

Obesity and Hypogonadism



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KEYWORDS

• Obesity • Hypogonadism • Testosterone • Diabetes

KEY POINTS

- The relationship between obesity and hypogonadism is bidirectional and there are numerous causative and correlative factors on both sides of the equation.
- Obesity is growing in prevalence in epidemic proportions. Likewise, we are beginning to see the rapid increase in the incidence of male hypogonadism.
- It is only recently that we are learning the ways in which these 2 conditions exacerbate each other.
- We are only beginning to understand how by treating one of these conditions, we can help to treat the other, as well.

INTRODUCTION

It will not be surprising to most people how ubiquitous obesity is today, both in America and throughout the world. Nor should it be surprising how frequently male hypogonadism is diagnosed in recent years. What is of great interest, however, are the mechanisms by which these 2 increasingly prevalent conditions may interact with and exacerbate each other. It is also important to understand how by treating one of these conditions, we may be able to help alleviate the effects of the other as well.

In recent times, obesity has become a global epidemic: the prevalence of obesity has rapidly increased, and obesity-related comorbidities have surged over the past few decades. It is estimated that more than one-third (34.9% or 78.6 million) of U.S. adults are obese and more than two-thirds of U.S. adults are overweight.¹ Obesity is known to lead to other comorbidities, such as hypertension, dyslipidemia, type 2 diabetes mellitus, coronary heart disease, stroke, gallbladder disease, osteoarthritis, sleep apnea, respiratory problems, as well as chronic liver disorders like

nonalcoholic fatty liver disease and its most severe subset, nonalcoholic steatohepatitis.²⁻⁴

It is also important to note that, although much work remains with regard to treatment of obesity, this field has rapidly developed over the past decade. It is no longer appropriate to simply surrender when a patient is unable to lose weight through diet and exercise alone and tell him that we can no longer help him. The specifics of the pharmacologic approaches to treatment of obesity are beyond the scope of this article and may be found in detailed form elsewhere.⁵

In addition to these sequelae, hypogonadism is an important comorbidity of obesity that is often overlooked. Hypogonadism, defined as the presence of low testosterone level measured on at least 2 occasions along with signs or symptoms that are owing to low testosterone, has been shown to be strongly correlated with obesity.⁵ In fact, it has been reported that obesity is probably the single most common cause of testosterone deficiency in the developed world, with approximately 52.4% of all obese men having testosterone levels below 300 ng/dL.⁶ Likewise, weight loss, as a result of diet, exercise, or bariatric

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surgery, can significantly increase testosterone levels in men.⁷ In addition to promoting obesity, hypogonadism has been implicated with a number of other sequelae as well, including sexual dysfunction, osteoporosis, depression, dyslipidemia, and the metabolic syndrome.⁸

Interestingly, the relationship between obesity and hypogonadism seems to be bidirectional, because there is an increase in deposition of abdominal adipose tissue in hypogonadal subjects.⁹ Furthermore, there is evidence to suggest that testosterone replacement therapy may improve body fat mass, waist circumference, and muscle mass, and may thereby be a potential treatment modality for obesity.^{10,11}

Clearly the relationship between hypogonadism and obesity is complicated and questions remain surrounding the degree of correlation and causality between the 2 conditions. What is known is that these 2 conditions have been discovered to coexist with frequency and treatment of one of these conditions may confer potential benefits on the other. There are numerous speculations as to the physiology behind these mechanisms.

The first step to understanding the complex relationship between obesity and hypogonadism is to take a closer look at the underlying driver of obesity itself, namely, adipose tissue. Whereas adipose tissue, or fat, was once considered to simply be a reservoir for storage of high-energy fuels, it is now understood to be a complex, essential, and highly active metabolic and endocrine organ.¹²

ADIPOSE TISSUE AS AN ORGAN

The traditional view of adipose tissue storage has changed over the past 20 years from that of a pure reservoir for energy to what we now recognize as a complex and highly active endocrine and metabolic organ, responding to incoming signals from both the central nervous system and various glands by expressing and secreting essential active proteins. It is also now well-known that adipose tissue is a major site for the metabolism of sex steroids and glucocorticoids. To better understand this relationship, we will analyze the function of adipose tissue with respect to the hormones it regulates and produces, and the different types of adipose tissue that exist.

