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THE METABOLIC SYNDROME AND MALE INFERTILITY

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Running Head: The Metabolic Syndrome and Male Infertility

Summary Sentence: This review article summarizes the growing body of literature which has identified a link between metabolic syndrome and impaired male reproductive health.

Abstract:

Metabolic syndrome (MetS) is highly prevalent, affecting over 47 million US residents. This condition is also multi-faceted, potentially leading to significant disturbance of numerous physiological processes. This review article evaluates the literature regarding metabolic syndrome and male reproductive health. Links between obesity, dyslipidemia, hypertension, and insulin resistance are each examined with regard to their associated detrimental effects on male fertility. At the end of this manuscript, we propose a new MetS/Male Infertility paradigm. Additional studies specifically addressing the components of MetS and their impact on male reproduction will enhance our understanding of the underlying pathophysiology. These studies may also help clarify the role for therapeutic intervention.

INTRODUCTION

In recent years, the Metabolic Syndrome (MetS) has garnished much attention due to its association with the development of non-insulin dependent diabetes mellitus (NIDDM) and cardiovascular disease. MetS represents a constellation of abnormalities including overweight (visceral abdominal fat distribution), dyslipidemia, hypertension and impaired glucose metabolism with insulin resistance as the hypothesized underlying pathogenic mechanism. Current estimates suggest a 23.7% prevalence among the United States population, with 47 million affected US residents as of the year 2000 (Ford et al, 2002). Though disparity exists in definition and exact diagnostic criteria, guidelines presented by the Adult Treatment Panel III (ATP III) are often cited in the literature and presented in Table 1. The numerous deleterious effects of MetS are being investigated throughout the medical community as MetS may potentially affect many aspects of human physiology due to its systemic nature.

Male factor infertility may represent one such perturbation in some male patients with MetS. It is estimated that 15% of couples attempting to conceive are not able to do so within one year. Male factor infertility is present in 20-50% of these couples, either independently or in conjunction with female factor infertility issues (Sigman and Jarow, 2002). In the setting of an increasing prevalence and understanding of MetS, investigators are actively studying the potential relationship between MetS and male factor infertility. Insight gained from this innovative work may provide increased therapeutic options for male partners in affected infertile couples. This review will evaluate MetS and its components in order to establish a paradigm with male factor infertility.

Obesity and Infertility

Obesity is a cardinal feature of MetS. Adverse effects of obesity on male fertility are postulated to occur through several mechanisms. First, peripheral conversion of testosterone to estrogen in excess peripheral adipose tissue may lead to secondary hypogonadism through hypothalamic-pituitary-gonadal axis inhibition. Second, oxidative stress at the level of the testicular microenvironment may result in decreased spermatogenesis and sperm damage. Lastly, the accumulation of supra-pubic and inner thigh fat may result in increased scrotal temperatures in severely obese men. These mechanisms are examined below.

Several studies have demonstrated perturbation in the hypothalamic-pituitary-gonadal axis in obese men with resultant significant depression in total testosterone and sex-hormone-binding globulin (SHBG) (Amatruda et al, 1978, Glass et al, 1977, Kley et al, 1980, Schneider et al, 1979, Strain et al, 1982, Zumoff et al, 1990). Variable results were noted for free testosterone in the various studies cited. While some authors argued that decreased SHBG allows for normalization of free testosterone in the setting of low total testosterone (Schneider et al., 1979), others have observed a decrease in all three (free testosterone, total testosterone and SHBG) (Amatruda et al., 1978, Strain et al., 1982, Zumoff et al., 1990). This latter finding is supported by Zumoff et al who reported a negative correlation between free testosterone and BMI (Zumoff et al., 1990). SHBG is especially relevant in obese males who are insulin resistant, as insulin is known to inhibit SHBG synthesis (Pasquali et al, 1995, Plymate et al, 1988). Several studies have demonstrated that SHBG and total testosterone are inversely correlated with both BMI and insulin levels (Osuna et al, 2006,Phillips, 1993,Seidell et al, 1990,Tsai et al, 2004,Vermeulen et al, 1996). In summary, total testosterone, free testosterone, and SHBG are all commonly decreased in obese males (Pasquali et al., 1995).

