

The Dark Side of Testosterone Deficiency: II. Type 2 Diabetes and Insulin Resistance

Review

ABDULMAGED M. TRAISH,* FARID SAAD,†‡ AND ANDRE GUAY§

*From the *Department of Biochemistry and Urology, Boston University School of Medicine, Boston, Massachusetts; †Bayer-Schering Pharma, Men's Healthcare, Berlin, Germany; the ‡Gulf Medical College School of Medicine, Ajman, United Arab Emirates; and the §Department of Endocrinology, Center for Sexual Function, Lahey Clinic, Peabody, Massachusetts.*

ABSTRACT: A considerable body of evidence exists suggesting a link among reduced testosterone plasma levels, type 2 diabetes (T2D), and insulin resistance (IR). Hypogonadal men are at higher risk for T2D. Here we evaluate the relationships between testosterone, metabolic syndrome (MetS), T2D, and IR and discuss the relationships among androgen deficiency and these factors, especially as it ultimately relates to the development of cardiovascular disease and erectile dysfunction (ED). Thus, a comprehensive literature search was carried out using PubMed, and relevant articles pertinent to androgen deficiency, T2D, IR, MetS, and ED were reviewed and discussed. Low testosterone precedes elevated fasting insulin, glucose, and hemoglobin A1c (HbA1C) values and may even

predict the onset of diabetes. Treatment of prostate cancer patients with surgical or medical castration exacerbates IR and glycemic control, strengthening the link between testosterone deficiency and onset of T2D and IR. Androgen therapy of hypogonadal men improves insulin sensitivity, fasting glucose, and HbA1c levels. We suggest that androgen deficiency is associated with IR, T2D, MetS, and with increased deposition of visceral fat, which serves as an endocrine organ, producing inflammatory cytokines and thus promoting endothelial dysfunction and vascular disease.

Key words: Erectile dysfunction, androgen deficiency, metabolic syndrome, vascular disease.

J Androl 2009;30:23–32

Androgen deficiency has recently come to the forefront of the medical literature after being ignored for decades. The prevalence of hypogonadism is greater than previously thought. Important associations are being developed and confirmed in the literature between androgen deficiency and metabolic disorders. The “dark side” of testosterone (T) deficiency extends beyond the symptoms of low T. More specifically, there is an important health impact related to metabolic syndrome (MetS), insulin resistance (IR), type 2 diabetes (T2D), and ultimately vascular disease and erectile dysfunction (ED). Low concentrations of T are linked with IR and implicated in hyperglycemia, hypertension, dyslipidemia, and an increased risk of vascular disease (Simon et al, 1997; Stellato et al, 2000; Oh et al, 2002; Dhindsa et al, 2004; Pitteloud et al, 2005a,b; Rhoden et al, 2005b; Corona et al, 2006; Kapoor et al, 2006, 2007;

Fukui et al, 2007, 2008; Selvin et al, 2007). Because of the known epidemic of obesity, the increasing prevalence of T2D and their vascular consequences, and in view of the increasing evidence linking these pathologies to androgen deficiency, we believe that review and discussion of this topic is very timely. In a previous review (Traish et al, 2008) we discussed the relationship between T deficiency and MetS and their links to ED. This review aims to explore the relationships among androgen deficiency, IR, and T2D and their relationship to endothelial dysfunction, vascular disease, and ED.

I. Androgen Deficiency and the Link to Glycemic Control, IR, and T2D

It has been well recognized that diabetes and IR are 2 important components of MetS (Figure 1). The prevalence of T2D has increased dramatically, and it is estimated that the number of individuals diagnosed with diabetes in the US has grown from approximately 6 million in 1980 to an astounding 15 million by 2004 (Steinbrook, 2006). This is mirrored by an increased prevalence of overweight and obesity, and a recent analysis found that this trend has been emerging during the past 5 decades (Parikh et al, 2007). More disturbing is the fact that MetS, of which IR is a key component, is

Correspondence to: Dr Abdulmaged M. Traish, Professor of Biochemistry & Urology, Director, Laboratories for Sexual Medicine, Institute for Sexual Medicine, Boston University School of Medicine, Center for Advanced Biomedical Research, 700 Albany Street, W607, Boston, MA 02118 (e-mail: atraish@bu.edu).

Received for publication May 5, 2008; accepted for publication August 21, 2008.

