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Metabolic Syndrome and Male Fertility: A Mini Review

Rabari Darshan Somabhai[1*], Maksood Khan[2], Kanika Sahal[3], Ganpat Rajpurohit Singh[4]

1. General Medicine Faculty, Sub-Internal Diseases, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan
2. Intern doctor at Jln Hospital Nagaur, Rajasthan, India
3. General Medicine Faculty, Sub-Internal Diseases, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan
4. General Medicine Faculty, Sub-Internal Diseases, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan

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Abstract

Metabolic syndrome is a cluster of conditions that have a negative impact on human health overall. Its prevalence has been rapidly increasing worldwide and has coincided with a global decrease in birth rates and fertility potential. This mini-review aims to address the observation by studying the relationship between Metabolic Syndrome and male reproductive health. The impacts of obesity, dyslipidemia, hypertension, and insulin resistance on male fertility were examined, and supporting evidence explaining the pathophysiology of sperm dysfunction with each Metabolic Syndrome component was described. Adopting a healthy lifestyle appears to be the single most important intervention to prevent the unwanted impacts of Metabolic Syndrome on men's health and fertility. Further studies addressing the components of Metabolic Syndrome and their impact on male reproduction are required to enhance our understanding of the underlying pathophysiology and to propose new methods for therapeutic intervention.

Keywords: Dyslipidemias; Glucose Intolerance, Obesity, Male Infertility, Metabolic Syndrome

Introduction

Metabolic syndrome (Metabolic Syndrome) describes a cluster of abnormalities including obesity, dyslipidemia, hypertension, and insulin resistance. Its discovery goes back to the early twentieth century when Kylin (1) first described a combination of metabolic disturbances, namely hypertension, hyperglycemia, and gout. In years of 1940, Sir Vague (2) noticed a correlation between upper body adiposity, diabetes, and hypertension, which then made Haller and Hanefeld (3) both, coin the term Metabolic Syndrome in 1975, defining it as a combination of simultaneous risk factors (diabetes, cardiovascular disease) that are hazardous to human health. Other nomenclatures came out in later years such as Syndrome X (1988) (4), the Deadly Quartet (1989) (5), and the Insulin Resistance Syndrome (1992) (6). Nevertheless, disparities are still expressed regarding the exact diagnostic criteria used to define Metabolic Syndrome; therefore, guidelines proposed by the International Diabetes Federation (IDF) (7), National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) (8), and World Health Organization (WHO) (9) are commonly utilized to recognize the condition in clinical practice (Table 1).

The systemic nature of Metabolic Syndrome motivated the investigation of its deleterious impacts once it may potentially affect many aspects of human physiology. Male infertility is one a direct association between the different components of Metabolic Syndrome and sperm production and function expressed. Infertility affects about 15% of couples attempting to conceive after 1 year of regular unprotected intercourse. Male factor contributes to 20% to 50% of the causes of infertility among couples. The increase in the prevalence of Metabolic Syndrome perceived in recent years has coincided with a decrease in semen quality among adult males. It is therefore intuitive to investigate the available literature linking these two conditions together, which was the primary objective of this review article.

Definitions and Epidemiology of Metabolic Syndrome:

Various definitions for Metabolic Syndrome exist and all of them are based on physiological parameters, such as obesity, glucose and lipid blood levels, and blood pressure (7-11). WHO first invented its true definition in 1998 (12). Because insulin resistance was felt to be central to the pathophysiology of Metabolic Syndrome, evidence for insulin resistance is an absolute requirement in the WHO definition, without it, even if all the other criteria were met, the patient would not have Metabolic Syndrome (Table 1). The NCEP ATP III (8) criteria classify an individual with Metabolic Syndrome when he presents with three of the 5 components described in Table 1.

[*]**Corresponding author:** Rabari Darshan Somabhai, General Medicine Faculty, Sub-Internal Diseases, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan, Email: drabari665@gmail.com

Metabolic Syndrome, according to IDF (7), is met when an individual presents with central obesity (high waist circumference (WC)) plus any two of the criteria present in Table 1.