In the aforementioned studies, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels were normal or low in obese men (Amatruda et al., 1978, Glass et al., 1977, Strain et al., 1982). Amatruda et al and Strain et al argue that even normal levels of gonadotropins in the context of low free testosterone signify suppression of the hypothalamic-pituitary axis, resulting in subclinical hypogonadotropic hypogonadism (Amatruda et al., 1978, Strain et al., 1982). In support of this argument is the observation that LH pulse-amplitude, but not pulse-frequency, is decreased in obese men with hypogonadism (Vermeulen et al., 1996). Elevated estrogens, made by aromatization of androgens in peripheral adipose tissue in obese men, provide a possible explanation for suppression of the hypothalamic-pituitary axis (Kley et al., 1980, Schneider et al., 1979, Strain et al., 1982). Thus, the observed decrease in testosterone levels in obese males is likely due to several factors including: decreased synthesis of testosterone, inhibition of SHBG synthesis, and decreased gonadotropin secretion (Pasquali et al., 1995). As a result, this population may be at an increased risk for infertility.

Jarow and colleagues studied 120 men categorized into obese or non-obese, and fertile or infertile groups (Jarow et al, 1993). Obesity was defined by Metropolitan Life Insurance tables as greater than 135% of ideal body weight, not by BMI. Fertility status was determined by records at an infertility clinic indicating infertile marriages greater than one year and abnormal semen parameters. The authors found that men who were both infertile and obese had significantly lower testosterone levels and testosterone/estradiol ratios than fertile/nonobese, fertile/obese and infertile/nonobese counterparts. Interestingly, infertile/obese males had significantly lower SHBG with significantly higher levels of bio-available testosterone and estradiol. No differences were noted between the groups when estradiol and LH were evaluated. FSH was not examined. The authors suggested that the primary aberration was decreased SHBG, leading to elevated bio-available testosterone and estradiol. They postulated that these changes, in turn, lead to establishment of a lower total testosterone set-point in the hypothalamic-pituitary-gonadal axis**.** Though this hypothesis differs from the others described above, the study reveals aberrations in male endocrine-reproductive homeostasis that may lead to decreased fertility. This study further highlights the need for additional evidence correlating hormonal dysregulation in obese males to infertility.

To date, few studies have examined the relationship between objective measures of obesity (weight, BMI, waist to hip (W/H) ratio, etc.) and semen quality. Magnusdottir et al examined life-style and environmental factors, which have been hypothesized to adversely affect semen quality (Magnusdottir et al, 2005). The study population included 72 men from a single clinic for assisted reproduction who had been categorized into three groups: male factor subfertility (MFS), female factor subfertility (FFS) and idiopathic subfertility (IS), with semen analyzed as per World Health Organization (WHO) criteria. The authors found a threefold increased incidence of obesity (BMI>30) in patients with MFS compared to the other two groups. Furthermore, patients in the MFS group had a significantly higher BMI (27.8 (21.8-38.6)) compared to those in the FFS group (25 (19.7-45.6)). Interestingly, after combining the IS and FFS groups, the authors found that BMI was negatively correlated with sperm concentration and sperm count. No such correlations existed within the MFS group. The authors also examined levels of work activity, defined as sedentary (office environment), intermediate (salesmen) and active (laborers). They found that when patients in the IS and FFS groups were stratified into groupings of “low normal” and “high normal” sperm concentrations, significantly more men with low normal sperm density had an associated sedentary level of work activity. These results were attributed by the authors to elevated scrotal temperatures associated with sedentary activity rather than with obesity itself. Though these results are intriguing, they are limited by sample size and self-reported heights and weights.