DOI: 10.2164/jandrol.108.005751

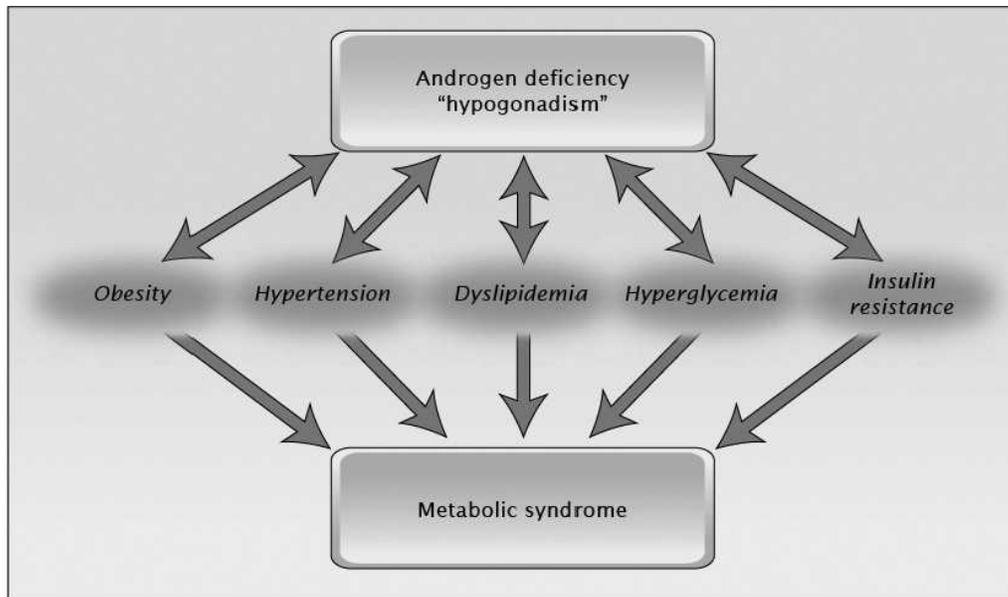


Figure 1. This diagram depicts the important links between androgen deficiency and key components of metabolic syndrome, especially obesity, hypertension, and dyslipidemia, together with glucose abnormalities (hyperglycemia) and insulin resistance (Mulligan et al, 2006). Color figure available online at www.andrologyjournal.org.

showing 4.5% prevalence in adolescents (Ford et al, 2008).

I. a. Is There a Relationship Between Reduced T Levels and T2D?—Several studies have suggested that men with low T are at a greater risk of developing T2D, and that low T may even predict the onset of diabetes (Haffner et al, 1997; Stellato et al, 2000; Oh et al, 2002; Rhoden et al, 2005a,b; Shores et al, 2006; Selvin et al, 2007). A systematic review by Ding et al (2006) of 43 studies including 6427 men suggested that higher T plasma levels were associated with lower risk of T2D and vice versa. Similarly, Haffner et al (1996) demonstrated that low sex hormone-binding globulin (SHBG) and T predict higher glucose and insulin levels and increased obesity. Low plasma T levels are commonly observed in men with T2D and IR (Grossman et al, 2008). Stellato et al (2000) reported findings from the Massachusetts Male Aging Study in which low levels of T and SHBG were thought to play some role in the development of IR and subsequently T2D. Fukui et al (2007) demonstrated that serum T levels are lower in a large number of Japanese patients with T2D when compared with healthy men and suggested that T supplementation in hypogonadal men could decrease IR and atherosclerosis. These observations suggest that androgen deficiency plays a central role in the various pathologies encompassing the components of MetS, including T2D, IR, obesity, and ED (Figure 2)

I. b. Is There a Relationship Between Reduced T Levels and IR?—Other observational studies have confirmed a

significant inverse relationship between total T and IR in men (Andersson et al, 1994; Simon et al, 1997; Pitteloud et al, 2005a,b; Osuna et al, 2006), with a stronger correlation with free T than with total T (Rhoden et al, 2005a,b; Basaria et al, 2006). Grossmann et al (in press) found that 43% of men with T2D have reduced total T, whereas 57% had reduced calculated free T. In type 1 diabetes, 7% had reduced total T, but 20% had low calculated free T, with similar incidences after age adjustments. Simon et al (1997) reported that total T concentrations were significantly associated with fasting plasma insulin, 2-hour plasma insulin levels, and glucose levels. Lower total T led to elevated insulin values and the authors hypothesized that body fat distribution might influence this relationship. Osuna et al (2006) correlated waist circumference, body mass index (BMI), insulin, and homeostatic model assessment of insulin resistance ($HOMA_{IR}$) to T levels and, in each case, found a significant negative correlation. Taken together, these findings raise the possibility that T may have a protective function against diabetes in men.