As an endocrine and metabolic organ, adipose tissue expresses and secretes active metabolic factors, such as leptin, tumor necrosis factor (TNF)-alpha, interleukin (IL)-6 and adiponectin.¹³ Leptin, the "satiety hormone," is a hormone made by adipocytes that helps to regulate energy balance by inhibiting hunger.¹⁴ Although the majority of leptin's effects are mediated via hypothalamic

pathways, some are mediated directly by peripheral tissues, including muscle cells and pancreatic beta cells. It is known that, with caloric restriction and weight loss, leptin levels decrease quickly, leading to an increase of appetite and lower basal level of energy expenditure. This response is preserved in morbidly obese humans who are leptin deficient, and returns to normal if low-dose leptin replacement is given. In turn, obesity is typically associated with increased levels of leptin, which do not decrease after administration of exogenous leptin, suggesting that these individuals are leptin resistant.¹⁵

TNF-alpha is also expressed in adipose tissue, and is implicated in causing obesity and insulin resistance. Plasma levels of TNF-alpha have been positively correlated with obesity in some studies.¹⁶ As of late, attention has focused on the adipose tissue production TNF-alpha in metabolic syndrome and type 2 diabetes mellitus, as the levels are elevated, creating a proinflammatory state associated with insulin resistance and endothelial dysfunction.¹⁷ Furthermore, higher levels of TNF-alpha (as well as other proinflammatory cytokines) may influence the secretion of pituitary gonadotropins.¹⁸

Likewise, IL-6 is another protein that is expressed by adipose tissue and is associated with obesity and insulin resistance.¹³ In fact, it has been reported that a sedentary lifestyle may be accompanied by the infiltration of immune cells with proinflammatory characteristics in adipose tissue, causing an increased release of cytokines such as IL-6 and generating a low-grade inflammatory state. This in turn, may lead to such conditions as insulin resistance, and this may improve with reduction of fat mass.¹⁹

Adiponectin, on the other hand, is a hormone derived from adipose tissue that seems to convey protection from cardiovascular disease and increased insulin sensitivity; it also has a beneficial effect on postprandial glucose and lipid metabolism.²⁰ In contrast with the majority of the other adipokines that have been identified, plasma levels of adiponectin are decreased significantly in obese patients, and are negatively correlated with body mass index.²¹

Over the years, we have also come to understand that the function of adipose tissue is largely determined by its location. Visceral adipose tissue secretes its endocrine hormones directly into the portal system, whereas subcutaneous tissue secretes into systemic circulation. Hence, visceral adiposity has a greater effect on hepatic metabolic function. Expression of IL-6 is higher in visceral adipose tissue, whereas expression of leptin is higher in subcutaneous tissue. Finally, these different

types of tissue respond differently to afferent signals, largely because visceral tissue has higher levels of glucocorticoid and androgen receptors. Most interesting, however, is that visceral fat is associated with increased metabolic risk and mortality, whereas subcutaneous fat expansion actually improves insulin sensitivity, and reduces the risk of type 2 diabetes.^{22,23}

Hence, we can see that adipose tissue acts as much more than just a store for excess energy—it plays a major role in energy regulation and metabolism.

HYPOGONADISM AS AN ENDOCRINE DISEASE

Before we discuss obesity and its relationship with low testosterone, we will take a brief look at the physiology of normal gonadal function, and the pathophysiology of hypogonadism.

