Published-Ahead-of-Print on September 4, 2008 by Journal of Andrology

The Emerging Link Between Hypogonadism & Metabolic Syndrome

Running Title: hypogonadism and metabolic syndrome

André T Guay MD, FACP, FACE

Director, Center For Sexual Function / Endocrinology, Lahey Clinic, Peabody, MA. Clinical Assistant Professor of Medicine (Endocrinology), Harvard Medical School, Boston, MA

Correspondence: André Guay MD, Lahey Clinic Northshore, One Essex Center Drive, Peabody, MA 01960. Tel. 978-538-4655 Fax 978-538-4712

E-mail: andre.t.guay@lahey.org

This work was not supported by the pharmaceutical industry

Abstract

The metabolic syndrome (MS) is comprised of various medical conditions that confer increased risk of diabetes and cardiovascular disease. The pathophysiological components of MS include glucose abnormality, obesity or increased waist circumference, increased blood pressure, and hyperlipidemia. There is an increased risk of hypogonadism in men with the metabolic syndrome and its individual components, including insulin resistance, considered by some to be at the core of metabolic syndrome. Hypogonadism may even predict the metabolic syndrome. These factors are interwoven and impact overall health including sexual dysfunction. One interesting and important question is whether treating hypogonadism with testosterone replacement will ameliorate the pathological components of the metabolic syndrome.

Key indexing words: low testosterone, insulin resistance, cardiovascular risk, obesity.

What is the Significance of the Metabolic Syndrome?

The M*etabolic syndrome* (MS) refers to a clustering of various medical conditions, with a number of pathological components that contribute to the development of diabetes and cardiovascular disease. Not all physicians believe the clustering of components is any more predictive of diabetes and heart disease than any one of its individual components. Recognizing and identifying these clusters of conditions allows the physician to more aggressively recommend lifestyle modifications, with the hope of preventing morbidity and mortality.

The MS takes on more meaning because it is widespread, and more common than once thought. In North America, the prevalence of MS has been estimated to be about 25% in Caucasians and 30% in Hispanics (Meigs et al, 2003). The prevalence increases with age, and the prevalence in women closely mirrors that in men (Ford et al, 2002). This has been related, in

part, to the worldwide epidemic of obesity, of which a number of components, if not all, are related to the MS, either directly or indirectly (Cameron et al, 2004).

An early definition was made by the World Health Organization, but the most commonly used one in North America is that of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Executive summary of the third report of the National Cholesterol Education Program (NCEP) (Expert Panel, etc, 2001), although the definition by the International Diabetes Federation (IDF) is gaining popularity (Balkau and Charles, 1999). The debate among the proponents and detractors of each definition is beyond the scope of this review, and is still ongoing, but the concept of the MS by whatever definition is related to cardiovascular risk and is favored by a majority of investigators.

The risk factors of the MS are concerned with abnormal glucose metabolism, insulin resistance, increased waist circumference and abdominal fat, increased blood pressure, and abnormalities of triglyceride and HDL cholesterol metabolism. Table 1 compares the NCEP ATP III and the IDF criteria, the former defining 3 of 5 criteria as consistent with MS, while the IDF insists on increased waist circumference plus 2 of the other 4 criteria as their definition.

Hypogonadism and Metabolic Syndrome

The definition of hypogonadism is at best arbitrary and imprecise. There are many opinions, such as should we use total testosterone, or free testosterone, and which type of assay in these categories?. There are many techniques for each type, which vary considerably between themselves and between the laboratories that perform them. To elucidate all of the variations would be impossible and beyond the scope of a brief review. We have the solace, in many studies, that levels are compared in a case-controlled fashion so that significant differences

between groups can be appreciated. In the United States, the standard definition of hypogonadism by the Federal Drug Administration (FDA) and the Endocrine Society is a total testosterone value < 300 ng/dL (< 10.4 nmol/L). Although less than ideal, this is the commonly used definition in the literature.