I. c. Bidirectional Relationship Between Hypogonadism, T2D, and IR—Hypogonadism and T2D are often diagnosed together in the same patient (Dhindsa et al, 2004; Kapoor et al, 2007). Hypogonadism was more prevalent in diabetic patients with increasing BMI, or in those who were severely obese (BMI > 40). In a large cohort of more than 1100 men, Corona et al (2007) showed that hypogonadism had a better correlation with visceral fat than diabetes. Dhindsa et al (2004) also

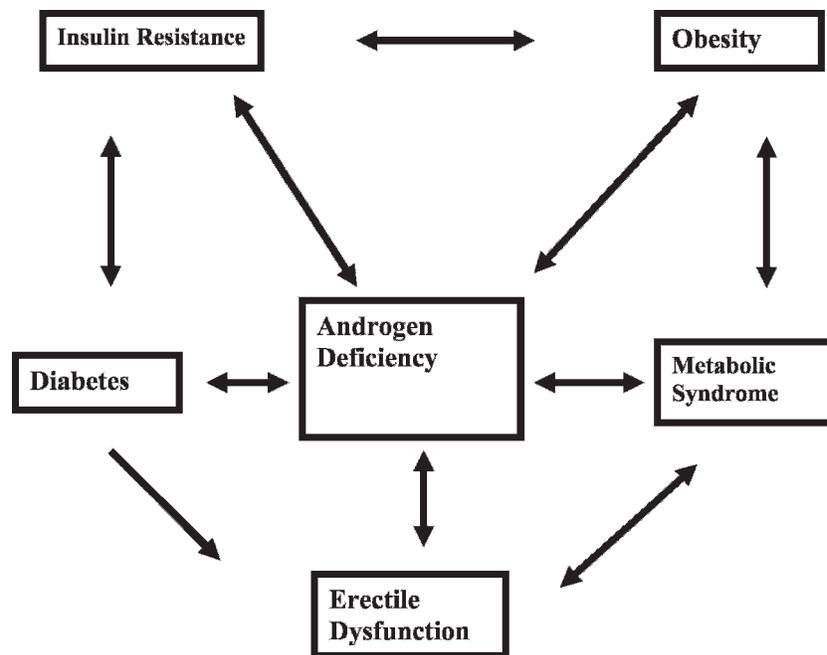


Figure 2. Postulated relationship among androgen deficiency, diabetes, insulin resistance (IR), metabolic syndrome (MetS), and erectile dysfunction (ED). The framework presented in this diagram postulates a bidirectional relationship between obesity and IR, as well as between obesity and MetS and between IR and type 2 diabetes (T2D). We further suggest that ED contributes to androgen deficiency through stress and/or depression. A bidirectional relationship between androgen deficiency and T2D is well known, and this may further contribute to ED. The indirect relationship between ED and T2D is likely to be mediated by multiple overlapping factors common to both pathologies.

showed that above the age of 50, with each successive decade (until age 79), the prevalence of hypogonadism increased, with 55% of individuals in the 70–79 age group having hypogonadism as compared with 24% in the 50–59 age group. Pasquali et al (1991, 1997) found that individuals with T2D are often obese—and obesity may be a major risk factor for significantly lower free T, total T, and elevated fasting insulin levels compared with nonobese male subjects. The authors (Pasquali et al, 1991, 1997) further elucidated these relationships by inducing glucose abnormalities with diazoxide in healthy human subjects and in men with obesity but no diabetes (Pasquali et al, 1995). They found that insulin was capable of stimulating T production in vivo and simultaneously reducing SHBG concentrations in both normal-weight and obese men. Isidori et al (2000) confirmed that individuals with a BMI >30 had significantly higher fasting plasma insulin, fasting IR index, and C-peptide and lower serum T than subjects with BMI <30. Blouin et al (2005) suggested that body fat distribution may influence the relationship between low total T and elevated insulin levels. Pitteloud et al (2005b), however, found body composition to have no effect on the relationship between serum T concentrations and insulin sensitivity, as compared with BMI, percentage body fat, and waist to hip ratio.

In a large study (the Kuopio Ischaemic Heart Disease Risk Factor Study), Laaksonen et al (2003) evaluated the

characteristics of 1896 nondiabetic middle-aged men according to the presence of MetS. The authors found that individuals with MetS had elevated fasting insulin levels as well as decreased total T when compared with controls, a finding that is relevant in the pathogenesis of T2D. Furthermore, Muller et al (2005) concluded that elevated T and SHBG led to increased insulin sensitivity and reduced risk of MetS. Hypogonadism was a stronger risk factor for the development of elevated insulin and glucose levels compared with overweight/obesity (Pagotto et al, 2003). This is substantiated by lower total T and free T levels in hypogonadal men than in overweight/obese men, and, consequently, exhibited higher fasting insulin, HOMA_{IR}, and fasting glucose values.

II. Androgen Deprivation Therapy and the Link to IR, Glycemic Control, and T2D

A considerable body of clinical evidence exists suggesting that acute induced hypogonadism has the same effects as a gradual decline in testicular function. Androgen deprivation therapy (ADT) increases IR, alters glycemic control, and may contribute to development of T2D.