Testosterone is an essential anabolic steroid hormone that is secreted primarily by the testes, along with minor contribution from the adrenal glands.²⁴ Synthesis of this hormone is regulated through feedback control over the release of hypothalamic gonadotropin-releasing hormone (GnRH), which then stimulates the anterior pituitary gland to release gonadotropins, follicle-stimulating hormone, and luteinizing hormone, which in turn promote production and secretion of testosterone and help regulate spermatogenesis.²⁵ Testosterone, along with its 5- α reduction metabolite, dihydrotestosterone, exerts its effects via activation of the androgen receptor as well as via activation of the estrogen receptor by its aromatization metabolite, estradiol (E2). The majority of circulating testosterone is bound to proteins, mostly to sex hormone binding globulin (SHBG) and to a lesser extent serum albumin. Only a very small fraction of testosterone (about 1%–2%) is unbound, or “free,” and thus biologically active and able to enter a cell and activate its receptor.²⁶ Upon binding to the androgen receptor, testosterone functions to regulate mitochondrial activity, increasing mitochondrial number, activating respiratory chain components, and increasing transcription of genes responsible for oxidative phosphorylation.²⁷

Hypogonadism in men refers to a diminished functional activity of the testes that results in diminished testosterone production and secretion. Hypogonadism can be subdivided into primary and secondary hypogonadism, according to whether the defect is inherent within the testes or lies outside of the testes, respectively.²⁸ Primary hypogonadism is much less common, and is typically owing to hypofunction of the testes in the

presence of normal function and anatomy of the hypothalamus and anterior pituitary. Causes of primary hypogonadism include injury, hemochromatosis, infections, and genetic disorders, such as Klinefelter syndrome. Secondary hypogonadism is much more common, and may be caused by a variety of different conditions, such as brain tumors, pituitary tumors, trauma, medication/drug toxicity, and other disease processes. For the past few decades, obesity has also become recognized an important cause of secondary hypogonadism.

INTERPLAY BETWEEN OBESITY AND LOW TESTOSTERONE

Among the numerous comorbidities associated with obesity, it has long been recognized that there is a strong association between obesity and low testosterone levels. In fact, reductions in testosterone levels correlate with the severity of obesity and men with a body mass index of greater than 35 to 40 kg/m² have more than a 50% reduction in total and free testosterone levels compared with lean men.²⁹ There are many different ways to look at the effects of androgens on adipose tissue and obesity, because the relationship is complicated and seems to be bidirectional.

Effects of Fat on Androgens

It is accepted that obesity-related decreases in total testosterone levels are primarily owing to reductions in SHBG, which are driven by obesity-associated hyperinsulinemia. Low SHBG has also been found to be a strong independent predictor of type 2 diabetes.³⁰ The degree of causality, however, is unclear. It has also become apparent as of late that there are a number of other factors involved in the interplay between obesity and hypogonadism, including the proinflammatory cytokines and hormones that are released by adipocytes.

We have alluded to some of the effects of adipose tissue (and hence, obesity) on testosterone. Specifically, higher levels of adiposity can lead to increased conversion of testosterone into estrogen, and deactivation of dihydrotestosterone, both of which may decrease circulating levels of androgens. This may then further lower the level of circulating testosterone, as the estrogens produced act as a negative feedback to the hypothalamic–pituitary axis, and suppress GnRH, thereby leading to lower luteinizing hormone levels and thus lower levels of testosterone released by the gonads. Additionally, as discussed, TNF- α and IL-6 have similar mechanisms of inhibiting GnRH secretion in the hypothalamus, and, thus,

higher levels of adiposity will lead to lower testicular stimulation of testosterone release.³¹

Leptin also plays a role in the maintenance of circulating testosterone levels, likely through the interaction of intermediary proteins known as kisspeptins and their effect on GnRH secretion. Because obese individuals often become insensitive to increased endogenous leptin production and develop a functional leptin resistance, the hypothalamus may lose this stimulation mechanism in this population. In fact, there is evidence that leptin therapy may restore gonadal function in morbidly obese individuals.³²

We now understand that adipose tissue also produces enzymes that are involved in the metabolism of sex steroids. Although these proteins are produced primarily in the adrenal glands and gonads, adipose tissue contains enzymes that activate, inactivate, and convert steroid hormones as well.³³ The sheer mass of adipose tissue increases its relative contribution to steroid metabolism, and in premenopausal women, it can contribute up to 50% of their circulating estrogen, in the form of E2.

