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SECONDARY HYPOGONADISM RELATED TO MALE OBESITY: A LITERATURE REVIEW

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ABSTRACT

Obesity is associated with several comorbidities, currently it has been an important cause of secondary hypogonadism in men, and can result in a wide range of symptoms, including infertility and impaired sexual function. The pathophysiological mechanisms of this condition are quite complex and not yet fully defined, involving a dysfunction of the hypothalamic-pituitary-testicle axis. Currently, a series of treatments have been instituted to reduce body weight and maintain male fertility, including changes in lifestyle, different classes of drugs and surgical approach, in order to improve the quality of life of these patients. This is a literature review, based on the search of scientific articles from the National Library of Medicine (MEDLINE) and Virtual Health Library (VHL) databases. The general objective of the study is to review male hypogonadism secondary to obesity. The specific objectives are to describe the pathophysiology of this condition, discuss the clinical picture and how to make its diagnosis, as well as the therapeutic forms currently available.

Keywords: Obesity. Male Hypogonadism. Testosterone.

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INTRODUCTION

Obesity is a global health problem characterized by the excessive accumulation of body fat, which is responsible for generating a chronic inflammatory state, associated with the release of free fatty acids into the bloodstream, with consequent deposition in vital organs (GENCHI et al, 2022; DE LORENZO et al, 2018). It has a multifactorial pathogenesis, which includes genetic, environmental, metabolic, and behavioral components. In these individuals, a pathological increase in body mass index (BMI) will be observed, which can be calculated by weight (kg) divided by the square of height (meters). A BMI greater than 30kg/m2 is indicative of obesity (NOCE et al, 2020). The World Atlas of Obesity 2023, published by the World Obesity Federation, predicts that more than half of the world's population will be overweight and obese by 2035, if current trends persist (LENART-LIPINSKA et al, 2023).

As causes of this significant increase, the lifestyle of individuals should be taken into account, including high carbohydrate intake, reduced physical activity, dysfunctional sleep routine (MOLINA-VEGA et al, 2018; WITTERT & GROSSMANN, 2023). When left untreated, the patient may have increased mortality and morbidity, including several complications, including: cardiovascular and cerebrovascular diseases, cancer, type 2 diabetes mellitus, systemic arterial hypertension, obstructive sleep apnea, among many others (LENART-LIPINSKA et al, 2023; MOLINA-VEGA et al, 2018; WITTERT & GROSSMANN, 2023).

Obesity also affects the reproductive system and is associated with polycystic ovary syndrome in women and testosterone deficiency, causing secondary hypogonadism in men (MUSHANNEN et al, 2019). Although the actual prevalence of Male Obesity associated Secondary Hypogonadism (MOSH) is still unclear, large-scale epidemiological studies and small surveys suggest that prevalence rates are as high as 45-57.5% (FERNANDEZ et al, 2019). MOSH is a diagnosis of exclusion, made after the primary causes of hypogonadism have been eliminated. It is defined as a syndrome of the inability to produce adequate testosterone and/or sperm in men with obesity (MUSSHANNEN et al, 2019).

Normal total testosterone (TT) levels in adult men range from 270 to 1,070 ng/dL and vary according to the age and pubertal stage of developing men. There is no universal definition of hypogonadism, even in adults, there are studies using TT levels, others using free testosterone (TL) or both. The multicenter European Male Aging Study (EMAS) conducted a study of 3,219 men over the age of 40 and established standardized criteria for the diagnosis of late-onset hypogonadism, including: the presence of at least 3 sexual symptoms, along with TT < 317 ng/dL and TL < 6.34 ng/dL (MUSHANNEN et al, 2019). In

MOSH syndrome, obesity corroborates with hypogonadism to give rise to reduced testosterone levels. This leads to a multitude of symptoms, such as impaired fertility and sexual function, poor bone mineralization, changes in fat metabolism, deterioration of muscle mass, among others (NOCE et al, 2020; DE LORENZO et al, 2018).

The objective of the present study is to make a literature review about MOSH, addressing its pathophysiological and diagnostic aspects, as well as its currently available therapeutic options.