II. a. Relationship Between ADT and Onset of T2D—Lage et al (2007) found that the estimated risk of incident diabetes associated with receiving ADT was 1.36, and that these patients were more likely to develop diabetes within 1 year, even when correcting for the

factors of older age, poorer health, and increased likelihood of other medical cofactors, especially hypertension. Haidar et al (2007) managed diabetic prostate cancer patients with ADT and kept their diabetes under control by administration of insulin. Upon ADT, insulin requirement increased progressively. The authors suggested that androgen deprivation has a negative impact on IR and glycemic control in prostate cancer patients (Haidar et al, 2007). In a large study of 396 men over 5 years, Derweesh et al (2007) included 77 men with pre-existing diabetes. For the diabetic men, an increase in HbA1C of >10% was observed in 20%, whereas fasting glucose levels increased by this magnitude in 29%. In the remaining men, there was a 4.65-fold chance of developing T2D when the BMI was >30. Taken together, these data strongly suggest that long-term ADT produces unfavorable hormonal and metabolic profiles, including IR and hyperglycemia, independent of age and BMI, and increases the risk of T2D.

II. b. Interplay Between Androgen Deficiency and Insulin Sensitivity—Recently, Yialamas et al (2007) demonstrated that acute sex steroid withdrawal for 2 weeks reduced insulin sensitivity in young healthy men with idiopathic hypogonadotropic hypogonadism, suggesting that T modulates insulin sensitivity directly and further suggesting that this pathway is not mediated by changes in body composition. On the other hand, Chen et al (2006) argue that androgen deficiency is a consequence of, and is not a cause of, poor metabolic status. Thus, it is possible that such interplay is bidirectional. Smith et al (2001) investigated the effects of ADT on insulin levels in patients with prostate cancer. Gonadotropin-releasing hormone (GnRH) agonist treatment in men for 12 weeks elevated HbA1c and decreased insulin sensitivity index and HOMA_{IR} measurements (Smith et al, 2001). The authors reported that patients treated with GnRH agonist for 3 months had significantly elevated fasting insulin levels at 1- and 3-month time points when compared with baseline.

II. c. Relationship Between Androgen Deficiency and Insulin Levels—Change in insulin levels also positively correlated with changes in fat mass. T suppression has led to hyperinsulinemia (Dockery et al, 2003) and ADT has produced elevated fasting glucose levels (Nishiyama et al, 2005). Yannucci et al (2006) demonstrated that the effect of ADT on change from baseline in HbA1c levels is independent of statin therapy, assessed after 85 days of treatment. Patients treated with ADT had elevated glucose and increased IR, as measured by HOMA index levels; these findings were independent of age and BMI. Basaria et al (2006) reported that even after adjusting for age and BMI, patients receiving ADT had significantly higher fasting insulin levels than patients with prostatic cancer who did not receive ADT and healthy

controls. These findings suggest that the ADT, rather than age or BMI, was directly responsible for elevated fasting insulin levels. Additionally, Basaria et al (2006) found a significant negative correlation between fasting glucose, fasting insulin, and HOMA levels in relation to total and free T in these 3 groups of men. The proportion of men with fasting glucose ≥ 126 mg/dL, as defined by the American Diabetes Association for diagnosis of T2D, in patients with prostate cancer on ADT, in patients with prostate cancer without ADT, and in healthy controls, was 44%, 12%, and 11%, respectively. Shahani et al (2008) suggested that ADT produces early metabolic changes (3–6 months) associated with development of hyperinsulinemia and that long-term (≥ 12 months) ADT results in higher prevalence of diabetes and MetS when compared with controls.

III. Androgen Therapy and the Link to Glycemic Control, IR, and T2D

T treatment in hypogonadal men reduces fasting insulin and IR by HOMA. Increased insulin sensitivity (measured as a change in glucose disposal rate) is negatively and significantly correlated with baseline T levels (Marin et al, 1992, 1993, 1996; Marin, 1995; Pagotto et al, 2003). Boyanov et al (2003) also showed that men with T2D receiving 3 months of T supplementation have decreased fasting glucose, postprandial glucose, mean daily glucose, and HbA1c values, compared with baseline. Kapoor et al (2006) reported that T treatment in insulin-dependent patients reduced their insulin dosages by a mean of 7 units. Naharci et al (2007) demonstrated that long-term T therapy improved insulin sensitivity and reduced body fat mass. Naharci et al (2007) also showed that the higher the delta in T, the greater the insulin sensitivity. This is consistent with observations by Pitteloud et al (2005a,b) in which they demonstrated such a dose relationship. This is particularly important because it points to the need to achieve high normal T levels rather than low normal T levels. Apart from T's effect on insulin sensitivity, it may have a direct effect on the pancreas and the beta cell (Morimoto et al, 2005). Early apoptotic damage induced by streptozotocin in castrated animals was reversed by T replacement, suggesting a protective effect on the pancreas. More work is needed to determine whether T replacement in hypogonadal men will ameliorate the parameters of T2D, IR, and MetS, as suggested above, and in doing so reduce cardiovascular risks.