The absence of a standardized definition for Metabolic Syndrome is one of the reasons why it became difficult to have a clear estimate of its prevalence. Representations of the global patterns of the components of Metabolic Syndrome in males have been published by the WHO. These metabolic issues are influenced by lifestyle factors, age, sex, and race and are increasing out there in the world, thus becoming a subject of concern and an object of research. When analyzing the prevalence of Metabolic Syndrome, it is necessary to take many factors into account. In younger generations, the prevalence of Metabolic Syndrome is mainly influenced by the adopted diagnostic criteria followed by age and ethnicity (13). The prevalence of Metabolic Syndrome is inversely related to the education level, lifestyle (high-fat diet and lack of exercise), and socioeconomic status. Rapid urbanization has been considered a principal factor for the increasing incidence of Metabolic Syndrome (13). It is currently believed that approximately one in five US adults meet the criteria for Metabolic Syndrome (14). The prevalence of Metabolic Syndrome worldwide can go from <10% to 84%; this high variation is dependent on geographic localization, age, race, and ethnicity, as well as the accepted definition (15). Moreover, all the already mentioned factors, genetic background, family history of diabetes, and smoking are additional risk factors that influence the prevalence of Metabolic Syndrome and its components (15).

Table 1. Diagnostic criteria of metabolic syndrome

Criteria	WHO [9]	NCEP ATP III [8]	IDF [7]
Central obesity	Men: waist/hip ratio >0.9 Women: waist/hip ratio >0.85 And or BMI >30 kg/m	Waist circumference: Men: ≥102 cm Women: ≥88 cm	Waist circumference has ethnicity-specific values.
Raised blood pressure	≥140/90 mmHg	Treatment of previously diagnosed hypertension or ≥130/80 mmHg	Treatment of previously diagnosed hypertension or ≥130/85 mmHg
Raised FPG	Impaired glucose tolerance Impaired fasting glucose Type 2 diabetes mellitus	Previously diagnosed of type 2 diabetes mellitus or FPG test ≥100 mg/dL	
Reduced HDL cholesterol	Men: <40 mg/dL Women: <50 mg/dL	Specific treatment for cholesterol or <40 mg/dL in men and <50 mg/dL in women	
Triglycerides	≥150 mg/dL	Specific treatment for lowering the triglycerides or ≥150 mg/dL	

WHO: World Health Organization, NCEP ATP III: National Cholesterol Education Program Adult Treatment Panel III, IDF: International Diabetes Federation, HDL: high-density lipoprotein-cholesterol, BMI: body mass index, FPG: fasting plasma glucose. https://doi.org/10.1161/CIRCULATIONAHA.105.169405

The link between metabolic syndrome and male fertility

Although each disease that represents part of the Metabolic Syndrome definition has impacts on male fertility separately, when put together, these metabolic elements may exert additive impacts on fertility. Studies exploring the impacts of Metabolic Syndrome on male fertility are recent. In 2013, Lotti et. al (16) studied the association between Metabolic Syndrome and clinical characteristics of men of infertile couples. In this study, an age-adjusted model showed that Metabolic Syndrome was associated with a decline in total testosterone without alterations in gonadotropin levels. The same study reported a negative correlation between the number of Metabolic Syndrome components and progressive motility as well as normal morphology in univariate analysis; however, adjusting the study for age and total testosterone, only normal morphology showed the same negative correlation. The risk of erectile dysfunction (ED) increased with the number of Metabolic Syndrome factors, even after adjusting for age and testosterone levels. This study demonstrated an association between Metabolic Syndrome and the presence of hypogonadism, decreased normal sperm morphology, and ED in men of infertile couples. The same group, one year later (17), explored the association between Metabolic Syndrome and prostatic abnormalities in infertile men. In an age-adjusted model, the authors identified that insulin levels increased as a function of Metabolic Syndrome components and showed an inverse correlation with total testosterone levels. This study also reported a negative correlation between Metabolic Syndrome components and normal sperm morphology and a positive correlation between Metabolic Syndrome components and interleukine-8 (a prostate inflammation marker), prostate total and transitional zone volume, arterial peak systolic velocity, texture homogeneity, and calcification size in an age-testosterone-insulin adjusted model. Leisegang et al (18) compared male patients, with and without Metabolic Syndrome, and reported lower sperm concentration, total sperm count, total motility, sperm viability, mitochondrial membrane potential, free testosterone and progesterone levels, and higher sperm DNA fragmentation in men with Metabolic Syndrome. In 2016, Ventimiglia et al (19) examined men presenting with primary infertility with or without Metabolic Syndrome according to the NCEPATPIII criteria. Compared with infertile men without Metabolic Syndrome, infertile men with Metabolic Syndrome were more likely to be hypogonadal, and had lower levels of total testosterone sex hormone-binding globulin (SHBG), inhibin B, and Müllerian hormone (AMH). However, No difference can be ascertained in the parameters of semen between the two groups (19). While somewhere else, a recent study compared the hormone and semen parameters of fertile men to infertile men. Except for a significant negative association between Metabolic Syndrome and total testosterone levels in both groups,

