

# The Influence of Leptin Resistance on the Development of Childhood Obesity

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## ABSTRACT

The rising global prevalence of obesity presents a diminished quality of life and life expectancy. Though a myriad of factors contributes to obesity, one of the leading factors is excessive adipose tissue accumulation increases the body's production of the leptin satiety hormone resulting in leptin resistance. Leptin resistance results in increased vulnerability to obesity through improper regulation of insulin, a decline in metabolic functions, and decreased sex hormone levels. Leptin resistance is treated with natural treatments, leptin replacement therapy, testosterone replacement therapy, and insulin-sensitizing drugs, although all are met with limited results. Since leptin vastly affects sex hormone levels, leptin resistance has an adverse effect on obese children and adolescents. In this review, we examine the causes of leptin resistance, treatments for leptin resistance, and the effect of leptin resistance on childhood development.

## Introduction

Obesity, defined by the World Health Organization as excessive fat accumulation, is a chronic medical condition that results from an imbalance of energy expenditure and consumption (CDC, 2022; Whitlock et al., 2009). Obesity presents a significant health challenge due to it substantially increases the risk of particular diseases, such as type 2 diabetes mellitus, fatty liver disease, hypertension, myocardial infarction, stroke, dementia, osteoarthritis, obstructive sleep apnoea, and several cancers, that contribute to a decline in both quality of life and life expectancy (Blüher, 2019). Moreover, the global prevalence of obesity among adults and children has tripled from 1975 to 2016, with obese children and adolescents of five to nineteen years old increasing from 4% to 18% (Shephard, 2011; *World Health Organization*, 2022).

Recently, obesity has become the leading cause of preventable illness, disability, and premature death due to various behavioral, socioeconomic, genetic, environmental, and psychosocial factors. Though the leading cause of obesity can be attributed to excess caloric intake, metabolic abnormalities that frequently occur within an obese individual's hormonal functions have been shown to contribute to obesity. For instance, studies have shown that mutations in the gene coding for leptin, leptin receptors, melanocortin receptors, and pro-opiomelanocortin might cause severe obesity in humans, underlining the importance of biological factors in the pathogenesis of obesity (Blüher, 2019). The body's metabolic functions are disrupted when excessive calories are consumed since the accumulation of adipose tissue, commonly known as body fat, fails to perform its metabolic functions. Abnormal levels of adipose tissues often diminish energy homeostasis, cause inflammation, induce endocrine dysregulation, and lead to insulin resistance (Revelo et al., 2014).

Obese individuals become notably susceptible to the multifactorial contributors to obesity. This increased vulnerability can be attributed to various interconnected factors, most notably the overabundance of leptin. Leptin, the satiety hormone that is produced by adipose tissue and manages multiple metabolic functions, can induce a phenomenon known as "leptin resistance" when overproduced (Hagan & Niswender, 2012; Friedman & Halaas, 1998). Leptin resistance results in abnormalities in the body's production of sex hormones, which can increase an individual's vulnerability to obesity. Unfortunately, studies have shown that obesity has

increased leptin levels, which begins a terrifying cycle of obesity: increased leptin production, failed hormonal functions, and increased susceptibility to obesity (Koerner et al., 2005; Moon et al., 2011; Kelly & Jones, 2015). Moreover, when such an imbalance of sex hormones is found within children, the effects of puberty are often detrimental to their development. Here we will discuss how leptin resistance emerges, its role in sex hormone development, and how both factors affect childhood development.

## The Relationship Between Leptin Resistance and Obesity

Adipose tissue acts as an endocrine organ that secretes hormones responsible for fuel storage during an energy surplus and fuel mobilization during an energy deficiency. Any alteration to the adipose tissue's ability to alter hormonally driven energy homeostatic processes leads to an imbalance in metabolism and an increased likelihood of obesity (Booth et al., 2016). Comprehensive results of a multitude of studies have shown that obese individuals' abnormally high BMI is a risk factor for the beginning of other pathological disorders, including diabetes, osteoporosis, cardiovascular diseases, and depression (Arora et al., 2019; Isidori et al., 1999; Milaneschi et al., 2012; B. Wang et al., 2014).

The most notable of the satiating hormones produced by the adipose tissue is leptin. The *ob* gene codes for leptin; a deficiency of the *ob* gene, often induced by increased adipose tissues, produces obesity. Leptin plays a critical role in managing many metabolic functions by serving as a satiety hormone that signals the hypothalamus to produce a feeling of fullness (Hagan & Niswender, 2012; Friedman & Halaas, 1998). In addition, leptin controls adipose function by modulating food intake and energy metabolism, which can affect various physiological processes ranging from total daily energy expenditure (TDEE) to fertility (Israel & Chua, 2010; Myers et al., 2010).