Recently, the close association between hypogonadism and MS has received more attention. This is because the prevalence of hypogonadism has been shown to be higher than previously thought, both in epidemiological studies (Morley et al, 1997) (Araujo et al, 2004) and in a survey of clinical practice (Mulligan et al, 2006). The epidemiological studies show a prevalence of hypogonadism of 10-12% (Morley et al, 1997) (Araujo et al, 2004), which has only been found to be slightly lower, at 6%, when men with symptomatic androgen deficiency are counted (Araujo et al, 20070. Data from physicians' clinical practices, however, show a higher prevalence of hypogonadism, in the range of 36-39% (Mulligan et al, 2006) (Guay and Seftel, 2008). This is due to the association of high prevalence of hypogonadism with chronic illnesses. Clearly, prior estimates of hypogonadism were underestimated.

Although age, geography, ethnicity, and lifestyle issues like obesity are related to MS, hypogonadism also has been shown to have a strong relationship with MS. Kupelian et al showed that low total testosterone (T) and low sex hormone binding globulin (SHBG) levels were risk factors for MS, even when they restricted the association to men who were asymptomatic from their androgen deficiency (Kupelian et al, 2006). They confirmed a previous study by Muller, et al, showing a high prevalence of low endogenous sex hormones with MS (Muller et al, 2005). Blouin, et al, showed that men with fewer than three components of the MS had higher T levels, and that men with three or more components of MS had lower levels of T (Blouin et al, 2005). This is in keeping with the findings of Kaplan, et al, who found a definite

inverse relationship between the number of components of MS and the total T levels, even in non-diabetic men (Kaplan et al, 2006).These findings suggest that the more medical problems a man has, which puts more stress on his body, the lower his testosterone will be. Stress of acute illness does lower testosterone, and one study did look at this relationship.Woolf, et al, studied men with head trauma and found that there was an inverse relationship between the level of noradrenaline and the level of testosterone, showing that, at least in acute medical stress, the more adrenalin the more the hypothalamic-pituitary suppression (Woolf et al, 1985). Longitudinal studies, from the Massachusetts Male Aging Study (Kupelian et al, 2006,) and from the Baltimore Longitudinal Aging Study (Rodriguez et al, 2007) have confirmed that the prevalence of MS increases with aging and that it is related to hypogonadism. The relationship of hypogonadism to MS remains even when using different definitions of MS, and when following patients prospectively for over ten years (Laaksonen et al, 2005).

Testosterone Levels, Hypogonadism and Components of the Metabolic Syndrome

The components of the MS, and correlates of these components, have been related to sex hormone levels and hypogonadism. Abnormal glucose metabolism, often with insulin resistance and glucose intolerance and resultant diabetes is a key component of MS. In a meta-analysis, Ding, et al (Ding et al, 2006), found approximately 20 studies that showed a high prevalence of hypogonadism in diabetic men. The relationship was so strong in four of these studies that it was stated that low testosterone levels predicted future diabetes.

Increased weight and obesity is a core element of MS. Visceral obesity is especially strongly related to MS and insulin resistance, and has been negatively associated with T levels (Seidell et al, 1990). Common thinking in the past indicated that obesity increased cardiac risk

by aggravating other cardiac risks, such as hypertension and hyperlipidemia, but Rogers, et al, showed in a meta-analysis of more than 300,000 persons, that obesity was an independent risk factor for MS.(Rogers et al, 2007). In a clinical study (Mulligan et al, 2006), and in a long term longitudinal study (Travison et al, 2007), obesity has also been shown to be negatively related to testosterone levels