the authors failed to reproduce a significant independent effect for Metabolic Syndrome on major fertility parameters of both groups (20). These studies suggest that Metabolic Syndrome may carry a detrimental effect on important reproductive functions such as endocrine status or semen parameters and call for the development of further research of superior design to accurately determine this association.

Obesity and Male Fertility

1. An overview on obesity

Obesity is classified according to body mass index (BMI) which was promoted by Ancel Keys in 1972 and describes a person's leanness based on their height and weight (weight per height squared, kg/m2) (21). The WHO defines overweight and obesity when the BMI is ≥25 kg/m2 and ≥30 kg/m2), respectively (22) . Obesity is further divided into three classes; class I (BMI, 30.0–34.9 kg/m2), class II (BMI, 35.0–39.9 kg/m2), and class III (BMI, ≥40.0 kg/m2) (21, 23). Obesity can also be diagnosed based on abdominal fat defined as WC ≥102 cm for men and WC ≥88 cm for women (24). The origin of obesity is multifactorial, and involves an interaction between the environment, genetic backgrounds, and hormones (25). Many hormones are involved in the patho-etiology of obesity especially that the adipose tissue is now recognized as an endocrine organ with its excess being a cause for comorbidities (26). Obesity results from excessive accumulation of adipose tissue and consequently weight gain, because of an imbalance between energy intake and expenditure (26, 27). Leptin, a hormone produced by the adipose tissue (28), regulates energy homeostasis (29) and is an essential intermediary of inflammation in obesity (30). Obese men develop leptin resistance and hence have high levels of leptin in their circulation (31). Ghrelin, a hormone secreted by the stomach, is responsible for regulating appetite (32) and is negatively correlated with BMI, meaning that it is lower in the obese (32). Peptide YY (PYY), glucagon like peptide-1 (GLP-1) and cholecystokinin (CCK) are produced by the gastrointestinal tract after food intake (21) is augmenting satiety (33). Obese people secrete lower levels of PYY, GLP-1, and CCK in comparison to people with normal weight (34, 35). The hormonal disturbances causing obesity may exert genetic and congenital backgrounds, such as PraderWill syndrome, leptin deficiency, and Cohen syndrome among others. The ingestion of extreme amounts of food increases inflammation (36), which is also observed with the excessive consumption of salt, sugars, alcohol, and fats (37). This, coupled with smoking and lazy lifestyle, places obese people at risk for a number of chronic diseases, such as hypertension, cancer, and diabetes. The increase in the BMI has been associated with an increase in risk of developing myeloma, leukemia, rectum, thyroid, kidney, colon, and esophageal cancer (38).