The above findings were corroborated by Fejes et al in a study of 81 infertile men of reproductive age (37±5.4yrs) (Fejes et al, 2005). The authors excluded those men with confounding factors such as chronic diseases, reproductive organ abnormalities, reproductive pathology, seminal infection and social factors. Correlations between anthropometric data and semen analysis parameters (WHO criteria) and reproductive hormonal levels were analyzed. The authors found that semen volume was negatively correlated with both waist circumference and W/H ratio; total sperm count was negatively correlated with weight, waist circumference, and hip circumference; total motile sperm was negatively correlated with weight, waist circumference, and hip circumference; and total rapid progressive motile sperm count was negatively correlated with hip circumference and waist circumference. Furthermore, weight, BMI, waist circumference, hip circumference and W/H ratio all significantly negatively correlated to testosterone, testosterone/17β-estradiol and SHBG, but not FSH, LH or 17β -estradiol levels. This data suggests a potential link between obesity, hypogonadism and infertility as indicated by semen analysis.

Similar to the above studies, Kort and colleagues analyzed the correlations between BMI and traditional semen parameters (volume, sperm concentration, percent sperm motility, percent normal sperm morphology) and sperm chromatin integrity in 520 male partners of infertile couples (Kort, December 8, 2005). The mean age was 34.6 years (26-45 years), and patients were excluded if they had undergone prior reproductive surgery. The authors also assessed semen quality by normal-motile spermatozoa (NMS), defined as volume*concentration*percent motility*percent normal morphology (with morphology defined by Tygerberg criteria). Sperm chromatin integrity was examined by DNA fragmentation index (DFI). Patients were stratified by BMI with ranges of normal (20-24), overweight (25-30) and obese (>30), and the groups were then compared by the above measures of semen quality. The authors found a significant negative correlation between BMI and NMS with significant differences among all BMI groups: normal 18.6×10^6 NMS, overweight 3.6×10^6 NMS, and obese 0.7×10^6 NMS. Additionally, a significant direct correlation was found between BMI and DFI, indicating increased DNA fragmentation with increased BMI. No statistically significant differences were found between the overweight and obese groups.

In summary, the above three studies suggest a paradigm in which obesity is negatively correlated with NMS and positively correlated with sperm DNA damage. This in turn suggests decreased reproductive potential in obese men. However, a biological correlate is necessary to simultaneously account for both decline in NMS and increase in DNA damage. As such, oxidative stress is an attractive candidate.

Oxidative stress is a pathophysiological process common in a number of disease states including autoimmune, cardiovascular and infectious processes. Oxidative stress arises when an excess concentration of reactive oxidative species (ROS), molecules harboring an unpaired electron, are present in a particular physiological environment. These highly reactive and unstable molecules are capable of inducing significant cellular damage throughout the body. In regard to male reproductive health, several studies have revealed that oxidative stress results in sperm membrane lipid peroxidation with impairment in sperm motility and sperm-oocyte interaction. Kodama and colleagues showed that the DNA of spermatozoa from infertile men had greater oxidative injury when compared to controls (Kodama et al, 1997), and Twigg et al (Twigg et al, 1998) reported similar findings using an in vitro study in which ROS generation led to an increase in sperm DNA fragmentation. In sum, oxidative stress may also result in lipid peroxidation of the sperm membrane leading to decreased motility and membrane dysfunction; excessive oxidative stress may also result in sperm DNA damage with diminished genetic viability of the affected sperm.

Numerous authors have noted that MetS and several of its components, namely obesity, insulin resistance, and dyslipidemia, are associated with systemic pro-inflammatory states and increased oxidative stress with lipid peroxidation (Dandona et al, 2005, Davi and Falco, 2005). The elevated DFI noted in obese men by Kort et al. may indeed reflect an abnormally increased oxidative state in the testicular microenvironment and excurrent ductal system explaining the increased DNA damage in obese men.