METHODOLOGY

The present study consists of an integrative literature review, carried out through the search of scientific articles from the National Library of Medicine (MEDLINE) and Virtual Health Library (VHL) databases. In the search strategy, the descriptors "Male obesity" and "Hypogonadism" were used, interspersed with the Boolean operator "AND". After that, inclusion criteria were used, which involved: free full texts, original articles and reviews published in scientific journals, available in Portuguese and English, published between the years 2014-2024, research on the human species, obtaining a total of 263 articles.

After that, duplicate works and titles that did not correspond to the theme to be addressed were excluded, ending the search with 20 articles to be reviewed.

RESULTS

Belloc et al (2014) analyzed 10,665 semen samples, observing that in individuals with a BMI greater than 40kg/m² there was a reduction in semen concentration and volume, a reduction in sperm count and motility.

Similarly, the cross-sectional observational study by Shende et al (2024) involved 80 male participants with a BMI greater than 25kg/m², who underwent clinical examinations and laboratory investigations, including: waist circumference (WC) and waist-to-hip ratio (WHR), measurement of the inflammatory marker c-reactive protein (CRP), TST measurement. The study found strong positive correlations between BMI, WHR, and CRP and negative correlations between these anthropometric measurements and TST. The negative correlation between CRP and TST is even stronger.

Several studies have demonstrated benefits related to the reproductive function of the man with MOSH after significant and sustained loss of body weight. EMAS conducted a study where it was shown that changes in total body weight greater than or equal to 15% are correlated with changes in testosterone (LENART-LIPINSKA et al, 2023)

The study by Al-Tahami et al (2017) randomly divided 76 individuals into two distinct groups. The first group was treated with daily doses of 120mg of orlistat and the other group with 10mg or 15mg of sibutramine, both for 9 months. BMI, WC, CRP, WHr, insulin sensitivity (HOMA%S), insulin resistance (HOMA-IR), and fasting glucose were measured at the beginning, during and at the end of treatment. At the end of the 9 months, 24 individuals completed the treatment and a reduction in the measured parameters was verified, with no significant differences between the two groups.

Huijben et al (2021) analyzed 19 distinct studies, including 4 randomized controlled trials and 15 observational studies, with a total of 1672 patients undergoing treatment for hypogonadism with clomiphene citrate. The duration of treatment in the studies read ranged from 1 month to 52 months. The authors observed an increase in TST after the end of treatment. Adverse reactions were observed in less than 10% of subjects and no serious adverse effects were reported.

DISCUSSION

REPERCUSSIONS OF MOSH

To evaluate a patient with suspected MOSH, detailed history along with a thorough physical examination is essential. This pathology is characterized by several signs and symptoms, with low libido and decreased frequency of erections being the main manifestations of secondary hypogonadism. For diagnostic confirmation, laboratory evaluation is necessary. The hormonal abnormalities that characterize MOSH are represented by a decrease in plasma levels of TT and TL together with a decrease in SHBG and an increase in estradiol levels, which were found in the index patient, thus confirming the diagnosis of MOSH. In many cases, TT levels may be falsely reduced due to the decrease in SHBG, for this, it is essential to evaluate TL, along with FSH and LH dosage, which will be normal or reduced (DI VINCENZO et al, 2018; OLIVEIRA et al, 2022).

Healthy erectile function depends on factors such as erectile tissue, central and peripheral nervous system, and various endocrine and psychological factors. Sexual stimulation activates cholinergic, non-adrenergic, non-cholinergic, and parasympathetic nerve fibers, which leads to the release of nitric oxide and acetylcholine. As a result, there is an increase in cyclic guanosine monophosphate (GMP) and a reduction in intracellular calcium, as a consequence, smooth muscle relaxation and vasodilation occur, increasing blood flow to the corpus cavernosum and occluding the subtonic venules. Any disturbance in one or more of these mechanisms can contribute to or lead to erectile dysfunction (ED) (SULTAN et al, 2020). In addition to affecting sex hormone levels, obesity can also have a

negative impact on overall sexual function. In addition to low testosterone levels, microvascular and vascular abnormalities are correlated with visceral adipose tissue expansion and chronic systemic inflammation, which may represent another possible link between obesity and ED (DI VINCENZO et al, 2018). Hypogonadism is related to many defects beyond the reproductive system, as obesity is not only associated with low testosterone, but also with high estrogen, high insulin, leptin resistance, among other hormonal abnormalities. Other symptoms include: Fatigue, depression, decreased bone mineral density, as well as sleep disturbances, as in the clinical case. On polysomnography, severe apnea was visualized (MUSHANNEN et al, 2019).

