

# The Metabolic Syndrome and Male Infertility

## Review

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**ABSTRACT:** Metabolic syndrome (MetS) is highly prevalent, affecting more than 47 million US residents. This condition is also multifaceted, potentially leading to significant disturbance of numerous physiologic 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.

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In recent years, the metabolic syndrome (MetS) has garnered 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 US population, with 47 million affected US residents as of the year 2000 (Ford et al, 2002). Although 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 are presented in the Table. 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 1 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 suprapubic 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; Glass et al, 1977; Amatruda et al, 1978; Schneider et al, 1979; Kley et al, 1980; Strain et al, 1982; Zumoff et al, 1990). Variable results were noted for free testosterone in the various studies cited. Although some authors argued that decreased SHBG allows for normalization of free

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Table. *Metabolic Syndrome—Adult Treatment Panel III (ATP III) Criteria*

1. Abdominal obesity (men: waist circumference > 102 cm)
2. Hypertriglyceridemia ( $\geq 1.69$  mmol/L;  $\geq 150$  mg/dL)
3. Low high-density lipoprotein cholesterol (men: <1.04 mmol/L; <40 mg/dL)
4. High blood pressure ( $\geq 130/85$  mmHg)
5. High fasting glucose ( $\geq 6.1$  mmol/L;  $\geq 110$  mg/dL)

testosterone in the setting of low total testosterone (Schneider et al, 1979), others have observed a decrease in all 3 (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 body mass index (BMI; Zumoff et al, 1990). SHBG is especially relevant in obese males who are insulin resistant, as insulin is known to inhibit SHBG synthesis (Plymate et al, 1988; Pasquali et al, 1995). Several studies have demonstrated that SHBG and total testosterone are inversely correlated with both BMI and insulin levels (Seidell et al, 1990; Phillips, 1993; Vermeulen et al, 1996; Tsai et al, 2004; Osuna et al, 2006). 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 (Glass et al, 1977; Amatruda et al, 1978; Strain et al, 1982). Amatruda et al (1978) and Strain et al (1982) 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. 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 (Schneider et al, 1979; Kley et al, 1980; 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 (1993) studied 120 men categorized into obese or nonobese, and fertile or infertile groups. 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 of more than 1 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 bioavailable 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 bioavailable 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. Although 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 (2005) examined lifestyle and environmental factors, which have been hypothesized to adversely affect semen quality. The study population included 72 men from a single clinic for assisted reproduction who had been categorized into 3 groups: male factor subfertility (MFS), female factor subfertility (FFS), and idiopathic subfertility (IS), with semen analyzed per World Health Organization (WHO, 1999) criteria. The authors found a threefold increased incidence of obesity (BMI > 30) in patients with MFS compared with the other 2 groups. Furthermore, patients in the MFS group had a significantly higher BMI (27.8 [range, 21.8–38.6]) compared with those in the FFS group (25 [range, 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. Although 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 (2005) in a study of 81 infertile men of reproductive age ( $37 \pm 5.4$  years). 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 with testosterone, testosterone/17 $\beta$ -estradiol, and SHBG, but not FSH, LH, or 17 $\beta$ -estradiol levels. These data suggest a potential link between obesity, hypogonadism, and infertility as indicated by semen analysis.

Similarly to the above studies, Kort and colleagues (2006) 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 in infertile couples. The mean age was 34.6 years (range, 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  $\times$  concentration  $\times$  percent motility  $\times$  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 then were compared with 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,  $18.6 \times 10^6$  NMS; overweight,  $3.6 \times 10^6$  NMS; and obese,  $0.7 \times 10^6$  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 3 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 biologic 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 pathophysiologic 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 physiologic environment. These highly reactive and unstable molecules are capable of inducing significant cellular damage throughout the body. With 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 (1997) showed that the DNA of spermatozoa from infertile men had greater oxidative injury when compared to controls, and 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 proinflammatory 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 (1981b) described both normal (28 normal cadavers) and infertile (44 infertile males) scrotal fat patterns. 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, nonobese 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, 1981a). 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 (2006) reported an inverse relationship between varicocele formation and BMI, suggesting that adipose tissue may protect against the “nutcracker effect.” Handel et al (2006) also demonstrated a decreasing prevalence of varicocele with increasing body mass in a study of 3213 infertile men. Finally, Prabakaran et al (2006) also reported varicoceles were more prevalent in tall boys with a lower BMI, who had quickly progressed through puberty.