In addition to the molecular and hormonal changes in obesity, gross mechanical causes may also play an important role in impairing male reproductive health. Suprapubic and thigh fat have been postulated by some investigators to cause elevated scrotal temperatures, thus decreasing fertility. Shafik and Olfat described both normal

(28 normal cadavers) and infertile (44 infertile males) scrotal fat patterns (Shafik and Olfat, 1981). The authors used the term "scrotal lipomatosis" to characterize abnormally distributed scrotal fat present along the spermatic cord and testes. Scrotal lipomatosis was present in 38 (86%) of the 44 infertile males, with 24 (63%) of these 38 being obese. The study also noted specific patterns of scrotal lipomatosis in obese infertile males not seen in infertile, non-obese patients. Shafik and Olfat reported that scrotal lipectomy resulted in significant improvement in semen quality (sperm count, percent motility and morphology) in 65% of patients. Additionally, 20% of the patients achieved pregnancies after lipectomy (Shafik and Olfat, 1981). No formal control group was included in this study, and selection bias may thus account for some of the observed findings. To our knowledge, no other groups have investigated scrotal lipectomy as a purported therapeutic modality for infertility due to obesity.

Shafik and Olfat also report in their series that all 38 cases of scrotal lipomatosis demonstrated varicosity of the cremasteric veins and 20 cases demonstrated varicosities of the pampiniform plexus; however, the varicosities were not clinically palpable. The authors suggest that the increased incidence of varices they observed with scrotal lipomatosis may contribute to infertility, especially in obese males. However, more recent studies argue against this assertion. In a study of 398 males with varices, Nielsen and colleagues reported an inverse relationship between varicocele formation and BMI, suggesting that adipose tissue may protect against the "nutcracker effect" (Nielsen et al, 2006). Handel et al. also demonstrated a decreasing prevalence of varicocele with increasing body mass in a study of 3,213 infertile men (Handel et al, 2006). Finally, Prabakaran et al. also reported varicoceles were more prevalent in tall boys with a lower BMI, who had quickly progressed through puberty (Prabakaran et al, 2006).

Handel et al. raise the relevant question as to whether the decreased prevalence of varicoceles in obese men is true anatomically or an issue of decreased detection due to body habitus (Handel et al., 2006). Scrotal lipomatosis in obese men, as described by Shafik and Olfat, may signify a distinct pathological manifestation of obesity involving the scrotum hindering varicocele detection. While the literature is thus not entirely clear regarding the true prevalence varicoceles in obese men, ample evidence suggests that varicoceles are associated with a large number of detrimental changes, including decreased sperm motility, increased germ cell apoptosis, and testicular atrophy which may compound the numerous potential hormonal and molecular aberrations in obese men with infertility (Barqawi et al, 2004, Schlesinger et al, 1994).

Diabetes and Infertility

Insulin resistance is considered by many investigators to be an underlying pathological aberration in MetS. As such, studies from patients with NIDDM provide important insight into a MetS-infertility paradigm.

A growing body of literature has detailed the relationship between hypogonadism and NIDDM, including three epidemiological studies that suggest hypogonadism is a risk factor for diabetes. Haffner and associates analyzed data from the MRFIT cohort (Haffner et al, 1996), demonstrating a significant risk of developing NIDDM in participants who had low SHBG. Stellato et al found that low SHBG values, as well as low free testosterone levels, were predictive of developing NIDDM using multiple regression models on data from the Massachusetts Male Aging Study (Stellato et al, 2000). Similar data was reported by Oh et al. from the prospective Rancho Bernardo Study, which found that low total testosterone levels predicted the subsequent development of NIDDM (Oh et al, 2002). While the above three studies suggest that hypogonadism is predictive of subsequent development of NIDDM, the underlying pathophysiology has not been fully established. Insulin resistance may indeed be a common etiology for both hypogonadism and onset of NIDDM.

Several other studies observed higher rates of hypogonadism in men with previously diagnosed NIDDM. Barrett-Connor et al found that both serum testosterone (free testosterone not assessed) and SHBG were significantly lower in men with NIDDM versus controls, even after adjustment for age and BMI (Barrett-Connor et al, 1990). These findings were corroborated by Anderson et al. In addition to serum testosterone, these authors also investigated free testosterone; however, they found no difference in free testosterone in patients with NIDDM versus controls (Anderson, 1994). Chang and associates noted significantly decreased levels of serum testosterone (free testosterone and SHBG not assessed), but not FSH and LH in elderly men with NIDDM versus age-matched controls (Chang et al, 1994). Most recently, Dhinsa et al observed a 33% incidence of hypogonadism in men with NIDDM in a diabetes management center (Dhinsa and al., 2004). Furthermore, these authors noted significantly decreased FSH and LH in participants from the hypogonadal group compared to the eugonadal group, suggesting a substantial rate of hypogonadotropic hypogonadism among men with NIDDM. Pitteloud et al. subsequently reported that increasing insulin resistance was associated with decreased testosterone secretion at the testicular level (Leydig cell) and not due to changes in hypothalamic or pituitary function (Pitteloud et al, 2005). While these studies collectively demonstrate an association between NIDDM and hypogonadism, the specific relationship between NIDDM and hypogonadism is still not fully elucidated and should be addressed in future studies.