IV. IR, Glycemic Control, T2D, and ED

IV. a. The Relationship Between T2D and ED—Several studies have investigated the relationship between

diabetes and ED. In a survey of 2869 men, Ponzolzer et al (2005) found that having diabetes increases the odds of having ED. The authors found that patients with diabetes were at the greatest risk for developing ED (with an odds ratio [OR] of 3) versus patients having other conditions such as hyperlipidemia (OR 2.29), hypertension (OR 2.05), psychologic stress (OR 1.68), or low physical activity (OR 1.35). ORs for ED were also calculated in population-based studies in Germany (Braun et al, 2000), Italy (Parazzini et al, 2000), and Turkey (Akkus et al, 2002), with data from all 3 countries showing patients with diabetes having a higher OR than those with hypertension (and cardiac disease in Turkey). Sun et al (2006) found that 20.0% of men with ED had diabetes mellitus and that 7.5% of the non-ED group of men had diabetes. The authors adjusted for census regions and 7 comorbidities and report that ED is associated with diabetes especially in young men, with the highest odds occurring in the 26–35 age range. They suggested using ED as a clinical marker for the onset of diabetes in men. Giuliano et al (2004) found that the prevalence of ED in patients with diabetes was 70.6% in a survey of 7689 men, whereas Shabsigh et al (2005) found, conversely, that 25% of patients with severe ED had diabetes in the cross-national survey on men's health issues. Bodie et al (2003) assessed laboratory abnormalities for 3547 men with ED and found that a large number of men presenting with a primary complaint of ED had elevated HbA1c levels. Additionally, Yamasaki et al (2004) measured the prevalence of ED (defined by International Index of Erectile Function < 18) in Japanese men with T2D and found that compared with healthy controls (20% ED prevalence), age-matched diabetics had 3 times the prevalence of ED (60%). Taken together, the aforementioned studies suggest that a strong link exists between diabetes and ED, with either condition being a risk factor for the other.

IV. b. The Relationship Between T2D, ED, and Endothelial Dysfunction—Peripheral vascular disease caused by endothelial dysfunction is common in both diabetes and ED. Cell-derived microparticles are involved in endothelial dysfunction, and Esposito et al (2007) showed that these particles correlated with ED in diabetic men. HbA1c levels have been shown to increase with the severity of ED (Rhoden et al, 2005a,b) and were found to be an independent predictor of the erectile function score in 78 men with T2D (Romeo et al, 2000). Besides usually having elevated HbA1c levels, compared with nondiabetics, diabetics typically have a higher incidence of organic ED (Corona et al, 2004). These authors found that in 1027 consecutive patients presenting with ED, those with diabetes mellitus, compared with those with impaired or normal fasting glucose, had

significantly elevated BMI and triglycerides, hypertension, high-density lipoprotein-c (HDLc), and cardiovascular disease, suggesting that there are multiple metabolic parameters for ED in men with diabetes. Lindmark et al (2006) found that glucotoxicity was associated with increased IR but also with increased levels of adipokines like tumor necrosis factor (TNF- α) and c-reactive protein (CRP), which may contribute to IR. Weyer et al (2001) showed an association between reduced levels of adiponectin in T2D and obesity with IR. The many factors that are associated with cardiovascular disease are also active in ED. These include advanced glycation end products, prothrombotic states, hypertension, and dyslipidemias (Rader, 2007).

Corona et al (2006) found a relationship between the prevalence of hypogonadism in 1027 diabetic and nondiabetic patients presenting with ED, with diabetics having a significantly greater prevalence of hypogonadism, especially in the sixth decade of life, compared with nondiabetics. Taking into account all ages, diabetics had a significantly increased prevalence of hypogonadism than did nondiabetics, and hypogonadism has been discussed earlier as a risk factor for ED. Corona et al (2006) also investigated the presence of hypogonadism in 1200 men with ED, of whom 16% had diabetes mellitus. Hypogonadism was found in 24.5% of men with diabetes, versus 12.6% in the rest of the sample. A predominance of secondary hypogonadism over primary testicular failure was also noted. Guay et al (1999) reported that in 990 men with ED, 23.1% had T2D. In this group, 35.6% were also hypogonadal, approaching the 36.0% found in the entire population, emphasizing that numerous chronic illnesses are related to hypogonadism in men with ED. Secondary hypogonadism was also predominant over primary testicular failure, 30.0% vs 6.0%.

