DOI: https://doi.org/10.53350/pjmhs22168597

ORIGINAL ARTICLE

Male Hypogonadism and Obesity: An Insight

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ABSTRACT

Obesity, a clinical condition that is on the rise internationally and is highly associated to lower testosterone levels in males, is the most strongly linked clinical condition. In addition to this, it is one of the most reliable signs that a guy may require testosterone replacement medication. When it comes to obesity, the severity of the condition can determine whether the hypothalamic-pituitary-testicular axis (HPT) is suppressed. Moderate obesity, on the other hand, is typically characterized by lower levels of sex hormone binding globulin. Even though there is a connection in both directions between hypogonadism and obesity, the effect of adiposity on testosterone levels is much more significant than the impact that testosterone has on adiposity. The relationship between hypogonadism and obesity is complex and multifaceted. There are various components, both causal and correlative, on both sides of the contact, which can be thought of as a connection that goes in both directions. The number of people who are overweight or obese is increasing at an epidemic rate. In a manner quite like this, we have begun to observe a significant increase in the frequency of male hypogonadism. We are just now starting to get a better understanding of how these two ailments might interact with one another and make each other worse, as well as how treating one of these conditions can help in the treatment of the other.

INTRODUCTION

The prevalence of obesity in modern society, both in the United States and elsewhere in the world, is not likely to come as a surprise to most individuals (James, 2008). The recent rise in the number of diagnoses of male hypogonadism is another development that does not come as a surprise. It is of considerable interest, however, to investigate the ways in which these disorders, which are becoming more prevalent, might interact with one another and make the other worse. It is essential that we have a solid understanding of how resolving one of these problems could also help us mitigate the effects of the other problem. In recent years, obesity has developed into a global epidemic, as seen by the precipitous rise in the prevalence of obesity and the accompanying rise in obesity-related comorbidities over the course of the last several decades (Nam et al., 2020). Estimates indicate that more than two-thirds of individuals in the United States are overweight, and that more than one-third (34.9% or 78.6 million) of people are obese (Lam et al., 2016). Obesity is known to cause several other conditions known as comorbidities. These conditions include chronic liver diseases such as non-alcoholic fatty liver disease and its most severe subset, non-alcoholic steatohepatitis, as well as hypertension, dyslipidaemia, type 2 diabetes mellitus, coronary heart disease, stroke, gallbladder disease, osteoarthritis, sleep apnea, and respiratory problems (Lim and Boster, 2021). It is also extremely important to keep in mind that, even though there is still a great deal of work to be done, the field of treating obesity has advanced quickly over the course of the past ten years. It is no longer appropriate to just give up on a patient and tell him that we are unable to help him lose weight if he is unable to lose weight using normal means of weight loss such as diet and exercise. The specifics of the pharmaceutical techniques of treating obesity are outside the scope of this page, but you can find additional information on them elsewhere. In addition to these aftereffects, hypogonadism is a serious comorbidity of obesity that is commonly disregarded (Molina-Vega et al., 2018). It has been discovered that obesity has a significant relationship with hypogonadism, which is defined as the existence of a low testosterone level that has been evaluated on at least two separate occasions in conjunction with signs or symptoms that can be attributed to low testosterone levels. Reports found that 52.4% of all obese men had testosterone levels that were below 300 ng/dL, making obesity the single most prevalent cause of testosterone deficiency in developed countries (Rastrelli et al., 2020). Weight loss that is brought about by dieting, increasing physical activity, or having bariatric surgery can also lead to a significant increase in testosterone levels in men. Hypogonadism has been related to several other adverse outcomes in addition to its role in the promotion of obesity. These adverse effects include the metabolic syndrome, osteoporosis, depression, and sexual dysfunction (Carrageta et al., 2019). It is interesting to note that hypogonadism is associated with an increase in the deposition of abdominal adipose tissue, which lends credence to the notion that the connection between hypogonadism and obesity may be a two-way street. New evidence suggests that testosterone replacement therapy could be an effective treatment for obesity because it has the potential to cut body fat mass as well as the waist circumference and the amount of muscle mass (Saad et al., 2012). There is no question that the relationship between hypogonadism and obesity is a complicated one; however, there are still questions that need to be answered concerning the extent to which the two conditions are causally related to one another and how closely they are correlated. Because it has been discovered that these two problems frequently occur simultaneously, it is common knowledge that treatment for one of these disorders may have the potential to have beneficial effects on the other. Regarding the physiology of these systems, there are a few different hypotheses. The first step in gaining a better understanding of this association is to do research on adipose tissue, which is the primary contributor to obesity and plays a complex role in the relationship between obesity and hypogonadism. Today, adipose tissue, more commonly known as fat, is understood to be a sophisticated metabolic and endocrine organ that plays an essential role. In the past, people thought of it as little more than a reservoir for the storage of high-energy fuels but now, people see its full potential.