Central or abdominal obesity, as measured by ***waist circumference,*** is a classical feature of the MS, and is the central feature of the IDF definition of MS. It has independently been associated with reduced testosterone levels (Pasquali et al, 1991) (Osuna et al, 2006). Svartberg, et al, (Svartberg et al, 2004,)not only found this association in a large number of community dwelling men, but also found that increasing waist circumference predicted low testosterone levels (Svartberg et al, 2003,). It has been suggested that waist circumference is better at predicting T levels than is BMI (Svartberg et al, 2004,). However, the inverse relationship of BMI with low T levels is very significant (Pasquali et al, 1991,) (Laaksonen et al, 2003,). The mechanisms by which T production is decreased as BMI increases are not fully understood, but several facts are known that might be pertinent. Obesity is associated with decreased SHBG production, which increases total T but decreases free T; this would seem contradictory, but other factors are at play. Obesity is associated with increased inflammatory cytokine production, as well as increased aromatization of T to estradiol in peripheral fat tissue. Both of these factors then decrease the pituitary production of gonadotropins, which, in turn, decrease testicular production of T. (Kalyani and Dobs, 2007) (Laaksonen et al, 2003). It has also been hypothesized that elevated leptin levels in obese individuals interfere with LH/hCG stimulation of androgen production, thereby decreasing androgen levels (Isidori et al, 1999,). Insulin resistance is an integral part of MS as it has a high prevalence in obesity and type 2 diabetes. A

definite inverse relationship has been found between T and insulin resistance, and persists whether total, free, or bioavailable testosterone measurements are used (Tsai et al, 2004).

Hypertension has also been associated with hypogonadism, as well as its long known affiliation with cardiovascular risk. Mulligan, et al, have shown that more men with hypertension have low T levels than normal T levels (Mulligan et al, 2006). The incidence of hypogonadism was found to be 30.8% in men with erectile dysfunction (Guay and Seftel, 2008), where the prevalence of hypertension in men with erectile dysfunction was found to be 44.0%, similar to that seen in primary care practices. Svartberg, et al, also found that individuals presenting with hypertension will have lower total T values than those who do not have hypertension, independent of age (Svartberg et al, 2004). Smith, et al, showed that androgen deprivation in men with prostate cancer could also induce hypertension and arterial stiffness, even after only several months (Smith et al, 2001).

Lipid abnormalities are also part of the MS, in the form of elevated triglycerides and decreased HDL cholesterol. Dobs, et al (Dobs et al, 2001) found that in hypogonadal men, before therapy, the BMI had strong negative correlations with both HDL cholesterol and T concentrations, while T had slight, and nearly significant correlation with HDL concentrations. T suppression in men with prostate cancer resulted in elevated total and LDL cholesterol levels over baseline values, after only 3 months of therapy (Dockery et al, 2003); these same authors also showed an increase in insulin resistance with testosterone depletion. Smith, et al, showed abnormalities in both cholesterol and triglycerides after both short and long term androgen deprivation therapy (Smith et al, 2006). Similar abnormalities in cholesterol and triglyceride metabolism have been demonstrated in diabetic men undergoing androgen deprivation as the testosterone levels declined (Haider et al, 2007).

Hypogonadism, Metabolic Syndrome and Sexual Dysfunction

The MS and erectile dysfunction are related as the same risk factors are seen in both conditions (Walczak et al, 2002). Thompson, et al (Thompson et al, 2007) studied over 9,000 men for over five years and found that the hazard ratio of men with new erectile dysfunction for cardiovascular events was 1.45. Corona, et al, (Corona et al, 2006) consecutively evaluated over 800 men seen for sexual dysfunction, and found MS in 29.4%; further 96.5% of the men with the MS had erectile dysfunction. Using strict criteria for hypogonadism, a total T < 8 nmol/L (<230 ng/dL), the incidence of hypogonadism in the men with the MS was 11.9%, versus 3.8% in the rest of the sample. Low T in men with the MS was also related to other sexual symptoms, such as hypoactive sexual desire, decreased frequency of sexual intercourse, and was also related to depressive symptoms, although it was not certain if these were primary or reactive to the sexual issues. The authors also showed an inverse relationship between the total T levels and the number of the MS components; the low testosterone levels were strongly related to the fasting glucose levels and the elevated waist circumference measurements. Of interest also was the inverse relationship between penile blood flow, erectile function, which also is significantly related to the number of MS components. As opposed to testosterone and the MS components, the strongest factors relating to penile blood flow were elevated blood pressure and elevated fasting blood glucose. The relationship of erectile physiology to the MS and hypogonadism is not surprising as a recent review of the literature proved that testosterone is related to many facets of erectile physiology and penile blood flow mechanics (Traish and Guay, 2006).