2. The link between obesity and male fertility

Recent reports showed a relationship between an increase in obesity rates and a decrease in birth rates. The impacts of overweight and obesity on male fertility is a hot topic in our days with a good number of studies reporting significant impacts of excessive weight on semen parameters and/or hormonal profile of men. A systematic review of 21 cross-sectional and prospective cohort studies originating from 12 countries and including a total of 13,077 individuals recruited from the general population or fertility clinics was conducted to assess the relationship between sperm count and BMI. The authors found a J-shaped association between BMI and abnormal sperm count. Compared with men of normal weight, the odds ratios (95% confidence interval) for oligozoospermia were 1.11 (1.01–1.21) for overweight men, 1.28 (1.06–1.55) for obese men, and 2.04 (1.59–2.62) for morbidly obese men. This meta-analysis quantifies a two-fold increase in risk of oligozoospermia in morbidly obese men (39).

More recent studies have also confirmed this negative association between BMI and various semen parameters. Tang et al (40) assessed the correlation between BMI and semen analysis parameters of infertile patients finding a significant negative correlation between BMI and sperm motility. Another study of similar design reported significant negative correlation between BMI and sperm concentration (41).

Bieniek et.al. (42) conducted a multi-institutional study including infertile men looking for a relationship between semen and hormone parameters and the patients' BMI. The authors found a significant inverse relationship between BMI and sperm concentration, sperm morphology, total testosterone, and testosterone: estradiol ratio. Studies exploring the impact of BMI on advanced sperm function test also have yielded detrimental impacts where a significantly increased rate of sperm DNA damage and lower mitochondrial activity have been observed in obese men compared with men of normal weight (43, 44). Furthermore, the impact of obesity on sex hormone levels has been more evidently acknowledged with a negative correlation between total or free testosterone (45-47), luteinizing hormone (LH) (45,46), SHBG (46,47), inhibin B (47), and AMH (47) and increasing BMI have been reported. Overall, a clear association between altered sperm parameters, DNA fragmentation and fluctuations in hormonal levels and obesity was detected by several studies.

The impacts of obesity on male fertility and sperm functions can occur as a consequence of several mechanisms: ix an imbalance between testosterone and estradiol ratio and consequently other sexual hormones due to the excessive aromatization in adipocytes; ii) excessive inflammation and oxidative stress resulting from the high levels of adipokines and toxins in adipose tissue of obese men; iii) increase of gonadal temperature due to an accumulation of fat tissue in the scrotal region impairing spermatogenesis; iv) dysregulation of several hormones, such as leptin that can alter the hypothalamus-pituitary-gonad (HPG) axis). The maintenance of testosterone levels is crucial for male fertility status.

The link between obesity and testosterone deficiency is supported by many studies (45-47). Testosterone levels in obese males are commonly related with levels similar to hypogonadal men (21, 48). In obese men, an increase in the activity of aromatase enzyme in the adipocytes results in the peripheral conversation of testosterone into estradiol (21, 48). Once the levels of estradiol rise, negative feedback on LH secretion is observed, leading to the suppression of the HPG axis and consequently a reduction in testosterone production by Leydig cells (48). Estradiol also plays a critical role in the development of germ cells and variations in levels of estrogen can affect spermatogenesis (49). Adipocytes are the main producers

of leptin, and this hormone per se affects LH and follicle-stimulating hormone (FSH) release from the pituitary, altering not only the amplitude of the released pulses, but also the pulsatility; this affects the balance of the HPG axis in case of excess of adipose tissue (50,51) . The deposition of fat tissue around the scrotal vessels can reduce spermatogenesis in obese men decreasing blood cooling and consequently increasing testicular temperature (52, 53). The relationship between scrotal lipomatosis and male infertility was described in a study that confirmed a diffuse pattern of fat deposition around the structures of the spermatic cord in obese men (52). Another study showed an improvement of sperm quality after a scrotal or suprapubic lumpectomy (53). More recent studies explored the connection between oxidative stress and the fertility status of obese men. Oxidative stress is an acknowledged cause of sperm dysfunction as it causes sperm membrane lipid peroxidation, DNA fragmentation, and aggravates apoptosis (54). Obese men are particularly prone to oxidative stress. The excess in adipose tissue is associated with an increase in local and systemic production of pro-inflammatory adipocytokines (55), which induce the production of reactive oxygen species (ROS). Furthermore, increased oxidative stress leads to important changes in adipose tissue, promoting a systemic low-grade inflammatory response with adverse impacts throughout the body including the reproductive tract (56). Finally, ED is another important factor to consider in patients seeking fertility. Obese men are at higher risk of ED (57) due to lower testosterone levels and high levels of inflammatory factors (58, 59).