Therapeutic metabolic effects of testosterone have been demonstrated in men with NIDDM and hypogonadism. In an open-label, randomized, controlled trial, Boyanov and associates showed that middle-aged men with NIDDM, (visceral) obesity and symptoms of androgen deficiency experienced statistically significant improvement in all of these parameters when treated with testosterone undecanoate daily for 3 months(Boyanov et al, 2003). Specifically, patients experienced decreased blood glucose and HbA1c values with improved symptoms of androgen deficiency. In a similar study, Kapoor and colleagues administered intra-muscular testosterone every 2 weeks for 3 months to 24 hypogonadal males with NIDDM in a double-blind, placebo-controlled study with cross-over (1 month washout). The authors demonstrated beneficial effects on glycemic control, insulin resistance, total cholesterol and visceral adiposity. These studies demonstrate a possible therapeutic role for testosterone in men with NIDDM and hypogonadism, with improvement in numerous metabolic deficiencies in co-morbid patients. Thus, future studies evaluating the impact of agents such as the LH agonist human chorionic gonadotropin (HCG), and the selective estrogen receptor modulator clomiphene citrate are necessary in order to assess efficacy in optimizing serum testosterone levels in these hypogonadal men with DM. Such studies will be very important as exogenous testosterone replacement therapy suppresses spermatogenesis, and is thus contraindicated in hypogonadal men striving to achieve pregnancy.

Ali and associates evaluated 314 men with NIDDM (N=314) with neuropathy and reported a higher sperm concentration and lower sperm motility compared with diabetic men without neuropathy and controls (Ali et al, 1993). Though limited, this data suggests sperm dysfunction in some men with NIDDM. The factors leading to paradoxically increased sperm concentration in men with NIDDM and neuropathy in this study are unclear, but the authors observed a decrease in semen volume in these patients, which may suggest decreased seminal secretion and an overall concentration of the ejaculated sperm.

Erectile dysfunction (ED), failure of seminal emission and retrograde ejaculation are known complications of NIDDM that impact male reproductive potential. ED in patients with NIDDM stems in part from autonomic neuropathy and vascular disease. Several epidemiological studies have demonstrated an increased risk of ED in men with DM (Braun et al, 2000,Johannes et al, 2000,Nicolosi et al, 2003) and an increased severity of ED with worsening NIDDM (De Berardis et al, 2003). Failure of emission and retrograde ejaculation also results from autonomic neuropathy, with an estimated 32% of men with DM affected by some degree of ejaculatory dysfunction (Shaban et al, 1991). In total, ejaculatory dysfunction may represent the most common cause of infertility in diabetic men (Sexton and Jarow, 1997). As such, clinicians evaluating diabetic patients with MetS should obtain postejaculatory urinalysis to rule out retrograde ejaculation if the clinical findings warrant, such as a low ejaculatory volume. Therapies such as oral sympathomimetics (i.e. pseudoephedrine) and certain tricyclic antidepressants (i.e. imipramine), sperm isolation from urine, electroejaculation and assisted reproductive techniques may facilitate reproductive efforts in these same patients.

Dyslipidemia and Infertility

Dyslipidemia is another sentinel feature of MetS that may impact semen quality and fertility. Ramirez-Torres and colleagues studied 106 male partners from infertile couples (Ramirez-Torres et al, 2000), reporting a 65% incidence of dyslipidemia defined by isolated hypercholesterolemia, triglyceridemia, or both. The incidence of obesity (18%), overweight (30.2%), hypertension (26%), glucose intolerance (15%) and DM (4.7%) were also reported, though no correlation with sperm abnormalities was observed. While this study suggests a relationship between lipid abnormalities and infertility, no clear mechanism was postulated. However, as described previously, oxidative stress is an attractive candidate.