Esposito, et al, has shown that the prevalence of ED among men with the MS increases with the number of MS components (Esposito et al, 2004). With increasing components, the prevalence increased from 20% to 35%. Heidler, et al, has further shown that the MS is an

independent risk factor for erectile dysfunction (Heidler et al, 2007). Bansal, et al, reviewed 154 men with organic erectile dysfunction, and found that 43% had MS by the NCEP ATP III criteria, versus 24% in a similar population of Caucasian men (Bansal et al, 2005). Of further interest, 79.2% of the men had insulin resistance, versus 25% in the general population. Insulin resistance is thought to be at the core of MS, and 90.9% of the men with MS in this population had insulin resistance. A further analysis showed that the more severe the erectile dysfunction, the higher the incidence of MS and of insulin resistance (Table 2). Guay, et al (Guay and Jacobson, JSM) made a further analysis of this population in which they examined the relationship between hypogonadism and insulin resistance. In men with hypogonadism, 92.3% had insulin resistance, and in the men without hypogonadism, 25.2% had insulin resistance. This highlights the strong relationship between low testosterone and insulin resistance. Clearly, erectile dysfunction represents a warning signal regarding the presence of MS and insulin resistance, all being clear risk factors for cardiovascular disease, and reinforcing the relationship shown in figure 1.

In a recent study by Zhody, et al, the relationship between erectile dysfunction, androgen deficiency, and the MS was solidified by another means: the measurement of BMI (Zhody et al, 2007). With increasing BMI, the incidence of erectile dysfunction and hypogonadism increased in a strong positive correlation. Using the corpus duplex ultrasound, the authors found that if BMI was < 25, approximately 23.1% of the men had vasculogenic erectile dysfunction, as compared to 59.3% of the men whose BMI was ≥ 25. It follows that if circulation is decreased, then oxygen saturation to the penis would be decreased. Padmanabhan, et al, found that men with erectile dysfunction had lower penile corporeal oxygen saturation than did men without erectile dysfunction (Padmanahbhan and McCullough, 2007). Recently, a good review of the

literature found a strong link between male infertility and MS, with good discussions of the contributions of the various components of the MS (Kasturi et al, 2008).

Could Treatment of Hypogonadism Help to Correct Components of the Metabolic Syndrome?

It is well known that testosterone therapy in men with androgen deficiency improves energy, body composition, and a number of other abnormalities. It is intriguing to speculate that correcting the hypogonadism associated with insulin resistance and MS might correct some or all its components. The data available in this area is preliminary but promising. Pittleloud, et al, showed that acutely lowering human Leydig cell production of testosterone rapidly caused insulin resistance (Pittleloud et al, 2005a), and later showed that testosterone replacement rapidly increased insulin sensitivity within a few days, eliminating implicating changes in BMI or fat mass (Pitteloud et al, 2005b). This also highlights the possible bidiredctionality of low testosterone with medical conditions. Here we have a very close and rapid relationship between low testosterone and insulin resistance, with very rapid reversal, suggesting bidirectionality of cause and effect. There is much more to be studied here.