Glucose Intolerance and Male Fertility

1. An overview on the impairment of glucose metabolism

The maintenance of plasma glucose is crucial for the physiological functions of the body. Glucose is the sole energy fuel for cells protected by blood-barriers, such as the brain (60) and testes (61). The diagnosis of glucose impairment is achieved through monitoring glucose levels in blood stream, such as measuring the fasting glucose or with an oral glucose tolerance test. For the measurement of fasting glucose, the cut point for prediabetes is 100–125 mg/dL, while that for diabetes mellitus (DM) is ≥126 mg/dL (62). After an oral glucose tolerance test, prediabetes is diagnosed when the blood sugar is 140–199 mg/dL and DM is diagnosed when the blood sugar is ≥200 mg/dL (62). Hypoglycemia is defined as abnormally low glucose concentration that is harmful for the patient with values <70 mg/dL considered alerting. On the other hand, hyperglycemia is detrimental to human health as a slight increase in plasma glucose concentrations can raise the risk of cardiovascular diseases. While obesity is considered a major risk factor for dysregulation of glucose metabolism, other environmental and genetic factors can also contribute to this condition (63). Impairment of glucose metabolism is a key component of Metabolic Syndrome. Insulin is the principle regulator of glucose metabolism. This hormone is produced by the pancreatic β-cells to facilitate uptake of glucose from the blood stream into cells and tissues. Insulin resistance is defined as the reduced sensitivity of cells to stimulation by insulin in normal or elevated levels of glucose. As a result, the pancreas will secrete more insulin, resulting in a state of hyperinsulinemia. With continued insulin resistance, hyperglycemia ensues, causing glucose intolerance and finally type 2 DM (T2DM) (63).

2. The link between impairment of glucose and male fertility

Similar to obesity, studies demonstrated a correlation between the increase in the incidence of DM and a decrease in the fertility rates (64). A study comparing patients with T2DM to non-diabetic men attending a fertility clinic showed lower progressive motility and an increase in sperm DNA fragmentation in diabetic patients (65). Also, the clinical pregnancy rate and the miscarriage rate were higher when the male partner was diabetic (65). Another study of similar design also confirmed the presence of lower sperm concentration and total count in semen of diabetic patients compared with healthy individuals (66). A study conducted in normozoospermic T2DM and non-diabetic men detected higher levels of malondialdehyde, a marker of oxidative stress, in diabetic patients that was consistent with lower sperm concentration, motility and normal morphology in this group compared with non-diabetic men (67). In addition to the negative impacts on sperm count, motility, and DNA integrity, lower ejaculate volumes were also observed in diabetic men (68). The aforementioned studies provide solid evidence on the negative impacts of diabetes on male fertility. The pathophysiology of these impacts has been studied in a number of human and animal models and are believed to occur secondary to alterations in testicular environment, testosterone homeostasis, ejaculatory function, and libido (69). Testicular environment is highly controlled by glucose homeostasis that can be deregulated in DM thereby impairing spermatogenesis (70, 71). Animal studies reported excessive damage to seminiferous tubules early in the development of DM impairing the gonadosomatic index, as well as sperm quality (72). Experimental induction of DM in mice resulted in enhanced lipid peroxidation in testis (cytosol and mitochondria) and epididymal sperm and increased ROS production as early as 5 days following the experiment (73). This suggests that oxidative stress is increased in diabetes due to overproduction of ROS. Associated with the ROS generation is a decreased efficiency of antioxidant defenses, which is a process that starts very early and worsens over the course of the disease. Many studies have focused on the derangement in testosterone levels in men presenting with DM. A cause– effect relationship exists between testosterone and DM where lower levels of testosterone are typically present in diabetic men, increasing the risk for developing T2DM occurs when testosterone concentrations are low (74). This is because testosterone improves insulin sensitivity and hence glucose homeostasis. Testosterone is also an important regulator of spermatogenesis as a number of genes and kinases on Sertoli cells are directly influenced by testosterone levels (75). Therefore, the decreased testosterone levels could help explain the alteration in sperm production seen in diabetic patients. Sexual dysfunctions such as erectile and ejaculatory dysfunction as well as decreased libido are common in patients with DM (76). Retrograde ejaculation (RE) occurs as a consequence of a diabetic autonomic neuropathy (77). It

