression is influenced by the nutritional status, regardless of adiposity. Energy deprivation results in decreased leptin levels prior to any discernible impact on body weight or overall body fat. This reduction in leptin levels stimulates appetite and initiates an anabolic response aimed at restoring energy stores. Conversely, upon refeeding, leptin levels promptly return to baseline.[86] This interplay between leptin, adipose tissue, and energy balance highlights the intricate role of leptin in the regulation of body weight and metabolic processes.

Circulating leptin concentrations are significantly influenced by gender, irrespective of total fat mass. In the adult human population, females exhibit approximately threefold higher leptin levels per unit of fat mass in comparison to males.[87] This gender-related disparity may be attributed to variations in body fat distribution, where women tend to have larger quantities of subcutaneous fat, which also contain higher levels of leptin.[88] In fact, it has been demonstrated that leptin expression in subcutaneous tissue of humans is three to five times higher than in omental adipose tissue.[89–92] Important to mention, prepubertal leptin concentrations per unit of fat mass do not display significant differences between boys and girls; however, across puberty,

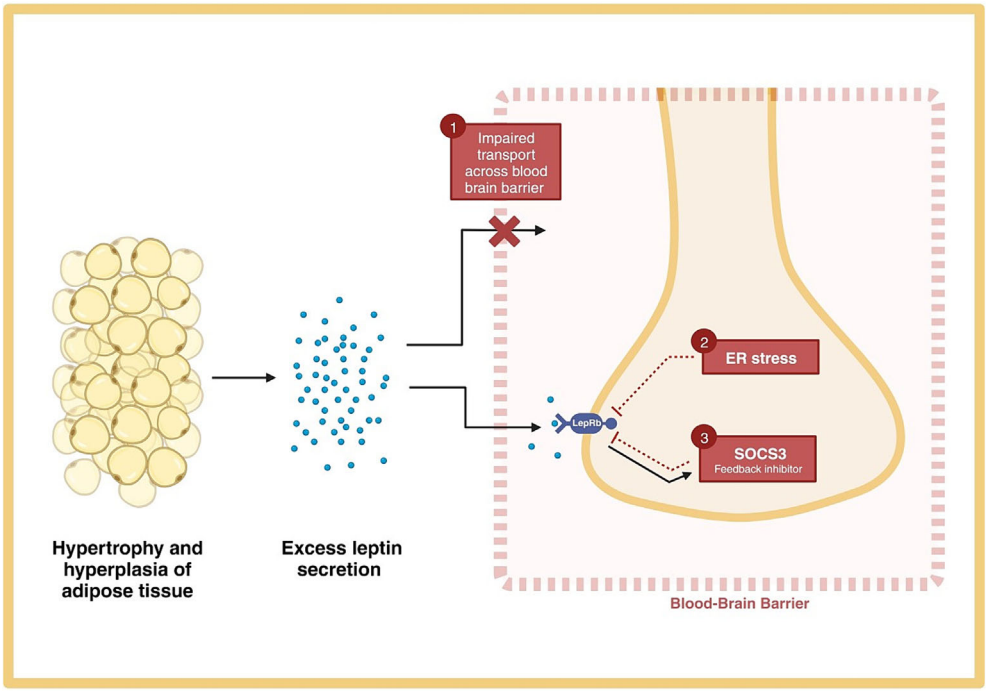

FIGURE 2 Mechanisms underlying leptin resistance. In diet-induced obesity, higher fat stores result in increased leptin secretion, leading to overactivation of the leptin receptor and elevated suppressor of cytokine signaling 3 (SOCS3) expression. This forms an inhibitory feedback loop, reducing leptin signaling. Furthermore, obesity is also linked to heightened endoplasmic reticulum (ER) stress and impaired transport of leptin across the blood–brain barrier. These factors collectively contribute to leptin resistance.