In another clinical situation, Kapoor, et al, studied men with type 2 diabetes. The authors found that a significant percentage of the men had symptomatic low testosterone levels and that the testosterone levels were negatively correlated with BMI and waist circumference (Kapoor et al, 2007). The authors treated hypogonadism in these diabetic men and found that there was improvement in a number of metabolic parameters related to the MS, including fasting glucose, fasting insulin, HbA1C, and weight (Kapoor et al, 2006). Muller, et al, (Muller et al, 2005)

actually found that for every standard deviation that testosterone is raised in aging men (approximately 152 ng/dL per SD) the risk of the MS is reduced by 57 %.

Saad, et al, compared the results of testosterone treatment in elderly men with late onset hypogonadism with either a testosterone gel or a long acting injection (Saad et al, 2008). Both treatment parameters aided sexual symptoms and also improved waist circumference and several lipid parameters, with a trend toward lowering blood pressure. Allen, et al (Allen et al, 2008), showed that testosterone replacement therapy for a year selectively lessened visceral fat accumulation, the fraction that best correlates with cardiovascular risk. Heufelder,et al (Heufelder et al, 2007), showed that lifestyle modifications, when used with T supplementations in hypogonadal men with type 2 diabetes, may have a synergistic effect on waist circumference.

Although these studies are promising, the numbers of patients studied are small, and the treatment courses are short term. Larger, prospective studies are needed in hypogonadal men with the MS, which will determine if testosterone therapy indeed correct multiple components of the MS and decrease the risk of cardiovascular disease.

References

Allen CA, StraussBJG, Burger HG,Forbes EA, McLachlan RI. Testosterone therapy prevents visceral adipose tissue and loss of skeletal muscle in non-obese aging men. J Clin Endocrinol Metab.2008; 93: 139-146.

Araujo AB, O'Donnell AB, Brambilla DJ, Simpson WB, Longcope C, Matsumoto AM, McKinlay JB. Prevalence and incidence of androgen deficiency in middle-aged and older men: estimates from the Massachusetts Male Aging Study. J Clin Endocrinol Metab 2004; 89: 5920-5926.

Araujo AB, Gretchen R, Esche MS, Kupelian V, O'Donnell AB, Travison TG, Williams RE, Clark RV, McKinlay JB. Prevalence of symptomatic androgen deficiency in men. J Clin Endocrinol Metab 2007; 92: 4241-4247.

Balkau B, Charles MA: Comment on the provisional report from the WHO consultation: European Group for the Study of Insulin Resistance (EGIR). Diabet Med 16: 442–443,

1999.Cameron AJ, Shaw JE, Zimmet PZ. The metabolic syndrome: prevalence in worldwide populations. Endocrinol Metab Clin North Amer. 2004; 33: 351-355.

Bansal TC, Guay AT, Jacobson J, Woods BO, Nesto RW. Incidence of metabolic syndrome and insulin resistance in a population with organic erectile dysfunction. J Sex Med. 2005; 2: 96-103.

Blouin K, Despres JP, Couillard C, Tremblay A, Prud'homme D, Bouchard C, Tchernof A. Contribution of age and declining androgen levels to features of the metabolic syndrome in men. Metabolism. 2005; 54: 1034-1040.

Corona G, Mannucci E, Schulman C, Petrone L, Mansani R, Cilotti A, Balercia G, Chiarini V, Forti G, Maggi M. Psychobiologic Correlates of the metabolic syndrome and associated sexual dysfunction. Eur Urol. 2006; 50: 595-604.

Ding, EL, Song Y, Malik VS, Liu S. Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. J Amer Med Assoc 2006; 295: 1288-1299.

Dobs AS, Bachorik PS, Arver S, Meikle AW, Sanders SW, Caramelli KE, Mazer NA. Interrelationships among lipoprotein levels, sex hormones, anthropometric parameters, and age in hypogonadal men treated for 1 year with a permeation-enhanced testosterone transdermal system. J Clin Endocrinol Metab. 2001; 86: 1026-1033.