Adipose Tissue: The Main Driver: Over the past 20 years, the traditional understanding of adipose tissue storage has undergone a significant change, moving from that of a straightforward organ for storing energy to that of a complex and highly active endocrine and metabolic organ that expresses and secretes essential active proteins in response to signals from the central nervous system and various glands (Sun et al., 2021). The finding that adipose tissue is a highly active endocrine and metabolic organ led to this shift in perspective. Additionally, the importance of the role that adipose tissue plays in the metabolism of glucocorticoids and sex hormones is being recognized by the medical community more and more. We will examine the role of adipose tissue in connection to the hormones that it both regulates and produces, as well as the many forms of adipose tissue, to obtain a clearer understanding of how these two aspects interact with one another. Adipose tissue is an endocrine and metabolic organ that produces and secretes several metabolically active substances, including leptin, tumor necrosis factor (TNF)-alpha, interleukin (IL)-6, and adiponectin (Adamczak et al., 2013). The hormone leptin, also referred to as

the "satiety hormone," is produced by adipocytes (Proenca et al., 2014). By lowering feelings of hunger, leptin helps to control the energy balance. Many of leptin's actions, including those on muscle cells and beta cells in the pancreas, are directly mediated by peripheral tissues, even though most of its effects are handled by pathways in the hypothalamus. It is well established that calorie restriction and weight loss because leptin levels to drop quickly, which in turn raises hunger levels and lowers basal metabolic rate (Coelho et al., 2013). In morbidly obese, leptin-deficient human individuals, this response is sustained; however, if a low-dose leptin replacement is administered, the response returns to normal. TNF-alpha is thought to contribute to the onset of obesity and insulin resistance in addition to being expressed in adipose tissue. Obese persons often have higher levels of leptin in their bodies, and since these levels do not drop when exogenous leptin is added, this suggests that these individuals are immune to the effects of leptin. Numerous studies have discovered a strong positive correlation between plasma TNF-alpha levels and obesity (Cao et al., 2008; Aguillera et al., 1998). Since levels of this protein are increased in metabolic syndrome and type 2 diabetes mellitus, recent study has concentrated on the production of TNF-alpha by adipose tissue (Jansson, 2007). TNF-alpha is linked to insulin resistance and endothelial dysfunction in these circumstances (Wascher et al., 2011). Additionally, the amount of gonadotropin that the pituitary gland produces may be impacted by elevated levels of TNF-alpha and other proinflammatory cytokines. Furthermore, it is known that adipose tissue expresses the protein IL-6, which has been linked to insulin resistance and obesity (Wascher et al., 2011). In instance, it has been shown that a sedentary lifestyle may be accompanied by immune cells attacking adipose tissue with proinflammatory properties. As a result, cytokines like IL-6 are released more frequently and there is low-grade inflammation. As a result, this can result in ailments like insulin resistance, which may become better if there is less fat in the body as a whole. However, the adiponectin hormone, which is made in adipose tissue, can provide both greater insulin sensitivity and protection against cardiovascular disease (Garaulet et al., 2007). Furthermore, it appears to be helpful for the metabolism of lipids and glucose after meals. Adiponectin plasma levels are much lower in obese individuals and have been demonstrated to have an inverse connection with body mass index, in contrast to the great majority of other adipokines that have been identified (Chandran et al., 2003). As time has gone on, we have also learned that the location of adipose tissue significantly affects how that tissue functions. Subcutaneous adipose tissue secretes hormones into the systemic circulation, whereas visceral adipose tissue secretes hormones directly into the portal system. Endocrine hormones are produced by both varieties of adipose tissue. Because of this, the metabolic process that takes place in the liver is more significantly impacted by visceral adiposity. IL-6 is expressed at higher amounts in visceral adipose tissue than in subcutaneous tissue, which also expresses leptin at higher levels. This is due to visceral adipose tissue's deeper abdominal cavity location. Visceral tissue responds to afferent signals differently from other types of tissue because it has a higher concentration of glucocorticoid and androgen receptors than other types of tissue. The most striking discovery is that visceral fat increases are linked to worse metabolic risk and higher mortality, whereas subcutaneous fat increases enhance insulin sensitivity and lower the risk of type 2 diabetes (Cordeiro et al. 2010). Because of this, it shouldn't be a surprise that adipose tissue plays a part in energy control and metabolism in addition to serving as a storage area for extra energy (Tencerova et al., 2018).