leptin levels increase in girls while decreasing in boys.[93] In this context, several reports highlighted leptin's potential role as a mediator between energy stores and pubertal timing. Studies have shown that leptin plays a permissive role in initiating puberty by acting on gonadotropin-releasing hormone (GnRH) neurons in the hypothalamus. Importantly, conditions characterized by leptin deficiency are often associated with delayed or absent puberty,[94] with the administration of leptin ameliorating these conditions by virtue of its ability to induce puberty onset in such cases. Similarly, reductions in leptin levels due to energy deprivation, such as in anorexia nervosa, are linked to disrupted gonadotropin secretion and secondary amenorrhea.[95] Intriguingly, individuals with obesity, who typically have elevated leptin levels, may exhibit a hypogonadal state. This phenomenon is partly attributed to leptin's inhibitory action on other components of the hypothalamus–pituitary–gonads (HPG) axis, particularly the gonads.[96]

Leptin expression is also regulated by endocrine signals (Figure 3). Notably, insulin and glucocorticoids appear to increase leptin expression, whereas catecholamines and thyroid hormone exert a downregulating effect.[97] Moreover, in vitro studies have shown that leptin secretion increases following the incubation of rat epididymal adipose tissue with insulin, suggesting that insulin also promotes leptin secretion.[98] Additionally, agents that inhibit lipolysis, such as prostaglandin E_2 (PGE_2), stimulate leptin synthesis, whereas hormones that increase lipolysis, such as growth hormone, have the opposite effect.[99] Certain pro-inflammatory cytokines, such as TNF-α, IL-6, and interleukin-8 (IL-8), elicit a biphasic change in leptin release, characterized by an acute increase in leptin secretion followed by a long-term suppression of both leptin expression and secretion.[100]

7 | MATERNAL LEPTIN LEVELS AS A POTENTIAL MARKER OF OFFSPRING OBESITY

Leptin levels exhibit a well-documented physiological increase during pregnancy and play a significant role in fetal–placental communication.[101] Research has unveiled a connection between maternal leptin levels during pregnancy and childhood obesity. Indeed, a study evaluating the effect of maternal leptin on neonatal adiposity, as measured by air displacement plethysmography, was conducted in a cohort of 61 pregnant women. This study reported that neonates born to mothers with leptin levels exceeding the median displayed a 2% higher adiposity compared to those born to mothers with lower leptin levels. Interestingly, this study did not find a significant correlation between neonatal adiposity and maternal body weight in this context.[102] In support of this, another study reports that higher maternal leptin levels are linked to a greater gain in BMI standard deviation score (BMI-SDS) in the first year of life, indicating that this effect is not limited to birth weight.[103] On the other hand, another group examined the rate and timing of leptin changes during pregnancy, rather than solely focusing on its absolute levels.[104] Although it is clear that serum leptin baselines are higher in pregnant women with obesity, this study suggested that a more rapid increase in leptin levels during the second half of pregnancy, particularly in these women, was associated with a decrease in fetal birth weight (aBW).[104,105] This is to say that the more the change in leptin levels resembles the physiologic changes in a normal pregnancy, the better the outcomes are on fetal birth weight.