Dockery F, Bulpitt CJ, Agarwal S, Donaldson M, Rajkumar C. testosterone suppression in men with prostate cancer leads to an increase in arterial stiffness and Hyperinsulinemia. Clin Sci. 2003; 104: 195-201.

Esposito K, Giugliano F, Martedi E, Feola G, Marfella R, D'Armiento M, Giugliano D. High proportions of erectile dysfunction in men with metabolic syndrome. Diabetes Care. 2004; 28: 1201-1203.

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486–97.

Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the Third National Health and Nutritional Examination Survey. J A M A. 2002; 287: 356-359.

Guay AT, Jacobson J. the relationship between testosterone levels,the metabolic syndrome (by two criteria) and insulin resistance in a population of men with organic erectile dysfunction. J Sex Med. 2007; 4: 1046-1055.

Guay A, Seftel A. Multiple chronic illnesses are associated with hypogonadism in men with erectile dysfunction. Int J Imp Res. 2008; submitted for publication.

Haider A, Yassin A, Saad F, Shapsigh R. Effects of androgen deprivation on glycemic control and on cardiovascular biochemical risk factors in men with advanced prostate cancer with diabetes. Aging Male. 2007; 10: 189-196.

Heidler S, Temml C, Broessner C, Mock K, Rauchenwald M, Madersbacher S, Ponholzer A. is the metabolic syndrome an independent risk factor for erectile dysfunction? J Urol. 2007; 177: 651-654.

Heufelder A, Gooren L, Bunck M, Saad F. Testosterone treatment enhances the favorable effects of exercise and diet on inflammation, metabolism and coagulation markers in hypogonadal men with the metabolic syndrome. The Proceedings of the Endocrine Society Meeting, June 2008, Abstract # OR35-1, page 137.

Isidori AM, Caprio M, Strollo F, Moretti C, Frajese G, Isidori A, Fabbri A. Leptin and androgens in male obesity: evidence for leptin contribution to reduced androgen levels. J Clin Endocrinol Metab. 1999; 84: 3673-3680.

Kalyani RR, Dobs AS. Androgen deficiency, diabetes, and the metabolic syndrome in men. Cur Opin in Endocrinol Diab Obesity. 2007; 14: 226-234.

Kaplan SA, Meehan AG, Shah A. The age related decrease in testosterone is significantly exacerbated in obese men with the metabolic syndrome. What are the implications for the relatively high incidence of erectile dysfunction observed in these men? J Urol. 2006; 176: 1524-1528.

Kapoor D, Goodwin E, Channer KS, Jones TH. Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes. Eur J Endocrinol. 2006; 154: 899-906.

Kapoor D, Aldred H, Clark S, Channer KS, Jones TH. Clinical and biochemical assessment of the hypogonadism in men with type 2 diabetes. Correlations with bioavailable and visceral adiposity. Diabetes Care.2007; 30: 911-917.

Kasturi SS, Tannir J, Brannigan RE. The metabolic syndrome and male infertility. J Androl. 2008; 29: 251-259.

Kupelian V, Page ST, Araujo AB, Travison TG, Bremner WJ, McKinlay JB. Low sex hormone-binding globulin, total testosterone, and symptomatic androgen deficiency are associated with development of the metabolic syndrome in nonobese men. J Clin Endocrinol Metab. 2006; 91: 843-850.

Laaksonen DE, Niskanen L, Punnonen K, Nyyssonen K, Tuomainen TP, Salonen R, Rauramaa R, Salonen JT. Sex hormones, inflammation and the metabolic syndrome: a population-based study. Eur J Endocrinol. 2003; 149: 601-608.

LaaksonenDE, Niskanen L, Punnonen K, Nyyssonen K, TuomainenTP, Valkonen VP, Salonen JT. The metabolic syndrome and smoking in relation to hypogonadism in middle-aged men: a prospective cohort study. J Clin Endocrinol Metab. 2005; 90: 712-719.