Obesity also can affect serum testosterone levels via its effect on SHBG. As discussed, the liver secretes SHBG into the blood where it binds testosterone with high affinity, regulating its bioavailability.³⁴ Changes in serum concentrations of SHBG thereby can alter the levels of free testosterone, effectively increasing or decreasing androgenic activity. Numerous factors have been implicated in both increasing or decreasing circulating SHBG levels, including obesity, as well as thyroid dysfunction, liver disease, and medications such as corticosteroids. Because of the direct effect of obesity on reducing circulating SHBG levels, it is important that the diagnosis of hypogonadism should depend on the measurement of free testosterone in this setting.³⁵

Another important way in which obesity promotes hypogonadism is via its effect on sleep. Certainly obstructive sleep apnea, which is characterized by recurrent episodes of complete or partial obstruction of the upper airway during sleep, is an obvious and potentially dangerous effect of weight gain. The increase in both the prevalence and the severity of obesity has led to an increase in the prevalence of obstructive sleep apnea in recent years.^{36,37} Obstructive sleep apnea, in turn is known to reduce circulating serum testosterone levels and, in fact, the degree is likely related to the severity of hypoxia during sleeping hours.³⁶ That said, that obesity is frequently associated with marked sleep disturbances, even when there is no evidence of obstructive sleep apnea.³⁸ In addition, the relationship between obesity and

sleep seems to be bidirectional; poor sleep has been implicated recently as a risk factor for the development of obesity and its complications. Although the exact mechanism is unclear, it seems to be mediated by alterations in concentrations of neuroendocrine modulators, including leptin and cortisol.³⁹

Effects of Androgens on Fat

Studies have shown an inverse correlation between testosterone levels and the amount of visceral fat on an individual.⁴⁰ Patients with prostate cancer who are undergoing androgen deprivation therapy tend to show increased central obesity and higher percentages of body fat, as well as decreased amounts of lean muscle mass.⁴¹ In turn, testosterone replacement has been shown to increase lean muscle mass.⁴² In fact, decreasing lean muscle mass is a key feature of obesity, and in combination with the increase in fat mass, it can lead to increased mortality, especially in older men.⁴³ The effects of testosterone on increasing muscle mass are extremely well-documented.

The exact mechanism of testosterone's effect on adipose tissue is unclear, but there are a few proposed theories, such as by stimulating lipolysis, decreasing lipogenesis, and inhibiting lipid uptake. It has been speculated that this may occur through lipoprotein lipase, an enzyme that has been linked multiple times to obesity. Lipoprotein lipase increases the amount of fatty acids and fatty acid uptake, and has been shown to be inversely correlated with testosterone levels in sedentary obese men.⁴⁴ In addition to promoting obesity, testosterone deficiency may lead to dyslipidemia, with elevations of total cholesterol, low-density lipoprotein cholesterol, and triglycerides. However, this relationship is not entirely clear, and multiple studies seem to contradict one another, with some stating that testosterone deficiency is associated with higher low-density lipoprotein cholesterol and some finding no relationship at all.

With this observation, we can describe a vicious cycle. The metabolic syndrome suppresses testosterone biosynthesis, which in turn predisposes these men to the onset and development of metabolic syndrome (and obesity), thereby reinforcing the cycle.⁴⁵

EFFECTS OF TREATMENT OF OBESITY ON TESTOSTERONE

Although there is an established correlative relationship between obesity and hypogonadism, it has recently also become evident that weight reduction can increase testosterone levels of

obese men.⁷ Furthermore, the degree of weight loss is proportional to the subsequent increase in testosterone. Researchers have proposed a number of mechanisms for this relationship.