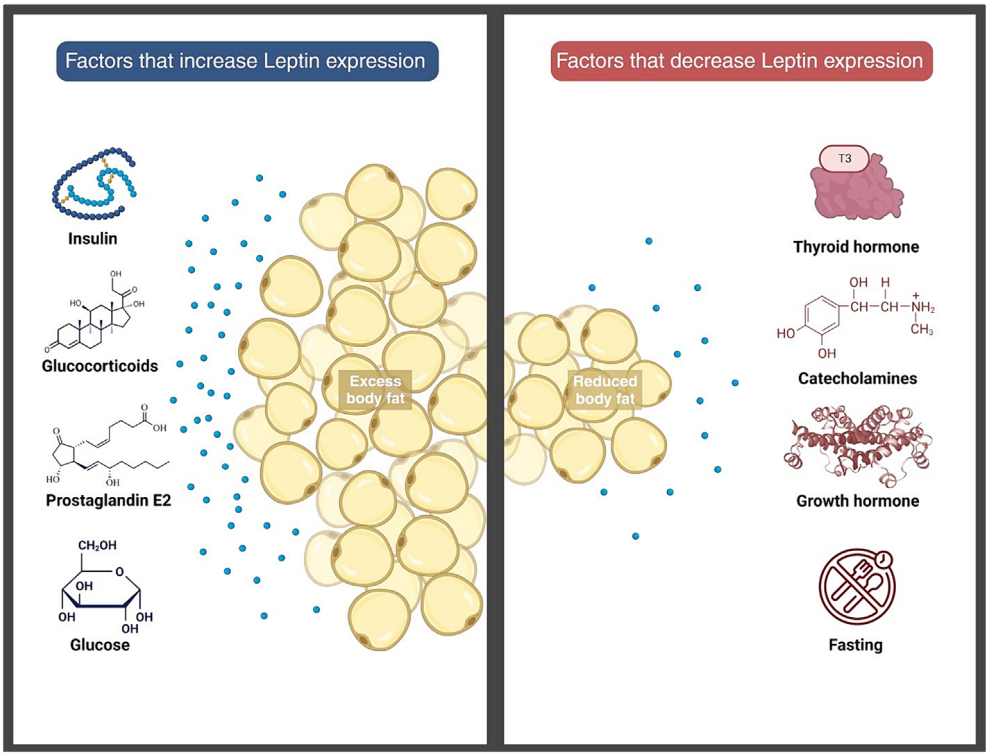

FIGURE 3 Factors regulating leptin expression. Leptin secretion is regulated by various factors. Increased secretion occurs in response to excess adiposity, elevated levels of glucose, insulin, glucocorticoids, and certain inflammatory cytokines, such as prostaglandin E_2. Conversely, secretion is downregulated by factors including thyroid hormone, catecholamines, growth hormone, and states of energy deprivation.

8 | CORD LEPTIN AND CHILDHOOD OBESITY

Cord leptin levels refer to the amount of leptin present in the blood of a newborn baby's umbilical cord. Cord leptin primarily originates from fetal adipose tissue and, to a lower extent, from placental tissue, as maternal leptin cannot readily cross the placenta. The presence of cord leptin can be detected as early as 18 weeks of gestation, with levels increasing progressively as pregnancy advances.[106] Interestingly, LepRs are identifiable in various fetal tissues, including cartilage, brain, lung, and kidney, suggesting a potential role for fetal leptin in regulating intrauterine development.[107] Indeed, a growing body of research is investigating the relationship between cord leptin levels and various health outcomes, including infant growth velocity, birth weight, and child growth trajectories. Lower levels of leptin in cord blood at birth are associated with smaller size and reduced adiposity, as assessed by measuring skinfold thicknesses.[108,109] However, these lower levels are correlated with more significant weight gain in the first 6 months of life, as well as a greater BMI *z* score at the age of 3 years.[103,108,109] Notably, a sexual dimorphism in leptin sensitivity programming, with this 3-year effect of cord leptin predominantly noted in boys, has been proposed. Moreover, a correlation between cord leptin levels and adiposity at the age of 5 was not established.[109] These observations might align with the hypothesis that a newborn experiences a critical period of leptin sensitivity, followed by a subsequent period of leptin resistance.

9 | CHILDHOOD LEPTIN AS A PREDICTOR OF ADULTHOOD OBESITY

Childhood leptin levels can emerge as a significant predictive factor in anticipating the development of obesity during adulthood. In a study involving children at a high risk for adult obesity due to early-onset childhood overweight and/or parental overweight, it was observed that higher baseline serum leptin concentrations were associated with greater BMI and DXA-estimated fat mass over time, irrespective of baseline BMI or fat mass.[110] Another prospective study on non-obese children aged 6–11 years reported that higher baseline leptin levels and leptin-to-adiponectin ratio positively correlate with greater increase in BMI *z* score and WC/HT over the 6-year follow-up period.[111] Nevertheless, it is crucial to address the age at which children begin to exhibit leptin resistance. For example, in a weight-loss intervention study, children with higher leptin concentration regained less weight following the intervention.[112] This suggests that the children had likely not yet developed leptin resistance, as a high level of leptin promoted satiety and hence resulted in decreased weight regain. The authors explained this observation by noting that the follow-up data were collected from younger children with less obesity. These findings, along with evidence highlighting the inverse association between cord leptin and body fatness during the early years of life, underscore the importance of accurately characterizing the pathophysiology of leptin resistance and developing indices to accurately estimate this resistance. Essentially, a lower degree of obesity and a younger age may maintain responsiveness to leptin and its appetite-regulating effects, emphasizing the need for early intervention in the treatment of childhood obesity before it progresses into adulthood obesity.