This hypothesis is supported in a recent study by Shalaby and associates (Shalaby et al, 2004). The authors examined the effects of a high-cholesterol diet and anti-cholesterol therapy on male rat fertility, finding that male rats fed with a high-cholesterol diet (1% by composition) had significant declines in fertility, testicular weight, and sperm characteristics compared to male rats with a cholesterol-free diet. Furthermore, the investigators treated male rats on a high-cholesterol diet with no-intervention, α-tocopherol (an anti-oxidant), simvastatin (a lipid-lowering agent), or both therapeutic agents. Treatment with α-tocopherol, simvastatin and the two in combination significantly increased the fertility index (mating success rate) from 42.5% to 71.5%, 61.25% and 79.5%, respectively. Increased fertility seen with combination therapy was significantly superior to simvastatin alone, but not to α-tocopherol alone. Additionally, all three treatment groups demonstrated significantly increased testicular weight, sperm count, sperm motility, sperm viability and significantly decreased sperm abnormalities. In this aspect of the study, combination therapy was superior to both individual therapies, which were not significantly different from one another. The authors not only demonstrated decreased fertility with a high-cholesterol diet, but they also showed therapeutic gain in fertility with antioxidant and lipid lowering agents. These results support a potential role for dyslipidemia-induced oxidative stress in the testes and/or excurrent ductal system leading to decreased fertility.

Hypertension and Infertility

Hypertension is defined as a blood pressure greater than 130/85 mmHg by ATP III criteria and represents a major risk factor for cardiovascular disease. While hypertension is a well-established risk factor for erectile dysfunction, the direct effect on male fertility, if any, is less well understood. End-organ damage is a well-documented aspect of hypertension, but to date, testicular end-organ injury caused by HTN has not been clearly defined. Several studies examining hypertensive men demonstrated a significant inverse relationship between blood pressure and total serum testosterone, which could be associated with impaired reproductive potential (Fogari et al, 2002,Khaw and Barrett-Connor, 1988,Phillips et al, 1993), free testosterone (Hughes et al, 1989,Phillips et al., 1993,Svartberg et al, 2004) and sex hormone binding-globulin (Svartberg et al., 2004). This observed relationship between elevated blood pressure and decreased androgens is not clear, although some authors suggest that androgen deficiency may be the root cause of HTN by inducing increased arterial stiffness (Dockery et al, 2003). Other studies demonstrate that male patients treated with androgen suppression have increased aortic and arterial stiffness compared to age-matched controls (Dockery et al, 2002, Dockery et al, 2000). Of note, studies examining the effects of antihypertensive agents on testosterone levels found treatment either decreases or has no effect on testosterone levels depending on the agent employed (Andersen et al, 1998, Fogari et al, 2002, Koshida et al, 1998, Suzuki et al, 1988). To date, there is lack of compelling data specifically linking HTN with impairment of male reproductive potential, but this issue has not been rigorously investigated.

Metabolic Syndrome and Infertility: Direct Lines of Evidence

Recently, Makhside and colleagues suggested the addition of hypogonadism to the constellation of aberrations seen in MetS (Makhside, 2005). The authors point to observational studies that report that low levels of testosterone and SHBG are significantly correlated with MetS and its associated components (including measures of BMI, waist circumference, waist:height ratio). In particular, Laaksonen and associates demonstrated that men with MetS (WHO criteria) had 19% lower total testosterone, 11% lower calculated free testosterone and 18% lower SHBG than controls (Laaksonen et al, 2003). Interestingly, the authors also found a significant positive correlation between MetS and the inflammatory marker CRP, which is implicated as another pathogenic correlate of MetS (Haffner, 2006, Malik et al, 2005). After adjusting for age and BMI, total testosterone, free testosterone and SHBG were found to be significantly inversely correlated with insulin, glucose, and triglycerides. Total testosterone, free testosterone and SHBG were also found to be directly correlated with HDL levels. Furthermore, men with hormone levels in the lowest third were more likely to develop MetS, even in strictest modeling.