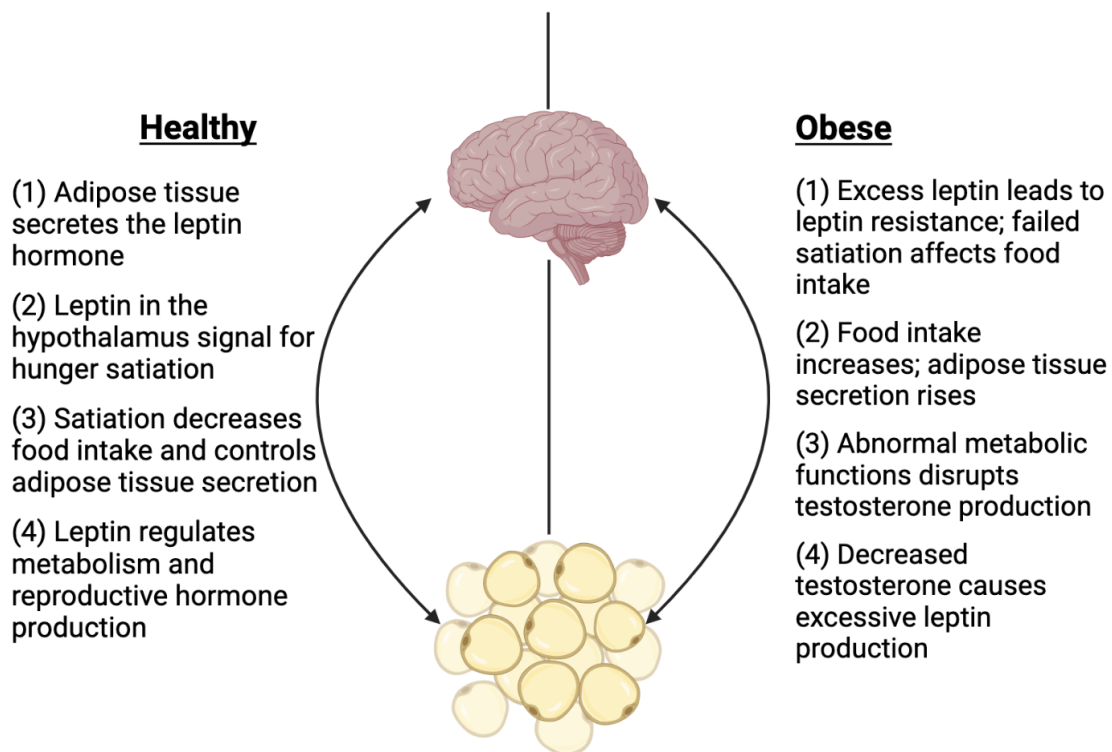


Figure 1. Excess adipose tissue's effect of leptin resistance

When adipose tissue production increases, leptin secretion increases proportionally (Harris, 2014). As such, obesity is most often associated with high circulating leptin levels due to adipose tissue expansion (Hebrand et al., 2007). Obesity-induced leptin overabundance may harm peripheral tissues such as the vasculature pancreas, liver, and skeletal muscle, inducing metabolic dysregulation and low-grade inflammation (Santoro et al., 2015). Under normal conditions, leptin secretion from adipose tissue is suppressed by testosterone (T), and leptin signals the production of T (Kershaw & Flier, 2004). Notably, the relationship between leptin secretion and T is disrupted within obese individuals. Although most obese people have high concentrations of leptin, due to the drastic increase in adipose tissues from their expanded fat mass, these individuals develop a condition known as “leptin resistance,” where they no longer respond to this elevated level of endogenous leptin (Koerner et al., 2005; Moon et al., 2011; Kelly & Jones, 2015). Leptin resistance results in abnormal levels of metabolic and reproductive hormones (Lin et al., 2005; Martin et al., 2008). Ultimately, through the kisspeptin expression pathway, leptin resistance lowers T output (Zhai et al., 2018; Khodamoradi et al., 2022; Isidori et al., 1999), affects the regulation of glucose homeostasis or insulin (Covey et al., 2006), and results in decline in sperm mobility (Zhao et al., 2014).