Handel et al (2006) 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. Scrotal lipomatosis in obese men, as described by Shafik and Olfat (1981b), may signify a distinct pathologic manifestation of obesity involving the scrotum hindering varicocele detection. While the literature is thus not entirely clear regarding the true prevalence of 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 (Schlesinger et al, 1994; Barqawi et al, 2004).

## **Diabetes and Infertility**

Insulin resistance is considered by many investigators to be an underlying pathologic 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 3 epidemiological studies that suggest hypogonadism is a risk factor for diabetes. Haffner and associates (1996) analyzed data from the MRFIT cohort, demonstrating a significant risk of developing NIDDM among participants who had low SHBG. Stellato et al (2000) 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. Similar data were reported by Oh et al (2002) from the prospective Rancho Bernardo Study, which found that low total testosterone levels predicted the subsequent development of NIDDM. While the above 3 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 (1990) 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. These findings were corroborated by Andersson 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 (Andersson, 1994). Chang and associates (1994) 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. Most recently, Dhindsa et al (2004) observed a 33% incidence of hypogonadism in men with NIDDM in a diabetes management center. Furthermore, these authors noted significantly decreased FSH and LH in participants from the hypogonadal group compared with the eugonadal group, suggesting a substantial rate of hypogonadotropic hypogonadism among men with NIDDM. Pitteloud et al (2005) subsequently reported that increasing insulin resistance was associated with decreased testosterone secretion at the testicular level (Leydig cell) and was not due to changes in hypothalamic or pituitary function. 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 (2003) 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. Specifically, patients experienced decreased blood glucose and HbA1c values with improved symptoms of androgen deficiency. In a similar study, Kapoor and colleagues administered intramuscular 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 comorbid patients. Thus, future studies evaluating the impact of such agents as the LH agonist human chorionic gonadotropin 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 (1993) 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. Though limited, these data suggest 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 have an impact on male reproductive potential. ED in patients with NIDDM stems in part from autonomic neuropathy and vascular disease. Several epidemiologic studies have demonstrated an increased risk for 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 result 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 (ie, pseudoephedrine) and certain tricyclic antidepressants (ie, 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 have an impact on semen quality and fertility. Ramirez-Torres and colleagues (2000) studied 106 male partners from infertile couples, reporting a 65% incidence of dyslipidemia as 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, although 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 (2004). The authors examined the effects of a high-cholesterol diet and anticholesterol 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 with male rats with a cholesterol-free diet. Furthermore, the investigators treated male rats on a high-cholesterol diet with no-intervention,  $\alpha$ -tocopherol (an antioxidant), simvastatin (a lipid-lowering agent), or both therapeutic agents. Treatment with  $\alpha$ -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  $\alpha$ -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 (HTN) is defined as a blood pressure greater than 130/85 mmHg by ATP III criteria, and it represents a major risk factor for cardiovascular disease. While hypertension is a well-established risk factor for ED, the direct effect on male fertility, if any, is not as 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 (Khaw and Barrett-Connor, 1988; Phillips et al, 1993; Fogari et al, 2002), free testosterone (Hughes et al, 1989; Phillips et al, 1993; Svartberg et al, 2004), and SHBG (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 with age-matched controls (Dockery et al, 2000, 2002). 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 (Suzuki et al, 1988; Andersen et al, 1998; Koshida et al, 1998; Fogari et al, 2002). To date, there is a 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 (2005) suggested the addition of hypogonadism to the constellation of aberrations seen in MetS. The author points to observational studies reporting that low levels of testosterone and SHBG are significantly correlated with MetS and its associated components (including measures of BMI, waist circumference, and waist-height ratio). In particular, Laaksonen and associates (2003) demonstrated that men with MetS (WHO criteria) had 19% lower total testosterone, 11% lower calculated free testosterone, and 18% lower SHBG than controls. 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 (Malik et al, 2005; Haffner, 2006). 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 high-density lipoprotein 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 (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 (2006) found total testosterone to be negatively correlated with insulin level, insulin resistance, and BMI in male patients with MetS ( $n = 10$ ). These observations are important when considering insulin resistance as the potential underlying aberration in MetS.