PATHOPHYSIOLOGY

Testosterone (T) synthesis is controlled by the hypothalamic-pituitary-testicle (HHT) axis, and is modulated by direct negative feedback from T. kisspeptins regulate the release of gonadotropin-releasing hormone (GnRH), which is pulsatilely secreted and stimulates the release of LH and FSH. In the testes, LH acts on Leydig cells, stimulating T secretion. FSH, in turn, will act on Sertoli cells, inducing spermatogenesis (BARBAGALLO et al, 2021; WITTERT & GROSSMANN, 2023).

The pathophysiological mechanisms involved in MOSH are highly complex, obesity generates an increase in the levels of leptin, insulin, pro-inflammatory cytokines, and estrogen, which can cause hypogonadotropic hypogonadism. (FERNANDEZ et al, 2019; WITTERT & GROSSMANN, 2023). In addition, hypogonadism is related to the accumulation of fat, leading to a self-perpetuating cycle (GENCHI et al, 2022).

Several mechanisms may favor hypogonadism, the impact and contribution of these are not yet fully elucidated (GENCHI et al, 2022).

1. Direct effects of adipose tissue: Aromatase is a cytochrome P450 enzyme present in adipose tissue (TA), responsible for converting androgens (MUSHANNEN et al, 2019). An elevated waist circumference reflects the expansion of visceral TA, which can result in increased aromatase activity (DI VINCENZO et al, 2018). This increase generates a greater conversion of androstenedione and testosterone into estrone and estradiol, respectively. The increase in estrogen formed from this process causes a negative feedback at the level of the hypothalamic-pituitary, further decreasing T levels and causing hypertrophy of adipocytes (FERNANDEZ et al, 2019).
2. Effects of inflammation: Accumulating evidence indicates that the exacerbated production of inflammatory mediators, in addition to generating metabolic

complications, is associated with reduced testosterone levels (GENCHI et al, 2022). The metabolic impairment generated by the increase in visceral fat is related to the increase in pro-inflammatory cytokines, such as Tumor Necrosis Factor-α, TNF-α, interleukins 1 and 6 (IL-1, IL-6), leptin, which influence hypothalamic function, in particular the decrease in kisspeptin signaling. Such a decrease also generates a reduction in GnRH, LH, FSH, and T levels (NOCE et al, 2020). Leptin acts on the hypothalamus, being responsible for regulating energy balance by suppressing appetite (LENART-LIPINSKA et al, 2023). Its circulating levels are positively associated with body fat percentage and adipocyte size (BARBAGALLO et al, 2021). In normal physiological situations, this adipocytokine acts through kisspeptin neurons to stimulate GnRH and thus LH secretion. In obesity, there is an increase in leptin release from adipocytes, which generates a central resistance to leptin at the hypothalamic-pituitary level. This decreases the expression of the hypothalamic kisspeptin gene, which consequently decreases the secretion of GnRH and LH and causes damage to testosterone levels in the body (FERNANDEZ et al, 2019). Other impairments include overeating and weight gain (LENART-LIPINSKA et al, 2023).

3. Insulin resistance: Insulin resistance in T deficiency occurs due to the effects of body composition, including increased adipocyte differentiation (visceral obesity) and independent effects of body composition, such as increased inflammation and release of inflammatory mediators (FERNANDEZ et al, 2019). Visceral obesity increases the arrival of free fatty acids to the liver, which results in a decrease in hepatic insulin clearance, increasing its blood levels. Inflammatory cytokines, in turn, have a significant influence on insulin signaling in responsive tissues, promoting systemic insulin resistance and hyperinsulinemia. In addition, in obese patients, the increase in this substance is associated with a decrease in SHBG levels by the liver, which increases the biological activity of estrogen (BARBAGALLO et al, 2021). Hyperinsulinemia acts on kisspeptin neurons by decreasing their signaling, which in turn reduces the release of GnRH and, therefore, LH secretion (FERNANDEZ et al, 2019).
4. Effect of oxidative stress: Several stressogenic stimuli occur in obesity, including hyperglycemia, hyperleptinemia, and mitochondrial insufficiency, all of which contribute to increased reactive oxygen species (ROS) generation and adipose tissue dysfunction. Intense oxidative stress can affect the steroidogenic cascade in Leydig cells, leading, in some cases, to decreased testosterone production. In

addition, the excessive production of ROS can participate in the hypogonadism process indirectly, through increased cortisol release, which affects the secretion of LH by the pituitary gland, also reducing the production of the male sex hormone (GENCHI et al, 2022).