Hypogonadism: A Disease: Following our examination of the relationship between obesity and low testosterone levels, we will give a quick summary of the pathophysiology of hypogonadism and the physiology of normal gonadal activity. A minor role is played by the testes and the adrenal glands in the production of testosterone, a crucial anabolic steroid hormone. This contribution is a little bit limited. Feedback regulation of the release of hypothalamic gonadotropin-releasing hormone (GnRH), which in turn stimulates the anterior pituitary gland to release gonadotropins, follicle stimulating hormone, and luteinizing hormone, all of which promote the production and secretion of testosterone and help regulate spermatogenesis, controls the synthesis of this hormone (Nett et al., 2002). Dihydrotestosterone, a metabolite of testosterone, works by activating androgen receptors to provide the effects that are unique to testosterone. Additionally, estradiol, a byproduct of testosterone that has undergone 5-alpha reduction, can activate the estrogen receptor (E2). Most of the protein-bound testosterone in blood is bound to serum albumin and sex hormone binding globulin (SHBG) (Zheng et al., 2015). The percentage of testosterone that is "free," or unbound, ranges between one and two percent. This portion of testosterone is biologically active and able to enter a cell and activate its receptor because it is unbound. Testosterone regulates mitochondrial activity when it binds to the androgen receptor (Ahmad and Newell-Fugate, 2022). This happens because of the activation of the respiratory chain's components, a rise in the number of mitochondria, and the stimulation of the transcription of more genes related to oxidative phosphorylation. When a man has hypogonadism, his testicles work less efficiently, which lowers their ability to produce and secrete testosterone. Based on whether the anomaly is seen inside the testes or outside of them, there are two types of hypogonadism that can be distinguished from one another. Primary and secondary hypogonadism are the names of these kinds, respectively. Primary hypogonadism is a disorder that develops when the testes do not function properly, but the hypothalamus and anterior pituitary do (Kumar et al., 2010). Secondary hypogonadism is much more common than this disorder (Kumar et al., 2010). Numerous conditions, including infections, hemochromatosis, trauma, and genetic diseases such Klinefelter syndrome, can result in primary hypogonadism. Compared to original hypogonadism, secondary hypogonadism is far more frequent and can be brought on by a range of disorders, including as head injuries, brain tumors, pituitary tumors, toxicity from drugs or medications, and other disease processes. The medical profession has recently become aware that obesity is a significant factor that contributes to secondary hypogonadism (Saad et al., 2012).