These results are corroborated by a recent study by Muller et al (Muller et al, 2005). The authors demonstrated that total testosterone, bioavailable testosterone and SHBG were inversely related to several of the risk factors of MetS as defined by the National Cholesterol Education Program. Linear regression models demonstrated that total testosterone, bioavailable testosterone and SHBG were positively correlated with higher insulin sensitivity. Similarly, Robeva and associates found total testosterone to be negatively correlated with insulin level, insulin resistance, and BMI in male patients with MetS (n=10) (Robeva et al, 2006). These observations are important when considering insulin resistance as the potential underlying aberration in MetS.

Kaplan and colleagues examined baseline total serum testosterone in men participating in two lipid treatment studies (Kaplan et al, 2006). The cohort was divided by presence or absence of MetS (3 or more ATP III criteria) across various BMI subgroups. Using Pearson correlation coefficients, the authors demonstrated an inverse correlation between BMI and serum testosterone in men with MetS and without MetS. Furthermore, multiple linear regression analysis among the five ATP III diagnostic criteria revealed significant negative associations between total serum testosterone level and triglyceride status (<150 mg/dl vs >150 mg/dl), BMI (<30 kg/m^2 vs >30 kg/m^2), and presence of diabetes (Kaplan et al., 2006). In light of the obesity-NIDDM-hypogonadism paradigm, it follows that hypogonadism is prevalent in some patients with MetS. Further studies of semen parameters in these patients with MetS would aid this developing discussion.

A final mention should be made regarding the increase in literature on the association of MetS to ED, as ED can impair reproductive capabilities. Numerous studies demonstrate not only the worsening of ED with the severity of MetS (Corona et al, 2006, Demir, 2006, Esposito et al, 2005), but also that ED may be predictive of MetS (Kupelian et al, 2006). The underlying pathophysiology of ED is purported to be similar to that of diabetes with an additional role for hypogonadism in patients with MetS (Corona et al., 2006, Makhside, 2005). As described earlier, the potential role of increased oxidative stress as a pathophysiological cause of ED is a plausible candidate in men with MetS. The association of oxidative stress and ED is reviewed elsewhere (Agarwal et al, 2006).

Conclusion

MetS is an important medical and epidemiological entity, as its deleterious effects on patients is firmly established. Male infertility may represent another physiological aberration observed in some patients with MetS. Currently, there is sufficient evidence to suggest a MetS-male infertility paradigm (Figure 1). Obesity/overweight may result in hypogonadism, increased scrotal temperatures, impaired spermatogenesis, decreased sperm concentration and motility, and increased sperm DNA damage. Similarly, NIDDM/insulin resistance may contribute to and compound this scenario. Dyslipidemia with increased oxidative stress in the testicular micro-environment and/or excurrent ductal system may further decrease fertility. Additional studies are needed to fully elucidate the pathophysiological link between the components of MetS and male infertility.