Meigs JB, Wilson PWF, Nathan DM, D'Agostino RB, Williams K, Haffner SM. Prevalence and characteristics of the metabolic syndrome in the San Antonio Heart and Framingham Offspring Studies. Diabetes 2003;52:2160–7.

Morley JE, Kaiser FE, Perry 3rd HM, Patrick P, Morley PMK, Stauber PM, Vellas B, Baumgartner RN, Garry PJ. Longitudinal changes in testosterone, luteinizing hormone, and follicle-stimulating hormone in healthy older men. *Metabolism* 1997; 46: 410-413.

Muller M, Grobbee DE, den Tonkelaar I, Lamberts SW, van der Schouw YT. Endogenous sex hormones and metabolic syndrome in aging men. J Clin Endocrinol Metab. 2005; 90: 2618-2623.

Mulligan T, Frick MF, Zuraw QC, Stemhagen A, McWhirter C. Prevalence of hypogonadism in males aged at least 45 years: the HIM study. *Int J Clin Pract* 2006; 60: 762-769.

Osuna JA, Gomez-Perez R, Arata-Bellabarba G, Villaroel V. Relationship between BMI, total testosterone, sex hormone-binding-globulin, leptin, insulin and insulin resistance in obese men. Arch Androl. 2006; 52: 355-361.

Padmanahbhan P, McCullough AR. Penile oxygen saturation in the flaccid and erect penis in men with and without erectile dysfunction. J Androl. 2007; 28: 223-228.

Pasquali R, Casimirri F, Cantobelli S, Melchionda N, MorselliLabata AM, Fabbri R, Capelli M, Bortoluzzi L. Effect of obesity and body fat distribution on sex hormones and insulin in men. Metabolism. 1991; 40: 101-104.

Pitteloud N, Hardin M,Dwyer AA, Valassi E, Yialamis M, Elahi D, Hayes FJ. Increasing insulin resistance is associated with a decrease in Leydig cell testosterone secretion in men. J Clin Endocrinol Metab. 2005a; 90: 2636-2641.

Pitteloud N, Mootha VK, Dwyer AA, Hardin M, Lee H, Eriksson KF, Tripathy D, Yialamas M, Groop L, Elahi D, Hayes FJ. Relationship between testosterone levels, insulin sensitivity, and mitochondrial function in men. Diabetes Care. 2005b; 28: 1636-1642.

Rodriguez A, Muller DC, Metter EJ, Maggio M, Harman SM, Blackman MR, Andres R. Aging, androgens, and the metabolic syndrome in a longitudinal study of aging. J Clin Endocrinol Metab. 2007; 92: 3568-3572.

Rogers RP, Bemelmans WJ, Hoogenveen RT, Boshuizen HC, Woodward M, Knekt P, van Dam RM, Hu FB for the BMI-CHD Collaboration Investigators. Association of overweight with increased risk of coronary heart disease partly independent of blood pressure and cholesterol levels: a meta-analysis of 21 cohort studies including more than 300,000 persons. Arch Int Med. 2007; 167: 1720-1728.

Seidell JC, Bjomtorp P, Sjostrom L, Kvist H, Sannerstedet R. Visceral fat accumulation in men is positively associated with insulin, glucose and C-peptide levels, but negatively with testosterone levels. Metabolism. 1990; 39: 897-901.

Smith MR, Lee H, Nathan DM. Insulin sensitivity during combined androgen blockade for prostate cancer. J Clin Endocrinol Metab. 2006; 91: 1305-1308.

Svartberg J, Jorde R, Sundsfjord J, Bonaa KH, Barrett-Connor E. Seasonal variation of testosterone and waist to hip ratio in men: the Tromso study. J Clin Endocrinol Metab. 2003; 83: 3099-3104.

Svartberg J, von Muhlen D, Sundsfjord J, Jorde R. Waist circumference and testosterone levels in community dwelling men. *The Tromso Study*. Eur J Epidemiol. 2004; 19: 657-663.