Obesity and testosterone: It has been known for a long time that, in addition to the various comorbidities that are associated with obesity, there is a significant association between obesity and low testosterone levels. When compared to men of normal weight, those with a body mass index of more than 35 to 40 kg/m^2 see a decline in total and free testosterone levels that is larger than 50 percent, and these declines in testosterone levels directly coincide with the degree to which an individual is obese (Batsis and Villareal, 2018). Because of the complexity and apparent bidirectionality of the connection between androgens, adipose tissue, and obesity, there are a great deal of views that need be taken into consideration.

Fat and Testosterone: It is common established that decreases in SHBG, which are caused by obesity-associated hyperinsulinemia, are the primary source of dips in total testosterone levels that are associated with obesity. Independent research has shown that having a low SHBG level is a substantial risk factor for developing type 2 diabetes (Vakan et al., 2010). On the other hand, it is not obvious how the causal factor plays a role. Recently, it has also been obvious that a range of additional variables play a role in the interplay between obesity and hypogonadism. Some examples of these additional variables include the proinflammatory cytokines and hormones that are created by adipocytes (Coppack, 2001). It has been suggested that adipose tissue, and the obesity that results from it, can have a variety of effects on testosterone. To be more specific, greater levels of adiposity can lead to increased conversion of testosterone to estrogen and deactivation of dihydrotestosterone, both of which may lead to reduced levels of androgen in the blood (Wang et al., 2012). Adiposity is a risk factor for cardiovascular disease. It is possible that this will further reduce

the amount of testosterone that is circulating in the body since the estrogens that are produced will act as negative feedback to the hypothalamic-pituitary axis and will inhibit GnRH. The gonads will produce less testosterone as a direct consequence of there being less luteinizing hormone in the body. Because, as was stated earlier, TNF-alpha and IL-6 have comparable ways of suppressing GnRH production in the hypothalamus, higher levels of adiposity will result in less stimulation of testosterone release from the testicles (La Vignera et al., 2011). This is because TNF-alpha and IL-6 are both produced by adipose tissue. Kisspeptins are intermediary proteins, and it is hypothesized that their effect on GnRH secretion interacts with leptin to maintain the levels of circulating testosterone. Because obese persons typically become hypersensitive to increased endogenous leptin production and develop a functional leptin resistance, the hypothalamus may lose this stimulation mechanism in this population (Lanaspa et al., 2018). This is because obese people have a functional leptin resistance. People who are severely obese and get leptin therapy have been shown in some studies to have an increased chance of regaining gonadal function. It is now common knowledge that adipose tissue is also responsible to produce enzymes that play a role in the metabolism of sexual hormones. Even though the gonads and adrenal glands are responsible for most of the protein synthesis in the body, adipose tissue has enzymes that can activate, deactivate, and convert steroid hormones (Soskin and Rachmiel, 2016). The sheer quantity of adipose tissue increases the relative contribution of adipose tissue to steroid metabolism, and in premenopausal women, adipose tissue can account for up to fifty percent of the circulating estrogen in the form of E2. Obesity, by virtue of the effect it has on SHBG, can also influence serum testosterone levels. As was noted before, the liver is responsible for secreting SHBG into the blood, where it very specifically binds to testosterone and limits the amount of bioavailability that testosterone has. Variations in the serum concentration of SHBG have the potential to effectively boost or reduce androgenic activity. These effects are exerted on the levels of free testosterone. There are several factors, including obesity, thyroid dysfunction, liver disease, and medications such as corticosteroids, that have been connected to either an increase or a decrease in the levels of circulating SHBG (Burra, 2013). The evaluation of free testosterone is necessary for making a diagnosis of hypogonadism in this circumstance; this is because obesity directly reduces the levels of SHBG that are circulating in the blood. Obesity, which disrupts sleep patterns, contributes greatly to the development of hypogonadism. Obstructive sleep apnea is undeniably one of the most obvious and potentially dangerous effects that comes along with being overweight. It is characterized by recurring bouts of either complete or partial obstruction of the upper airway while the patient is sleeping. Because of the increased frequency and severity of obesity in recent years, obstructive sleep apnea has grown more widespread (Mushannen et al., 2019). This is due to the growth in the prevalence of obesity. In turn, obstructive sleep apnea is known to lower blood levels of serum testosterone, and the degree is presumably connected with how severe hypoxia is during sleep (Melehan et al., 2016). In other words, obstructive sleep apnea causes lower testosterone levels. Obesity, on the other hand, is almost always connected to significant sleep interruptions, and this is true even in situations when obstructive sleep apnea is not present. Poor sleep quality has lately been linked to an increased chance of acquiring obesity and the comorbidities that come along with it. In addition, there is evidence that there is a reciprocal relationship between obesity and the quality of sleep that one gets (Melehan et al., 2016). Although the mechanism is not entirely understood, it appears to be regulated by shifts in the concentrations of neuroendocrine modulators such leptin and cortisol.