Kaplan and colleagues (2006) examined baseline total serum testosterone in men participating in 2 lipid treatment studies. 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 and without MetS. Furthermore, multiple linear regression analysis among the 5 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<sup>2</sup> vs  $>30$  kg/m<sup>2</sup>), 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 with ED, as ED can impair reproductive capabilities. Numerous studies demonstrate not only the worsening of ED with the severity of MetS (Esposito et al, 2005; Corona et al, 2006; Demir, 2006), 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 (Makhside, 2005; Corona et al, 2006). As described earlier, the potential role of increased oxidative stress as a pathophysiologic

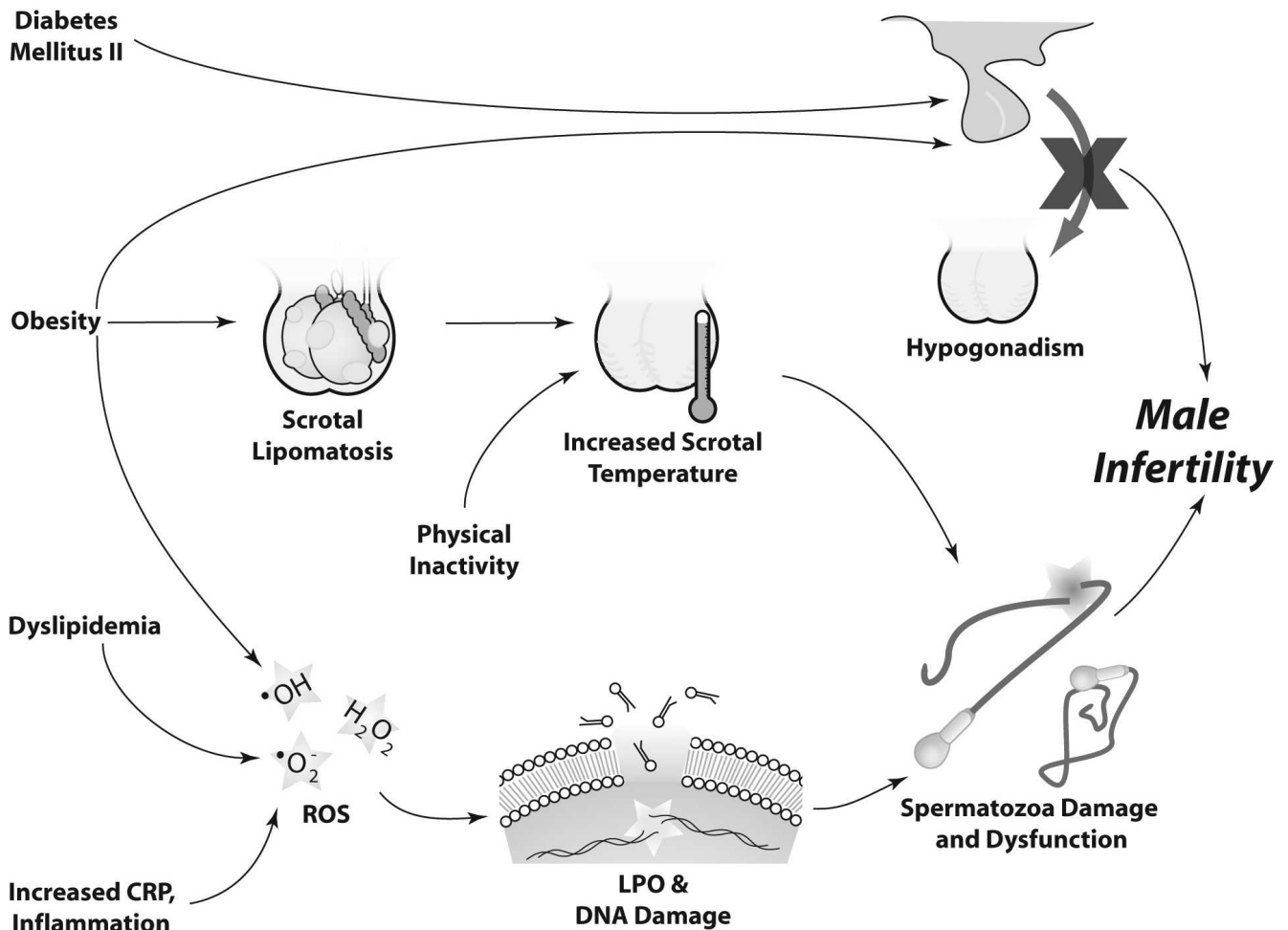


Figure. CRP indicates C-reactive protein; ROS, reactive oxygen species;  $\cdot\text{OH}$ , hydroxyl free radical;  $\cdot\text{O}_2^-$ , superoxide anion;  $\text{H}_2\text{O}_2$ , hydrogen peroxide; and LPO, lipid peroxidation.

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 epidemiologic 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). 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 microenvironment 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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