5. Effect of SHBG decrease: It is a glycoprotein produced by the liver. In the circulation, about 98% of testosterone is bound to albumin and SHBG. Low levels of SHBG may be responsible for the exacerbation of testosterone through pro-inflammatory effects and increased lipid deposition in macrophages and adipocytes. This will exacerbate the inflammatory state of obesity (SULTAN et al, 2020).

SLIMMING TREATMENT

Weight loss requires changes in behavioral habits, including lifestyle and cognitive changes. It is assumed that obese patients present dysfunctional behaviors in relation to food, reacting with feelings of anxiety, worry, guilt, and sadness. Referral to psychology is a fundamental point for the success of the treatment, seeking to help identify dysfunctional thoughts and persist healthy habits (SULTAN et al, 2020).

The current management of obesity involves the patient's relationship with secondary and tertiary care services, which allow access to a multidisciplinary team responsible for assisting in weight loss and maintenance. Lifestyle modifications, such as calorie-deficit diets and physical activity, are the basis of non-surgical treatment (SULTAN et al, 2020). The recommended individual calorie deficit should lead to a reduction in body weight by 5-10% within 3 to 6 months of initiation of therapy, and is usually the first line of treatment. However, even with numerous documented studies showing the beneficial effects of this calorie restriction, medical nutrition therapy alone is associated with limited effectiveness. Regarding physical activity, aerobic exercises of 30 to 60 minutes with moderate intensity are recommended for obese patients at least 4 times a week, aiming at weight loss, reduction of visceral adipose tissue, and improvement of cardiometabolic factors for better quality of life (LENART-LIPINSKA et al, 2023; FERNANDEZ et al, 2019). The prospective cross-sectional cohort study by Bacon et al, demonstrated that physical activity is also associated with a 30% decrease in the risk of erectile dysfunction, one of the consequences related to MOSH (SULTAN et al, 2020).

The U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved pharmacotherapy with proven significant weight reduction effects as an adjunct therapy to lifestyle modification, which is recommended for patients with a BMI

BMI ≥ 30 kg/m2 or ≥ 27 kg/m2 with obesity-related comorbidities, which increases cardiovascular risk. Currently, drugs approved for this therapy include: Orlistat, Naltrexone/Bupropion, Sibutramine, Liraglutide, Semaglutide, and Sibutramine (LENART-LIPINSKA et al, 2023).

1. Liraglutide and Semaglutide: These medications are peptide 1 receptor agonists (GLP-1), which consists of a class of antidiabetic drugs that act as incretin mimetics, represent one of the pharmacological approaches for the treatment of obesity (GENCHI et al, 2022).
2. Naltrexone/Bupropion: It consists of a combination medication, with bupropion being a dopamine and norepinephrine reuptake inhibitor and a nicotinic receptor antagonist and naltrexone an opioid antagonist. In the treatment of obesity, bupropion inhibits food intake through the activation of the neuropeptide proopioomelanocortin (POMC), responsible for reducing appetite and causing the activation of dopamine, which is pathologically reduced in obese individuals. On the other hand, Naltrexone inhibits the appetite-enhancing effect promoted by beta-endorphins (LENART-LIPINSKA et al, 2023).
3. Orlistat: It is a drug that acts by inhibiting lipases in the gastric mucosa, small intestine and pancreas, which limits the degradation of triglycerides into free fatty acids, consequently reducing their absorption in the intestine. It may also promote beneficial effects on insulin resistance, fasting glucose, low-density lipoprotein cholesterol (GENCHI et al, 2022; LENART-LIPINSKA et al, 2023). However, Orlistat treatment has not been proven to induce substantial effects on testosterone levels, so recovery from hypogonadism in obesity is only a speculation (GENCHI et al, 2022).
4. Sibutramine: It was synthesized in the 80's initially to act with an inhibitory action on the reuptake of norepinephrine and serotonin in order to be used with antidepressant action, but the drug demonstrated action to reduce appetite, and can be used in conjunction with behavioral changes to manage MOSH. It is classified as an anorectic drug, with action on the CNS preventing the reuptake of serotonin and norepinephrine, causing a feeling of satiety and thermogenesis (AL-TAHAMI et al, 2017)