Testosterone impacting Fat: According to the findings of several studies, an individual's testosterone levels have been shown to have an inverse association with the growth of visceral fat (Bredella et al., 2011; Tsai et al., 2000). Androgen deprivation therapy for individuals with prostate cancer frequently results in increased central obesity, larger percentages of body fat, and decreased lean muscle mass. It has also been established that testosterone replacement can result in an increase in the amount of lean muscle mass (Sinclair et al., 2016). One of the primary signs of obesity is a decrease in the amount of lean muscle mass, which, when coupled with an increase in the amount of fat mass, may be associated with an increased risk of death, particularly in older men. It is common knowledge that testosterone influences the development of new muscle mass. Although the precise mechanism by which testosterone exerts its effect on adipose tissue is not known, several hypotheses have been proposed regarding how this effect takes place. One of these hypotheses suggests that testosterone may work by stimulating lipolysis, lowering lipogenesis, and inhibiting lipid uptake (Holland et al., 2016). An enzyme that is often linked to obesity is called lipoprotein lipase, and it has been hypothesized that this may occur because of this enzyme (Schwartz and Brunzell, 1981). It has been discovered that lipoprotein lipase causes a drop in testosterone levels in sedentary obese males while simultaneously increasing the quantity of fatty acids and fatty acid consumption (Wang and Eckel, 2009). A low amount of testosterone can lead to dyslipidemia, which is characterized by high levels of triglycerides, low-density lipoprotein cholesterol, and total cholesterol. In addition to increasing obesity, dyslipidemia can be caused by low levels of testosterone (Haring et al., 2011). Some studies indicate that low testosterone levels are associated to increased levels of low-density lipoprotein cholesterol, while others show no correlation at all. The precise nature of this association is unknown, and multiple studies appear to be in contradiction with one another. Because of this discovery, we are now able to describe a vicious cycle. Due to the metabolic syndrome's reduction of testosterone production, which feeds back into the cycle, these men are prone to the initiation and development of metabolic syndrome (and obesity) (Corona et al., 2011). This is because metabolic syndrome makes them more likely to become obese (Stanworth and Jones, 2009).

CONCLUSION

Metabolism is caused by the overexpression of metabolic enzymes and transcription factors, particularly in mitochondria. Hypogonadism can affect mitochondrial activity, which can lead to fatigue, insulin resistance, type 2 diabetes, cardiovascular disease, and metabolic syndrome. These conditions can also be caused by obesity. Testosterone has the potential to switch the lineage of mesenchymal pluripotent cells from adipogenic to myogenic, resulting in a decrease in fat mass and an increase in lean body mass. Treatment with testosterone boosts the rate of weight reduction by increasing both motivation and energy. According to findings from past research, motivation can lead to increased energy expenditure and weight loss that is maintained over time.

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