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Metabolic syndrome with involvement of the male reproductive system

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ABSTRACT

Metabolic syndrome is an endocrine disorder that involves systemic alterations of intermediate metabolism, cardiovascular, hormonal, and reproductive systems. It is characterized by central obesity, elevated blood pressure, insulin resistance, and dyslipidemia, which lead to the development of type 2 diabetes mellitus, cardiovascular and renal diseases. At the clinical level, the central axis of patients with metabolic syndrome focuses on the prevention of cardiorenometabolic comorbidities, however, it's not common that the physician addresses the issue of male reproduction and its implications. Currently there is increasing evidence that patients with metabolic syndrome have low levels of testosterone, GnRH, FSH and LH and high levels of estrogen which impacts sperm quality, fertility, and sexual health, which can undoubtedly be reversible upon remission of the metabolic syndrome. This review addresses clinically how metabolic syndrome impacts the male reproductive system, addressing male fertility, testicular endocrine function, and sexual health.

KEYWORDS: Metabolic syndrome, fertility, testosterone, sperm quality, sexual health.

MANUSCRIPT

Introduction

Metabolic syndrome (MetS) is a group of endocrine disorders caused by excess fatty tissue characterized by visceral obesity, insulin resistance, hyperglycemia, hypertriglyceridemia, atherogenic dyslipidemia (increased LDL/VLDL cholesterol and decreased HDL cholesterol), high blood pressure, microalbuminuria, prothrombotic and proinflammatory state etc. Chronically, metabolic syndrome promotes the development of type 2 diabetes mellitus, cardiovascular complications, chronic kidney damage, cancer, and infertility [1]

It is estimated that the prevalence of MetS in the world ranges between 20-25% in the adult population. However, in Mexico the prevalence of MetS almost doubles the global results (25% vs 41%) [2,3].

Although the diagnostic criteria overlook the reproductive function as a parameter of the MetS, there is increasing evidence that recognizes this as a disruptor of male fertility, in part due to alterations in the hypothalamic-pituitary-testicular axis presenting low levels of GnRH, FSH, LH and testosterone and high

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levels of estrogens which negatively impact spermatogenesis resulting in a decrease in seminal volume, sperm concentration, DNA fragmentation and finally alterations in fertility [4].

In this review we focus on the effects of MetS on the male reproductive system, including endocrinological disorders, male fertility, and sexual health.

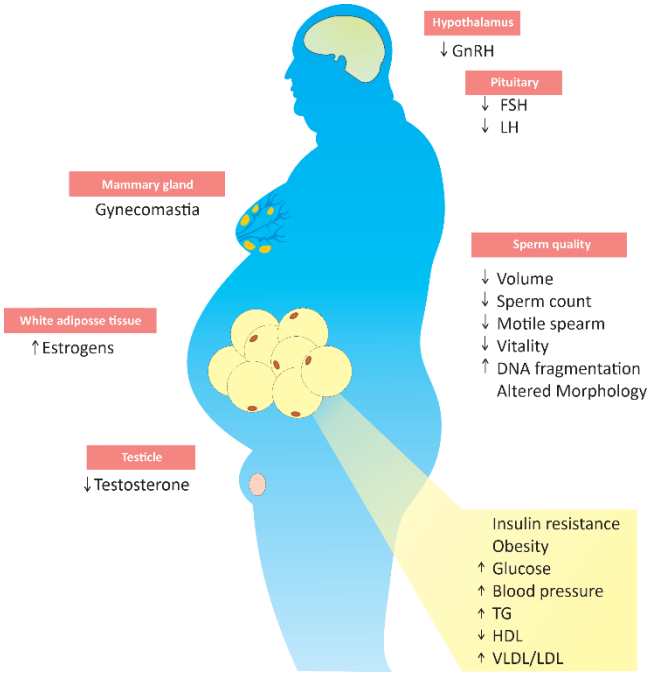

Figure 1. The impact of the metabolic syndrome on male fertility.