Despite the promising results of dietary intervention, a subset of patients with obesity will require surgical intervention in the form of bariatric surgery, which represents the best treatment choice for morbid obesity today. It is globally accepted that the procedure may be an appropriate option for individuals with a BMI > 40 kg/m2 or those with a BMI of 35-40

kg/m2 with comorbidities. There are different techniques, but they all seem to be associated with good results in these patients (SULTAN et al, 2020; FERNANDEZ et al, 2019).

The improvement in testosterone concentrations after bariatric surgery seems to be related to the beneficial effects on some parameters such as body weight, BMI, leptin, adipocytoones), regardless of the surgical technique (GENCHI et al, 2022). In addition, bariatric surgery appears to improve the sexual health of obese men in terms of increased sex drive, erectile and ejaculatory function, proportional to weight loss, leading to a healthier metabolic profile (SULTAN et al, 2020; GENCHI et al, 2022). With the maintenance of weight loss, the effects of this therapy on the levels of male sex hormones can be observed by more prolonged levels. However, bariatric surgery does not always guarantee complete normalization of erectile function, which may be related to weight regain or the persistence of metabolic abnormalities (DI VINCENZO et al, 2018).

CLOMIPHENE AND MALE REPRODUCTION

Currently, the treatment for secondary hypogonadism involves the use of exogenous testosterone, which acts on HHT generating a negative feedback, with this there is a reduction in FSH production, associated with testicular atrophy and infertility (VEIGA et al, 2023). Other disadvantages of the treatment include gynecomastia, erythrocytosis, and acne, and it is contraindicated for patients with a history of breast cancer, thrombophilia, untreated severe obstructive sleep apnea, uncontrolled heart failure, among other conditions (IDE et al, 2021).

Selective estrogen receptor modulators (SERMs) currently consist of an off-label pharmacological strategy for stimulating endogenous testosterone production. Clomiphene citrate is the most common SERM for the treatment of secondary hypogonadism. (RODRIGUEZ et al, 2016). Initially, this drug was developed for the treatment of female ovulatory disorders in the 1960s, however, it has currently been used in the treatment of male infertility. Advantages of this drug include oral administration, maintenance of fertility and decreased risk of erythrocytosis. The usual dose used consists of 25-50mg daily, raising T usually after 4 weeks of treatment (DA ROS et al, 2022; IDE et al, 2021).

Its mechanism of action consists of the occupation of estrogen receptors in the hypothalamus and pituitary gland, leading to increased secretion of LH and FSH, thus increasing testicular testosterone production and conserving spermatogenesis, a very important fact especially for young men who have reproductive desire (VEIGA et al, 2023; HUIJBEN et al, 2022).

Regarding the side effects of this drug, as they are used off-label for males, most of the data on side effects come from females. However, some small studies on the effects in men are available, showing that its use in this population appears to be safe for use in secondary hypogonadism, showing only a few possible mild side effects such as headache, fatigue, dizziness, and hot flashes (IDE et al,2021; DA ROS et al, 2022).

CONCLUSION

Obesity generates a state of chronic inflammation in the individual and has a negative impact on male sex hormones, generating complaints of erectile dysfunction and loss of libido. Currently, several therapeutic options are available on the market, ranging from lifestyle changes to the prescription of pharmacotherapy and surgical approach, choosing the treatment according to the preferences and profile of each patient. Different published studies show the correlation of weight loss with increased levels of male sex steroids and improved sexual function. For the success of the treatment, patient adherence is essential. For this, in addition to the physical approach, it is important to analyze the psychological of this patient, in order to improve dysfunctional habits and ensure comprehensive care.

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