10 | LEPTIN MODIFICATION IN RESPONSE TO WEIGHT REDUCTION

The regulation of food intake and body weight involves a complex interplay between the brain and peripheral organs. The hypothalamus in the brain assumes a central role in this process, orchestrating food intake by integrating both peripheral and central signals through a combination of homeostatic and hedonic mechanisms.[113] Following a meal, specialized chemoreceptors and mechanoreceptors on the surface of gut neuroendocrine cells detect nutrient stimuli. This prompts the release of key satiety hormones, including cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), and pancreatic polypeptide (PP). These neurohormonal satiety signals, originating in the gastrointestinal tract, then travel through the bloodstream and the vagal afferents to reach the brain. They provide pivotal information regarding the body's nutritional status on a meal-to-meal basis, effectively regulating appetite between meals.[114] Leptin, produced by adipose tissue, serves as another key player by communicating the body's fat stores to the brain. It exerts its influence by inhibiting orexigenic neurons and stimulating anorexigenic neurons in the arcuate nucleus of the hypothalamus, helping to suppress food intake during periods of energy surplus.[115] Despite these homeostatic mechanisms aimed at maintaining body weight stability, individuals with obesity often consume quantities of food that exceed their metabolic needs. In fact, the hedonic pathway related to the pleasurable aspects of food consumption can override the homeostatic pathway and stimulate food intake independently of energy deficits.[116]

Energy-restricted weight loss prompts compensatory adjustments in the biological pathways regulating food intake and energy hemostasis, which are aimed at restoring energy stores and increasing nutrient availability.[117,118] One significant feature of weight loss is the decrease in circulating leptin levels. This reduction in leptin concentration is related to the reduction in fat mass, as leptin gene expression is proportional to body fat mass.[119] Importantly, this reduction in leptin levels occurs independently of the modality used for weight loss. For instance, in a study involving children and adolescents with obesity, a 2-month inpatient weight-loss program comprising dietary restriction and daily physical activity led to a significant decrease in plasma leptin levels.[120] Furthermore, a recent systematic review and meta-analysis demonstrated that pharmacologic treatment of obesity by GLP-1 agonists leads to a significant decrease in leptin concentrations.[121] Similarly, weight loss through surgical interventions is associated with a comparable reduction in leptin levels.[122] In a study evaluating the impact of Roux-en-Y gastric bypass or vertical sleeve gastrectomy surgery on adipokines in adolescents with severe obesity, leptin levels