Metabolic syndrome and Sperm Quality

The causal relationship between MetS and male fertility is not new. The molecular mechanisms involved in male infertility caused by MetS have been known for decades. However, in the MetS primary care consultation there is a lack of interest in knowing the Male fertility status compared to the approach given to female fertility, this is partly since male fertility continues be a taboo subject [5].

Evidence shows that patients with MetS have negative effects on sperm quality, showing lower seminal volume, decreased total sperm count, decreased motility and vitality, and high levels of sperm DNA fragmentation. It is imperative to take a complete medical and sexual history as well as perform a thorough physical examination in addition to the semen analysis to provide a complete diagnostic assessment. Early diagnosis of MetS may provide an advantage of comprehensive management to promote short-term remission. Reduction of body weight and alleviation of MetS improves the parameters of sperm quality, showing a significant increase of semen volume, sperm motility and motile sperm count. On the other hand, it has also been observed that treatment with aGLP-1 enhances weight loss and can be used for preserving sperm quality in the long term, contrary to what was thought that liraglutide therapy was detrimental to sperm concentration and motility. Finally, there is still discrepancy about the relationship between bariatric surgery and sperm quality, since some studies report a null or worse influence, while others report an improvement after bariatric surgery, so further long-term studies are required period to elucidate the impact of bariatric surgery on sperm quality [6-10].

Metabolic syndrome and its alteration in the hypothalamus pituitary testis axis

The are many endocrinology alterations that can cause male infertility since it has been observed that patients with MetS present hypogonadism because of alterations in the hypothalamus-pituitary-testicle axis (HPG axis). Adipokines have been shown to be functionally involved in the HPG axis. Plasma levels of some adipokines are associated with specific metabolic states. In men with MetS, aromatase enzyme activity is markedly increased, causing excessive conversion of androgens to estrogens. Therefore, gonadotropin secretion by the adenohypophysis is decreased through negative feedback loop inhibition of the HPG axis, having a direct impact on Leydig cells and Sertoli cells, leading to a significant decrease in testosterone production and spermatogenesis, which then impacts further through drops in gonadotropin-releasing hormone (GnRH) pulses [11-13].

Weight loss and gain have been associated with reciprocal changes in luteinizing hormone (LH) and testosterone concentrations, suggesting the reversibility of secondary hypogonadism. Thus, weight loss due to lifestyle changes is associated with a significant increase in LH and testosterone levels [14].

It has been seen that physical exercise (PhyEx) has an impact on the HPG axis, normalizing the infiltration of macrophages related to a high-fat diet and increasing the expression of steroidogenic enzymes, which results in increased levels of LH and the production of testosterone [15].

Regarding drug therapy, previous studies have shown that exenatide plus dapagliflozin combination therapy increased SC lactate production, which has been reported to improve testosterone levels and spermatogenesis [16].

Metabolic syndrome and aromatase activity

The excess of visceral adipose tissue generates a decrease in the serum concentration of sex hormone binding globulin (SHBG), inhibin B (INHB) and levels of free and total concentration of testosterone, however it increases the conversion of testosterone to 17B-estradiol (E2) through aromatase, which is increased.

It has been found that there is a relationship between the increase in aromatase activity and the increase in adipose tissue, which generates a greater conversion of testosterone to E2, resulting in hyperestrogenism. [17-19].

Being a proinflammatory state, obesity generates insulin resistance, so the body tries to maintain homeostasis by producing hyperinsulinemia; which in this case causes a reduction in the hepatic synthesis of SHBG, a glycoprotein which decreases the activity of sex hormones; therefore, when SHBG is decreased, there is a greater activity of E2. INHB is a growth factor that acts by inhibiting FSH, thus stimulating the secretion of testosterone. Leptin resistance decreases kisspeptin expression in the rostral periventricular region of the third ventricle as well as in the arcuate nucleus, thus decreasing GnRH release, and thus FSH, LH, and T secretion [20-22].