has a devastating effect on male fertility potential as it decreases the ejaculate volume and hence the sperm quantity. The sympathetic nervous system plays an important role during emission and expulsion phases of ejaculation. It orchestrates smooth muscle contraction of the seminal vesicles and ejaculatory ducts and simultaneously ensures bladder neck closure to prohibit retrograde flow of semen into the bladder. Sympathetic nervous system dysfunction has been detected in patients with DM resulting in RE (78). One study reported the presence of RE in 34.6% of diabetic men in comparison to 0% in nondiabetic men, demonstrating the presence of aspermia in diabetic men with RE (77). ED is more prevalent in diabetic men compared with the general population (79). Diabetic patients are prone to neurovascular alterations which can induce impairment of the endothelial function of the corpus cavernosum and therefore result in organic ED (80, 81). Endothelial dysfunctions are a reflection of a decrease/loss in nitric oxide (NO) biological activity and/or biosynthesis at endothelial level (82). Although, in diabetic men, the pathogenic mechanisms of endothelial function still remain unclear; impairment of NO activity, an essential molecule for penile vascular and cavernous smooth muscle activity has been observed in diabetic men (83).

Does The Treatment Of Metabolic Syndrome Affect Fertility?

Weight loss through adoption of a healthy lifestyle in addition to regular physical activity is the cornerstone treatment for Metabolic Syndrome. An improvement in sperm quality is expected as weight reduction would alleviate the previously mentioned deleterious impacts of obesity on human reproduction. This belief has been proven in studies that explored the effect of natural weight reduction on male fertility. Håkonsen et al (84) studied semen samples men with BMI>33 kg/m^2 who underwent a 14-week weight loss program. Following the intervention, the median percentage weight loss was 15%. An increase in total sperm count, semen volume, testosterone, SHBG, and AMH were also observed. A larger study by Jaffar (85) included obese men who underwent diet counselling and exercise resulting in mean BMI loss of 2.2 kg/m^2. The author observed a significant positive correlation between weight loss and percentage of progressive sperm motility and static percentage. On the other hand, the effect of weight loss following bariatric surgery on semen parameters and male fertility is still controversial with some studies reporting no or worse influence while others finding an improvement in semen parameters following bariatric surgery. The imbalance in electrolytes and nutrients observed after these mal-absorptive surgeries may explain the observed worsening in semen parameters that occur shortly after surgery (86, 87). However, newer evidence detected significant improvements in semen parameters with longer periods of follow-up after surgery (88).

Conclusions

Metabolic Syndrome is increasing worldwide almost approaching the pandemic state. Its key components, namely, obesity, insulin resistance, dyslipidemia, and hypertension may exert detrimental impacts on various aspects of human health. Male fertility is one condition that can be influenced by Metabolic Syndrome through several mechanisms. Endocrine system dysregulation, scrotal temperature elevation, oxidative stress, and alteration of the erectile and ejaculatory functions are well recognized Metabolic Syndrome consequences that can impair sperm production and function, ultimately affecting male fertility. A healthy lifestyle characterized by good nutrition and regular physical activity is key to prevent the unwanted impacts of Metabolic Syndrome not only on fecundity but also on health and well-being overall.

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