significantly decreased 12 months after surgery.[123] Interestingly, plasma leptin levels decrease to a greater extent than what would be expected for the lost fat mass. For example, a 10% decrease in fat mass among adult women with obesity results in an average drop of plasma leptin levels by 30%.[124] This disproportionate reduction in plasma leptin is consistent across various weight-loss protocols and can be attributed to the reduction in adipocyte volume during weight-loss interventions.[125,126] In a study involving 10 women with obesity who reached a non-obese state (BMI < 30 kg/m^2) after either bariatric surgery or lifestyle modification, weight loss was accompanied by reductions in fat cell volume, leptin secretion, and plasma leptin concentrations. Interestingly, the fat cell volume and adipocyte leptin production were lower in the post-obese subjects compared to controls matched for the percent body fat and BMI.[127] This decline in leptin levels following weight-loss interventions results in a state of leptin insufficiency. In fact, leptin supplementation as an adjunct of energy restriction enhances weight loss in human adults in a dose-dependent fashion.[128,129] Furthermore, the decrease in leptin levels after weight loss increases the risk for weight regain by inducing changes in energy intake and expenditure. Specifically, human adults who maintain a reduced body weight at 10% below initial body weight demonstrate brain activity consistent with heightened sensory and emotional responses to food and reduced control over food intake. These changes are reversed by leptin administration, resulting in a neural activity similar to that observed prior to weight loss.[130] Additionally, leptin repletion has been shown to reverse the decrease in satiation observed in individuals attempting to maintain weight loss.[131] Maintenance of reduced body weight is also associated with reduced energy expenditure. This reduction can be attributed to increased skeletal muscle work efficiency, decreased sympathetic tone, and decreased thyroid hormone levels. Notably, these changes are reversed by leptin supplementation.[132,133] The alterations in energy intake and expenditure observed in individuals maintaining a reduced body weight, combined with their responsiveness to leptin, suggest that neural circuits interpret the weight-reduced state as a state of leptin insufficiency, which predisposes the individual to weight regain.

11 | LEPTIN AS A PREDICTOR OF RESPONSE TO WEIGHT-LOSS INTERVENTIONS

The role of the neuroendocrine system in predicting responses to weight-loss interventions remains inadequately identified. Attempts have been made to forecast the outcomes of lifestyle interventions by assessing baseline plasma leptin levels. Among adult individuals with obesity, it has been observed that higher baseline leptin concentrations were inversely correlated to the extent of weight loss achieved through lifestyle interventions.[134–136] This inverse relationship between hyperleptinemia and weight loss is likely due to the presence of leptin resistance in subjects with obesity. In such cases, elevated leptin levels fail to effectively suppress appetite and increase energy expenditure. Similar trends have been identified in children with obesity who participated in weight-loss programs, where a higher baseline leptin level was found to be a poor predictor of weight loss during the intervention.[120,137,138] Furthermore, the percentage reduction in leptin levels showed a positive correlation with the amount of fat loss in children. Interestingly, children with high baseline leptin levels who experienced substantial reductions in leptin during weight loss exhibited the most significant improvements in lipid profile and insulin sensitivity. Hyperleptinemia in children may thus not necessarily signify leptin resistance; instead, weight loss can lead to significant reductions in leptin levels that, in turn, predict favorable metabolic outcomes.[120]

The link between baseline leptin and weight-loss maintenance has also been explored. However, studies have yielded inconsistent findings, showing negative, positive, or no correlation between baseline leptin levels and weight regain.[139–141] For instance, in a study involving children aged 8–18 years, a high baseline leptin level was associated with less weight regain following a weight-loss intervention.[112] Conversely, opposite results were observed in studies involving adults.[140–142] These conflicting outcomes may be attributed to variations in leptin responsiveness, with children suffering from obesity not yet displaying leptin resistance. Consequently, higher leptin levels promote satiety and assist in maintaining weight.

12 | CONCLUSION

Childhood obesity is a pressing concern in many countries today. While BMI is commonly employed to anticipate the development of obesity, its accuracy is limited. Moreover, BMI proves suboptimal for monitoring a child's weight changes and response to weight-loss treatments, as it cannot discern the proportion of body mass attributable to body fatness. Given this inability to distinguish between adipose tissue and lean tissue, it is imperative to replace BMI with markers that provide a more precise assessment of a child's excess fat. Maternal serum leptin concentration holds promise as a potential marker for predicting a neonate's susceptibility to childhood obesity. Moreover, substantial evidence has consistently demonstrated that a child's serum leptin concentration can forecast the success of weight-loss interventions and even anticipate the risk of adult obesity. Future research in this domain should prioritize addressing gaps in our understanding of the link between a child's serum leptin concentrations, those of the prenatal mother, and the child's subsequent development of obesity. Additionally, forthcoming investigations should delve deeper into gender-specific variations in the utility of leptin for predicting adult obesity and evaluating the effectiveness of weight-loss interventions.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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