The pathophysiologic mechanisms encompassing the complexity of T deficiency, IR, T2D, and vessel damage may stem from the unrecognized endocrine function of the adipose tissue resulting from visceral obesity (Jang et al, 2003; Gustafson et al, 2007). This adipose tissue of the visceral fat responds to multiple signals to produce proinflammatory substances and adipokines, resulting in altered lipid and glucose metabolism, oxidative stress, endoplasmic reticulum stress, increased fatty acid content, and adipose tissue necrosis (Gustafson, 2007). The effects of these factors are not limited to the adipose tissue but may also affect skeletal muscle and liver. The adipokines and inflammatory factors produced by the visceral fat include interleukin (IL)-6, IL1b, plasminogen activator inhibitor 1, TNF- α , angiotensin converting enzymes, vascular endothelial growth factor, angiotensinogen, and serum amyloid A proteins, among others. Some of these adipokines and proinflammatory factors

may stimulate recruitment of macrophages, which stimulate increased adipogenesis, with concomitant reduction in anti-inflammatory factors, such as adiponectin. Furthermore, IL6 and TNF- α are associated with obesity and IR and impair insulin signaling in mature adipocytes. Further, androgens have been shown to inhibit the expression and release of cytokines and chemokines (Malkin et al, 2004; Kapoor et al, 2006; Norata et al, 2006). Androgen deprivation therapy is thought to be associated with increased levels of proinflammatory factors and decreased anti-inflammatory cytokines (Maggio et al, 2005, 2006). Interestingly, T therapy prevents gain in visceral adipose tissue in nonobese aging men, and reduces the production of proinflammatory cytokines (Schroeder et al, 2004; Nielsen et al, 2007; Allan et al, 2008a,b). It is therefore reasonable to suggest that androgens attenuate adipogenesis as well as inflammatory factor production. Because androgen deficiency is linked to the development of IR and T2D and the latter contributes profoundly to endothelium dysfunction (Ginsberg, 2000; Cersosimo and DeFronzo, 2006), the concept of androgen deficiency reinforces the important role of androgens in vascular health (Figure 2).

IV. c. The Relationship of Androgens in Phosphodiesterase Action in Diabetic Patients With ED—An animal study conducted by Zhang et al (2006) used 2 different models of chemical diabetes and found that T reinstates sildenafil responsiveness in both, suggesting that T supplementation in human diabetics with ED receiving pharmacologic treatment might be advantageous in diabetic men in whom phosphodiesterase type 5 inhibitors given for ED do not work. Indeed, studies have tested this concept, and Kalinchenko et al (2003) assessed diabetic ED patients and found that different baseline T levels in these patients determined a differential response to sildenafil. Responders typically had a total T value of 18.6 ± 1.2 nmol/L, whereas nonresponders had a total value of 6.9 ± 1.3 nmol/L. The authors found that although sildenafil therapy alone was insufficient to reverse ED in diabetic patients with low T levels, administration of oral T in combination with sildenafil reverses ED in these patients. In addition to low T levels predicting a poor response to sildenafil in diabetic individuals, Park et al (2005) found uncontrolled diabetes itself to be a risk factor in predicting poor response to sildenafil in 162 consecutive elderly ED patients (mean age 64.1 years). Fonseca et al (2004) also showed that the efficacy of tadalafil treatment in 519 diabetic patients was a function of glycemic control. The authors found that though this treatment had a significant benefit in all HbA1c ranges, there was a downward trend of drug efficacy with increasing HbA1c values. As such,

predicting the efficacy of pharmacologic treatment in patients with ED and diabetes is tenuous, and may be governed by the severity of the metabolic and hormonal profile of these individuals. Apart from lowering blood sugar, another approach is to affect the IR, which predominates in T2D. Kovanez et al (2006) used the insulin sensitizer pioglitazone in diabetic rats with corpora cavernosa fibrosis. This drug treatment ameliorated the fibrosis, oxidative stress, and veno-occlusive dysfunction, suggesting a separate protective effect on the smooth muscle.

V. Cellular Mechanisms Linking Androgen Deficiency to IR, Glycemic Control, and T2D

V. a. Insulin Action on Leydig Cell Function—T biosynthesis is regulated primarily by pulsatile secretion of luteinizing hormone (LH), and compelling evidence exists that Leydig cell steroidogenesis is further modulated locally by circulating hormones, growth factors, and cytokines (Saez 1994). Serum T levels reflect the integrity of the hypothalamic-pituitary-gonadal (HPG) axis, and low T levels noted in cases of IR may indicate a defect at 1 or more functional levels of the HPG axis. In the insulin-resistance state Leydig cell function, particularly steroidogenesis, may be impaired by changes in the production of hormones and cytokines locally in the target tissue and in adipose tissue. Although several studies suggest that increasing IR may be attributed to a decrease in T secretion in men, it is not fully clear how the HPG axis mediates the interplay between T and insulin levels. Pitteloud et al (2005a,b, 2008) explored the effect of suppression of endogenous reproductive hormones, followed by sequential stimulation of the pituitary and the testes with GnRH and human chorionic gonadotropin (hCG), respectively. hCG-stimulated T levels at 48 hours were positively correlated with insulin sensitivity as well as with baseline serum T levels. The authors suggested that alteration in Leydig cell function may account in part for the mechanisms by which a decrease in T leads to IR.