While there is no consensus on the mechanism of leptin resistance, there are two prominent hypotheses. The most popular mechanism of leptin resistance suggests that the increase in leptin levels results in decreased blood-brain barrier (BBB) permeability. Once produced in the adipose tissues and circulated throughout the blood, leptin must cross the BBB to act on the hypothalamus. It was shown that when serum leptin levels reach about 25-30 ng/mL, leptin concentration in the brain does not increase proportionally (Gruzdeva et al., 2019). The leptin receptor (LepR) in the BBB is responsible for the hormone to enter the CNS (Di Spiezio et al., 2018). Therefore, high leptin levels can cause saturation of LepR and slow leptin transport across the BBB (Liu et al., 2018). Another suggested mechanism of leptin resistance is the overexpression of leptin signaling inhibitory regulations such as SOCS3 and PTP1B. This is proposed to be enacted through proinflammatory cytokines, such as IL-6, responding to prolonged heightened leptin levels. The overexpression of these leptin signaling inhibitory regulators causes the further suppression of leptin signaling (Liu et al., 2018).

## Therapies for Leptin Resistance



**Figure 2.** Therapies for leptin resistance.

Studies have proposed a wide variety of promising strategies to overcome resistance, including, but not limited to, natural methods (e.g., caloric restriction and regular exercise) and hormone therapy. Specifically, natural treatments attempt to increase leptin receptor expression and improve leptin transport (Santoro et al., 2015). However, while leptin resistance is theoretically reversible, the strict diet and lifestyle changes required may be unsustainable and inefficient for obese patients with extreme BMI levels (Berkheiser 2018). As such, leptin replacement therapy is an extreme countermeasure offered to patients with severe leptin deficiency; leptin-based therapies have demonstrated the normalization of the endocrine axes, which can reduce leptin resistance, regulate energy levels, and enhance immune response (Paz-Filho et al., 2011). In addition, leptin-based therapies have been linked to significant weight loss in patients and treatment for prevalent obesity-associated diseases (Paz-Filho et al., 2015). Furthermore, research has shown that leptin administration can help obese children with congenital leptin deficiency and hyperleptinemia patients with extreme insulin resistance by restoring gonadotrophin secretion and the leptin hormone pulsatility pattern.

Alternatively, researchers have supported using T replacement therapy to help remedy leptin resistance and low T levels in obese individuals. It has been suggested that T therapy, in addition to diet, exercise, glycemic control, and PDE-5 inhibitors, should be considered for managing symptomatic hypogonadism in men with type 2 diabetes and serum T below the normal range (C. Wang et al., 2011). Furthermore, Janjgava et al. showed that six months of T treatment in obese men with diabetes mellitus and androgen deficiency could lead to increased free T and leptin levels. Whether these therapies are truly effective for restoring leptin sensitivity is still being evaluated.

Furthermore, studies have shown the efficacy of using insulin therapies to restore leptin sensitivity. One of the most commonly prescribed and practical drug classes to treat leptin resistance is Glucagon-like peptide-1 receptor (GLP-1 agonists). Initially approved by the FDA to treat insulin resistance, these drugs mimic glucagon-like proteins to increase insulin synthesis. This has been shown to increase leptin sensitivity and promote weight loss (Ronveaux et al., 2015). The most popular GLP-1 agonists on the market are Saxenda, Victoza, Byetta, Bydureon, Trulicity, Ozempic, Tanzeum, and Lyxumia.

Another class of drugs approved for insulin resistance that also acts to overcome leptin resistance is sodium-glucose cotransporter-2 (SGLT-2) inhibitors. SGLT-2 is a sodium-dependent glucose cotransporter responsible for glucose absorption in the kidneys. It is shown that SGLT-2 inhibitors result in lowered leptin levels. This is suggested by inhibiting leptin synthesis in adipose tissue (Xu & Ota, 2018). SGLT-2 inhibitors on the market include Invokana, Farxiga, and Jardiance.

## **Leptin Resistance and Childhood Obesity**

Normal puberty consists of two distinct processes: maturation of gonadal function, known as gonadarche, and increased adrenal androgen secretion, known as adrenarche. Leptin has been shown to play an influential role in both pubertal functions. The hormone accelerates gonadotropin-releasing hormone (GnRH) pulsatility in hypothalamic neurons, resulting in the pulsatile secretion of luteinizing hormones (LH) and follicle-stimulating hormones (FSH) during puberty. LH stimulates the T secretion in boys but has shown little effect in girls who have yet to undergo ovulation. On the other hand, FSH stimulates follicle formation and estrogen secretion in girls, with little effect in boys until they undergo sperm production (Shalitin & Phillip, 2003).

Extensive studies have demonstrated that excessive weight gain can alter hormonal parameters, which affect the timing and tempo of pubertal development (Zumoff et al., 1990). As such, obese children may suffer premature adrenarche, thelarche, or precocious puberty (PP) (Pasquali et al., 2003). Though leptin levels induce significant alterations during progressive pubertal stages, there appears to be a distinct dimorphism in the effects of leptin on boys and girls. In boys, a prepubertal peak of serum leptin levels occurs before free testosterone, growth hormones, and insulin-like growth factors (IGF-I) are expressed. Leptin levels then fall to baseline concentrations about three years after the initial rise in serum testosterone levels. On the contrary, increased

leptin levels contribute to increased secretion of estrogen in girls. Even after correcting for body weight and fat mass, girls tend to have higher serum leptin levels than boys (Clayton et al., 1997; Saad et al., 1997).