Hyperestrogenism includes clinical signs of gynecomastia, sexual dysfunction, loss of body hair, low libido, low sperm quality, fatigue, weight gain and loss of muscle mass, hypogonadism and atrophy of testicles, osteoporosis, hot flashes, decline in cognition and memory loss [23-26].

Although testosterone replacement therapy alleviates the effects of metabolic syndrome by improving insulin and leptin sensitivity, reducing adiposity, and increasing muscle mass, treatment with testosterone is not recommended because it causes hypothalamic axis blockade. -hypo-testis showing defects in spermatogenesis. However, the use of aromatase inhibitors (Letrozole and anastrozole), selective estrogen receptor modulators (Tamoxifen and clomiphene), and LH analogs (Human Chorionic Gonatrophin) have been reported to suppress the conversion of testosterone to estrogens, compete by the estrogen receptor or simulate the effect of LH, respectively, positively impact spermatogenesis, also increase testosterone levels and decrease estrogen levels, relieving the effects of metabolic syndrome on male reproduction, however, the impact of these long-term treatment on fertility and male hormonal regulation needs to be studied [27-30].

Sexuality in metabolic syndrome

It is important to highlight that there are not only physiological aspects that condition sexual deterioration; obesity in these patients prevails a high rate of dissatisfaction with their body image that is altered increasing the frequency of psychiatric conditions such as depression, mood disorders and the use of antidepressants; impairing sexual function. Other added factors that influence the negative results of sexual function and self-esteem are advanced age, lack of marriage, depressive symptoms, fatigue, low energy level, lack of interest, difficulty getting aroused, reaching orgasm and other functional difficulty. Use of antidepressants (except bupropion, trazodone, nefazodone, and mirtazapine) was also found to be associated with less frequent sexual desire. Questionnaires have been used in patients with obesity to collect data focused on symptoms of depression and their consequences, such as the Beck Depression Inventory version 1 and the IWQOL-Lite; where the participants supported the need to reduce their food intake to lose weight, due to associated mood disorders, because that leads to dysfunctional physical activity and sexual limitation. Carrying out physical activity and a hypocaloric diet together with adequate treatment decreases the severity of erectile dysfunction and improves self-esteem, interpersonal relationships, and quality of sexual life. Previous studies have associated depression with candidates for patients seeking bariatric surgery. Finally, it is an analysis that shows deterioration of different predisposing psychosocial factors that continues in the search for future research [30-35].

CONCLUSIONS

Metabolic syndrome is an endocrine disorder that involves systemic alterations of intermediate metabolism, cardiovascular, hormonal, and reproductive systems. There is sufficient evidence showing that men with MetS present infertility and endocrinological disorders of sexual hormones, the main factor is an excess of adipose tissue that secretes adipokines (increase in leptin and decrease in inhibitor B) that deregulate the hypothalamus-pituitary-testis axis (decrease in GnRH, FSH, LH and testosterone and increase in circulating estrogens). It is common to observe low sperm quality, showing lower seminal volume, decreased total sperm count, decreased motility and vitality, and high levels of sperm DNA fragmentation, gynecomastia, sexual dysfunction, loss of body hair, low libido, low sperm quality, fatigue, weight gain and muscle loss, hypogonadism and testicular atrophy, osteoporosis, hot flashes, decreased cognition and memory loss as well as changes in sexual health presenting a high rate of dissatisfaction with their body image reflected in depression, mood disorders and the use of antidepressants. Despite everything, these conditions are reversible, since there are more and more clinical trials showing that weight loss and remission of MetS, whether through diet, exercise or pharmacological and/or surgical treatment, improves sperm quality, increased testosterone levels and decreased estrogen (restoration of the hypothalamus-pituitary-testis axis) and improvement in sexual function. However, in clinical practice it is rare to observe an evaluation of the male reproductive system in patients who are MetS both physically and psychologically, which is why we

strongly recommend that physicians take a complete medical and sexual history of all patients who have been diagnosed with MetS.

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CONFLICT OF INTEREST

The authors declare they have no conflict of interest.

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