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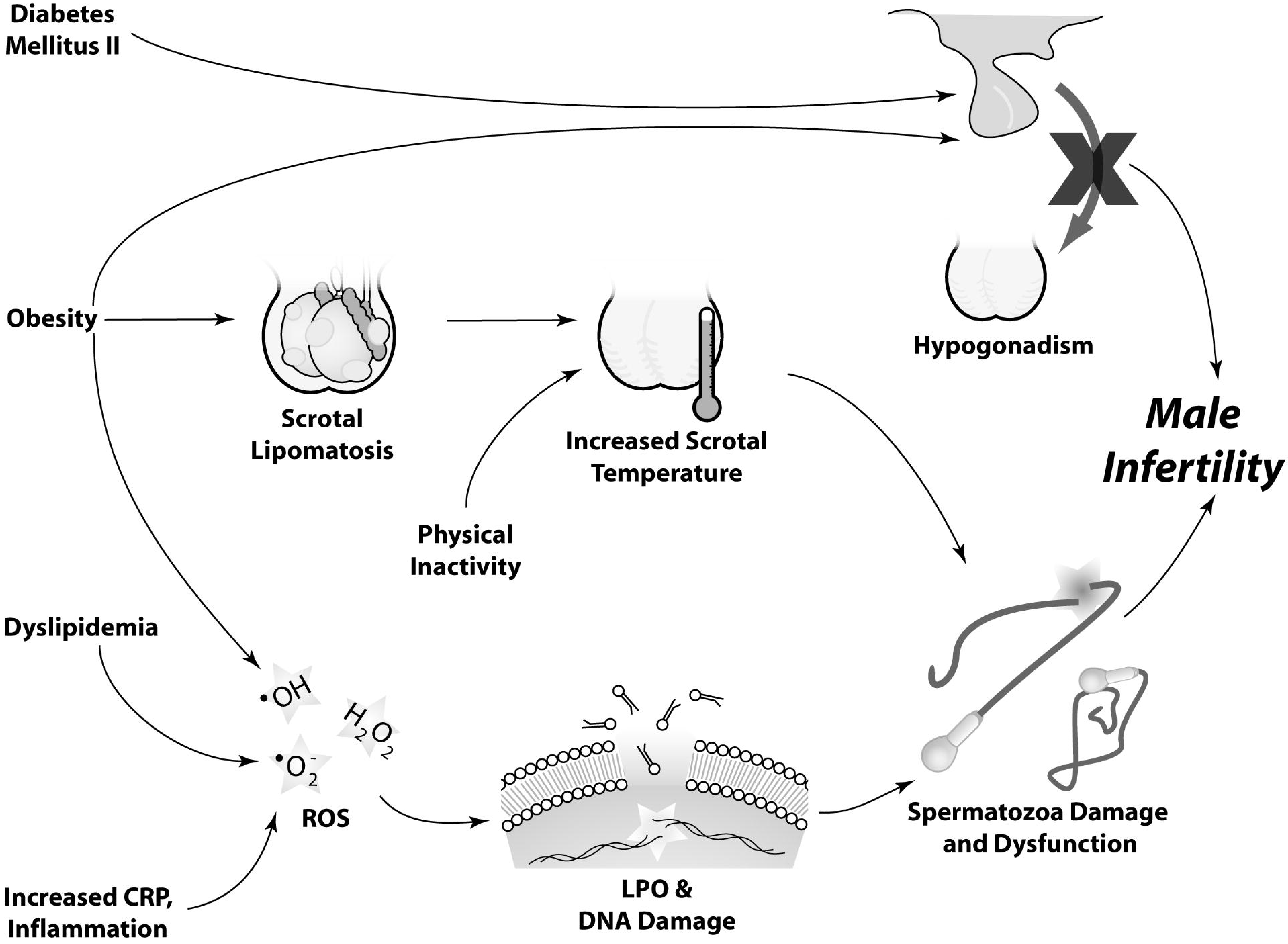
Table 1

Metabolic Syndrome
ATP III Criteria
1. Abdominal Obesity (Men: Waist Circumference > 102cm)
2. Hypertriglyceridemia (≥1.69mmol/L; ≥150mg/dl)
3. Low High-Density Lipoprotein Cholesterol (Men <1.04mmol/L; <40mg/dl)
4. High Blood Pressure (≥ 130/85 mmHg)
5. High Fasting Glucose (≥6.1 mmol/L; ≥110 mg/dl)

Figure Legend

Figure 1:

CRP= C-reactive protein, ROS= reactive oxygen species ($^{\bullet}OH$= hydroxyl free radical, $^{\bullet}O_2^-$= superoxide anion, H_2O_2=hydrogen peroxide), LPO= lipid peroxidation, DNA= deoxyribonucleic acid.


Diabetes Mellitus II
Obesity
Scrotal Lipomatosis
Increased Scrotal Temperature
Physical Inactivity
Hypogonadism
Male Infertility
Dyslipidemia
•OH
H2O2
•O2-
ROS
Increased CRP, Inflammation
LPO & DNA Damage
Spermatozoa Damage and Dysfunction