Studies have concluded that this sexual dimorphism can be attributed to pulse amplitude of leptin secretion, subcutaneous fat distribution, total serum leptin levels, and variability in hormone sensitivity. More specifically, girls tend to exhibit higher leptin secretion pulse amplitudes, higher subcutaneous visceral fat ratios, higher total serum leptin levels, and higher leptin hormone sensitivity in adipose tissues compared to boys (Halleux, 1998; Licinio et al., 1998; McConway et al., 2000; Montague et al., 1997).

The differences in data available for obese girls and boys perpetuate this perceived dimorphism. The association of early pubertal changes with obesity is well-reported and consistent for girls. A cross-sectional study, Healthy Lifestyle in Europe by Nutrition in Adolescence (HELENA), showed that in obese girls, there is an indirect relationship between elevated leptin levels, early puberty, and cardiometabolic or inflammatory markers (Bliss et al., 2010; Palmer et al., 2012). Additionally, obese girls with PP display high leptin levels (Kansra et al., 2020). Moreover, studies have shown that obese girls with premature adrenarche, the sexual maturation of the adrenal gland, carry a higher risk of developing polycystic ovary syndrome (PCOS) in the future (Guercio et al., 2020). Unfortunately, data on the relationship between obesity and pubertal onset in boys has been relatively sparse; for instance, one US study conducted on a group of racially diverse boys showed that obesity brought about both delayed and early puberty in boys, hinting at the multitude of additional components to determine the interconnected relationship between obesity, hormones, and pubertal development in children (Dumesic et al., 2020).

The findings that overweight children, especially girls, tend to mature earlier than lean children have led to the hypothesis that obesity may trigger the neuroendocrine events that lead to an earlier onset of puberty. While androgens and estrogens do not contribute substantially to growth before puberty, they play a crucial role in a pubertal growth spurt. Obese adolescents may experience a premature growth-promoting effect in response to increased leptin levels inducing changes on their IGF-I axis. Moreover, certain clinical conditions allow for normal growth to be accelerated in the presence of low GH serum levels; in these particular cases, the accelerated growth has been associated with obesity (Geffner, 1996; Sorva, 1988). Children with exogenous obesity initially show tall stature for their age, associated with accelerated epiphyseal growth plate maturation (Vignolo et al., 1988). Still, this rapid growth effect stops prematurely because of the advanced bone age, with obese children affected by abnormal growth rates ending up shorter than their adult height potential.

## Conclusion

In obese individuals, the accumulation of adipose tissues is responsible for the overproduction of leptin, reducing the satiety effect of leptin despite its high circulation: a phenomenon known as “leptin resistance.” The reduced sensitivity to the satiety hormone results in improper regulation of insulin, a decline in metabolic functions, and decreased sex hormone levels; this decrease in testosterone production results in an inability to suppress leptin secretion. Abnormal levels of leptin create a cycle of increasing leptin resistance and, as a result, exacerbate the patients’ vulnerability to obesity. While still debated, the possible mechanisms of leptin resistance have been attributed to decreasing blood-brain barrier permeability and/or overexpression of leptin signaling inhibitory regulars.

Researchers note that leptin resistance is reversible and have offered promising solutions: natural methods (e.g., caloric restriction and regular exercise), leptin-based therapies, and T replacement therapy. Researchers note that, despite the favorable results shown by leptin-based therapies, they must be used solely as a “last-resort” countermeasure to patients with severe leptin deficiency. Additionally, drugs used to treat insulin resistance have shown clinical promise to restore leptin sensitivity in obese patients and congenital leptin deficiencies in children.

Leptin has been shown to play an influential role in the maturation of gonadal function and increased adrenal androgen secretion, the two distinct pubertal functions. Though data has revealed sexual dimorphism in the effects of leptin on children, extensive studies have demonstrated that excessive weight gain can alter hormonal parameters for both boys and girls, affecting the timing and tempo of pubertal development. Moreover, while androgens and estrogens show minimal impact on growth before puberty, they play a crucial role during puberty. As such, children with exogenous obesity show rapid but temporary growth induced by accelerated bone growth.

Much work is still to be done to improve understanding of the relationship between leptin resistance and obesity. Most notably, a better understanding of the molecular mechanisms of leptin resistance would be advantageous for developing new drug therapies. Moreover, there is still much to be learned about the influence of leptin resistance on pubertal development.

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