Saad F, Gooren LJ, Haider A, Yassin A. A dose-response study of testosterone on sexual dysfunction and features of the metabolic syndrome using testosterone gel and parenteral testosterone undecanoate. J Androl. 2008; 29: 102-105.

Thompson IM, Tangen CM, Goodman PJ, Probstfield JL, Moinpour CM, Coltman CA. Erectile dysfunction and subsequent cardiovascular disease. J A M A. 2007; 294: 2996-3002.

Traish AM, Guay AT. Are androgens critical for penile erections in humans? Examining the clinical and preclinical evidence. J Sex Med. 2006; 3: 382-407.

Traish AM, Guay A, Feeley R, Saad F. The dark side of testosterone: I. Metabolic syndrome and erectile dysfunction. J Androl, (in press).

Traish AM, Saad F, Guay A. The dark side of testosterone deficiency: II. Type 2 diabetes and insulin resistance. J Androl 2008; (in press).

Travison TG, Araujo AB, Kupelian V, O'Donnell AB, McKinlay JB. The relative contribution of aging, health, and lifestyle fafctors to serum testosterone decline in men. J Clin Endocrinol Metab. 2007; 92: 549-555.

Tsai EC, Matsumoto AM, Fujimoto WY, Boyho E. Association of bioavailable, free, and total testosterone with insulin resistance: influence of sex hormone-binding globulin and body fat. Diabetes Care. 2004; 27: 861-868.

Walczak MK, Lokhandwala N, Hodge MB, Guay AT. Prevalence of cardiovascular risk factors in erectile dysfunction. J Gend Spec Med 2002; **5**; 19-24.

Woolf PD, Hamill RW, McDonald JV, Lee LA, Kelly M. Transient hypogonadotropic hypogonadism caused by critical illness. J Clin Endocrinol Metab 1985; **60**: 444-450.

Zhody W, Kamal EE, Ibrahim Y. Androgen deficiency and hormonal duplex parameters in obese men with erectile dysfunction. J Sex Med. 2007; 4: 797-808.

Table 1. The various components of the NCAEP ATP III and IDF definitions of the metabolic syndrome in men

	NCEP–ATP III[ref # 12] ≥ 3 of 5 criteria	**IDF**[ref # 4] Criteria #2 plus 2 of the other 4
1. Hyperinsulinemia Hyperglycemia	FBS ≥ 110 mg/dL (≥ 6.1 nmol/L) or T2DM	FBS ≥ 100 mg/dL or T2DM
2. Increased Body Size	WC ≥ 102 cm	WC ≥ 94 cm
3. Triglyceride	≥ 150 mg/dL (≥ 2.3 mmol/L)	≥ 150 mg/dL (≥ 2.3 mmol/L)
4. HDL Cholesterol	< 40 mg/dL (< 1.03 mmol/L)	< 40 mg/dL (< 1.03 mmol/L)
5. Blood Pressure	BP ≥ 130/85 mmHg or HTN on Rx	Systolic BP ≥ 130 mmHg Diastolic BP ≥ 85 mmHg or HTN on Rx

Table 2. The relationship between severity of erectile dysfunction and the incidence of metabolic syndrome and insulin resistance in a population of men with organic erectile dysfunction.

SEVERITY OF ED	METABOLIC SYNDROME (%)	INSULIN RESISTANCE (%)
Mild ED SHIM 17-21	14.5	19.1
Moderate ED SHIM 11-16	35.5	25.5
Severe ED SHIM 1-10	50.0	46.8

SHIM = Sexual Health Inventory for Men
Adapted from Bansal, et al, 2005.

Figure 1. The interrelationships between metabolic syndrome and hypogonadism with chronic illnesses and cardiovascular risks are shown and do appear to be quite interwoven. (Reprinted with permission from the *Journal of Andrology*, Traish et al. 2008.)