A framework is needed to explain the potential biochemical and physiological mechanisms involved in reduction of T biosynthesis because of changes in insulin/glucose levels in diabetes, and how this may alter the function of the pituitary/testicular axis remains under intensive investigation. Several observations have suggested that a relationship exists between insulin/glucose and LH/follicle-stimulating hormone (FSH) levels. Diabetic men often have reduced serum levels of FSH, LH, prolactin, and growth hormone, consistent with secondary hypogonadism (Hutson et al, 1983; Benitez and Perez Diaz, 1985).

V. b. Effects of T2D on Leydig Cell Function—Leydig cell function is under regulation by LH and other hormones (Saez, 1994; Zirkin and Chen, 2000); therefore, it is possible that increased IR or hyperglycemia may result in reduced T biogenesis because of decreased central stimulation. Interestingly, Pitteloud et al (2005a, 2008) did not observe a correlation between insulin sensitivity and parameters of LH secretion or LH response to exogenous GnRH, suggesting that low T levels associated with IR are not attributable to a major decrease in hypothalamic or pituitary hormone secretion. The authors have demonstrated a strong positive correlation between hCG-stimulated T secretion and insulin sensitivity in men using physiological doses of hCG in the presence of experimentally induced hypogonadism. Ballester et al (2004) proposed several potential mechanisms that affect T biogenesis in diabetes. The authors suggested that diminished Leydig cell function and T production in insulin-dependent diabetes is attributed to reduced or absent stimulatory effect of insulin on Leydig cells. Oltmanns et al (2001) presented data suggesting that hypoglycemia but not insulin suppresses T secretion and that this is mediated by pituitary decrease in LH output. Adipose tissue, which is considered an endocrine organ and produces a host of hormones and cytokines, may modulate insulin action and regulate Leydig cell function. Leptin production is tightly coupled to IR and may play a key role in steroid biogenesis and reduced T levels. Leptin levels have been shown to be inversely correlated with serum T levels (Haffner et al, 1997; Wabitsch et al, 1997; Luukkaa et al, 1998), and increased circulating leptin may be involved in the pathogenesis of Leydig cell dysfunction (Isidori et al, 1999). The expression of leptin receptors in Leydig cells and the inhibition of hCG-stimulated T secretion from rat Leydig cells by leptin suggest a role of this hormone in the biogenesis of T (Caprio et al, 1999). Hong et al (2004) proposed that TNF- α inhibits steroid biosynthesis in Leydig cells and proposed a molecular mechanism by which proinflammatory factors could contribute to inhibition of androgen biosynthesis. Clearly, additional studies are needed to fully delineate the biochemical and physiological mechanisms underlying reduced T synthesis in diabetes.

Discussion

Androgen deficiency may be central to the components of MetS, which encompasses IR, T2D, and obesity, among others (Figures 1 and 2). The relationship between these various components and androgen deficiency is depicted in the diagram in Figure 2. The postulated potential interactions between T deficiency

and the various pathologic states, including IR and T2D, represent a framework from which the interplay among the various pathologies needs to be investigated. T plays a crucial role in maintaining metabolic homeostasis; thus, this hormone may play a vital role in maintaining glycemic control. The exact mechanism by which diabetes and/or IR impairs T biosynthesis and how reduced T levels increase IR and development of T2D remain poorly understood. Low T levels in men with hypogonadism or patients receiving ADT for prostate cancer are considered risk factors for IR and T2D. T therapy may provide protective effects against the onset of diabetes or may ameliorate the pathology of diabetic complications. Low T levels represent a risk factor for IR and T2D, thus contributing to the onset of MetS and vascular consequences, including ED.

We postulate that androgen deficiency plays a central role in the pathology of MetS, T2D, and IR, and contributes significantly to processes of adipogenesis and increased accumulation of visceral fat, resulting in obesity. Visceral fat serves as an endocrine organ, which produces proinflammatory cytokines affecting multiple tissues and organs and further increasing the risk for IR, T2D, MetS, and endothelial dysfunction. We conclude that androgen deficiency is of a central importance in the development of the various pathologies contained within the definition of MetS, leading to vascular complications.

Acknowledgments

This work was supported by the Departments of Biochemistry and Urology, Boston University School of Medicine and Department of Endocrinology, Center for Sexual Function, Lahey Clinic, Peabody, Massachusetts.