As discussed, aromatase expressed by adipocytes is responsible for the conversion of testosterone to E2, thus lowering the circulating androgen concentration. It follows that a decrease in adipocyte mass, via a downregulation of aromatase activity, will thereby lead to an increase in the serum testosterone concentration. As well, the decrease in E2 in turn decreases negative feedback of E2 on the hypothalamus. GnRH and luteinizing hormone increase as a result, providing further support for testosterone synthesis in the gonad. This “virtuous” cycle of course can only occur in the patient with an intact hypothalamic–pituitary–gonadal axis.

A potential effect of weight loss on testosterone levels relates to the earlier summarized idea of adipose as an endocrine organ. This premise, referred to as the hypogonadal–obesity–adipokine hypothesis, suggests that a decrease in adipose mass will in turn reduce the inflammatory factors secreted by adipocytes, such as TNF- α and IL-6. This in turn reduces the inhibitory effect of these molecules on hypothalamic GnRH secretion, ultimately promoting an increase in the degree of testosterone production.⁴⁶

Another proposed mechanism of improvement of testosterone levels after weight loss is via changes in SHBG. Even minor weight loss (<15% over 4.4 years) is associated with modest increases in total testosterone. Free testosterone levels, however, did not change in the same population, likely owing to the trend toward normalization of SHBG levels.⁴⁷ Again, it is important for this reason to stress measurement of both total and free testosterone levels as part of the evaluation of hypogonadism in the obese population.

Finally, as discussed, changes in sleep patterns can have dramatic effects on serum testosterone levels. Weight loss is known to reduce the risk of obstructive sleep apnea. In addition to this, major improvements in sleep quality, excessive daytime sleepiness, snoring, and nocturnal choking have all been observed after weight loss.⁴⁸ These improvements in sleep patterns after weight loss subsequently play a part in subsequent trends toward resolution of hypogonadism.

EFFECTS OF TREATMENT OF TESTOSTERONE ON OBESITY

Similar to the bidirectional relationship of obesity and hypogonadism, treating either of these conditions can subsequently help to treat the other. Just

as weight loss helps to normalize testosterone levels and ameliorate the symptoms associated with hypogonadism, the normalizing of testosterone levels can help to promote weight loss. Significant improvement in body composition has been noted after testosterone therapy in multiple studies.⁴⁹

Randomized controlled trials have shown beneficial effects of testosterone on body composition. In 1 study, a weekly administration of 100 mg IM of testosterone enanthate showed a significant increase in lean body mass and decline in serum cholesterol, and another study of 108 men over the age of 65 showed a net loss of 2.9 kg and increase in lean mass after testosterone treatment.^{50,51} Additionally, testosterone administration to men with type 2 diabetes with testosterone deficiency led to a reduction of leptin, as well as a decrease in waist circumference and waist/hip ratio.⁵² As with the effect of weight loss on testosterone levels, there are several theories regarding the relationship between testosterone therapy administration and the promotion of weight loss.

It has been proposed that the effect of testosterone on metabolic function may be related to its upregulation of multiple enzymes and transcription factors important to metabolic function, especially in mitochondria. The impairment of mitochondrial function in hypogonadism is believed to contribute to fatigue, insulin resistance, type 2 diabetes mellitus, cardiovascular disease, and the metabolic syndrome.⁴⁴ Testosterone may also have a positive effect on the lineage of mesenchymal pluripotent cells, shifting them from an adipogenic lineage to a myogenic lineage, thereby decreasing fat mass in favor of increased lean body mass.⁵³ Another, perhaps more simplistic albeit obvious way in which testosterone therapy leads to increased weight loss is via its positive effect on motivation and energy. Certainly, as demonstrated in other studies, this improvement of motivation can lead to an increased energy expenditure that may lead to sustained weight loss.⁵⁴

SUMMARY

The relationship between obesity and hypogonadism is complicated. The relationship is bidirectional and there are numerous causative and correlative factors on both sides of the equation. Obesity is increasing in prevalence in epidemic proportions. Likewise, we are beginning to see the rapid increase in the incidence of male hypogonadism. It is only recently that we are learning the ways in which these 2 conditions exacerbate each other, and we are only beginning to

understand how by treating one of these conditions, we can help to treat the other as well.

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