References

- Akkus E, Kadioglu A, Esen A, Doran S, Ergen A, Anafarta K, Hattat H, Turkish Erectile Dysfunction Prevalence Study Group. Prevalence and correlates of erectile dysfunction in Turkey: a population-based study. *Eur Urol*. 2002;41:298–304.
- Allan CA, Forbes EA, Strauss BJ, McLachlan RI. Testosterone therapy increases sexual desire in ageing men with low-normal testosterone levels and symptoms of androgen deficiency. *Int J Impot Res*. 2008a;20:396–401.
- Allan CA, Strauss BJ, Burger HG, Forbes EA, McLachlan RI. Testosterone therapy prevents gain in visceral adipose tissue and loss of skeletal muscle in nonobese aging men. *J Clin Endocrinol Metab*. 2008b;93:139–146.
- Andersson B, Marin P, Lissner L, Vermeulen A, Bjorntorp P. Testosterone concentrations in women and men with NIDDM. *Diabetes Care*. 1994;17:405–411.
- Ballester J, Muñoz MC, Domínguez J, Rigau T, Guinovart JJ, Rodríguez-Gil JE. Insulin-dependent diabetes affects testicular

- function by FSH- and LH-linked mechanisms. *J Androl.* 2004;25:706–719.
- Basaria S, Muller DC, Carducci MA, Egan J, Dobs AS. Hyperglycemia and insulin resistance in men with prostate carcinoma who receive androgen-deprivation therapy. *Cancer.* 2006;106:581–588.
- Benitez A, Perez Diaz J. Effect of streptozotocin-diabetes and insulin treatment on regulation of Leydig cell function in the rat. *Horm Metab Res.* 1985;17:5–7.
- 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.
- Bodie J, Lewis J, Schow D, Monga M. Laboratory evaluations of erectile dysfunction; an evidence based approach. *J Urol.* 2003;169:2262–2264.
- Boyanov MA, Boneva Z, Christov VG. Testosterone supplementation in men with type 2 diabetes, visceral obesity and partial androgen deficiency. *Aging Male.* 2003;6:1–7.
- Braun M, Wassmer G, Klotz T, Reifenrath B, Mathers M, Engelmann U. Epidemiology of erectile dysfunction: results of the 'Cologne Male Survey'. *Int J Impot Res.* 2000;12:305–311.
- Caprio M, Isidori AM, Carta AR, Moretti C, Dufau ML, Fabbri A. Expression of functional leptin receptors in rodent Leydig cells. *Endocrinology.* 1999;140:4939–4947.
- Cersosimo E, DeFronzo RA. Insulin resistance and endothelial dysfunction: the road map to cardiovascular diseases. *Diabetes Metab Res Rev.* 2006;22:423–436.
- Chen RYT, Wittes GA, Andreson GR. Relative androgen deficiency in relation to obesity and metabolic status in older men. *Diabetes Obes Metab.* 2006;8:429–435.
- Corona G, Mannucci E, Mansani R, Petrone L, Bartolini M, Giommi R, Forti G, Maggi M. Organic, relational and psychological factors in erectile dysfunction in men with diabetes mellitus. *Eur Urol.* 2004;46:222–228.
- Corona G, Mannucci E, Petrone L, Balercia G, Paggi F, Fisher AD, Lotti F, Chiarini V, Fedele D, Forti G, Maggi M. NCEP-ATPIII-defined metabolic syndrome, type 2 diabetes mellitus, and prevalence of hypogonadism in male patients with sexual dysfunction. *J Sex Med.* 2007;4:1038–1045.
- Corona G, Mannucci E, Petrone L, Ricca V, Balercia G, Mansani R, Chiarini V, Giommi R, Forti G, Maggi M. Association of hypogonadism and type II diabetes in men attending an outpatient erectile dysfunction clinic. *Int J Impot Res.* 2006;18:190–197.
- Derweesh IH, DiBlasio CJ, Kincade MC, Malcolm JB, Lamar KD, Patterson AL, Kitabchit AE, Wake RN. Risk of new-onset diabetes mellitus and worsening glycemic variables for established diabetes in men undergoing androgen-deprivation therapy for prostate cancer. *BJU Int.* 2007;100:1060–1065.
- Dhindsa S, Prabhakar S, Sethi M, Bandyopadhyay A, Chaudhuri A, Dandona P. Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes. *J Clin Endocrinol Metab.* 2004;89:5462–5468.
- 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. *JAMA.* 2006;295:1288–1299.
- 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 hyperinsulinaemia. *Clin Sci.* 2003;104:195–201.
- Esposito K, Ciotola M, Giuliano F, Schisano B, Improta L, Improta MR, Beneduce F, Rispoli M, DeSio M, Giuliano D. Endothelial microparticles correlate with erectile dysfunction in diabetic men. *Int J Impot Res.* 2007;19:161–166.
- Fonseca V, Seftel A, Denne J, Fredlund P. Impact of diabetes mellitus on the severity of erectile dysfunction and response to treatment: analysis of data from tadalafil clinical trials. *Diabetologia.* 2004;47:1914–1923.
- Ford ES, Li C, Zhao G, Pearson WS, Mokdad AH. Prevalence of the metabolic syndrome among US adolescents using the definition from the international diabetes federation. *Diabetes Care.* 2008;31:587–589.
- Fukui M, Soh J, Tanaka M, Kitagawa Y, Hasegawa G, Yoshikawa T, Miki T, Nakamura N. Low serum testosterone concentration in middle-aged men with type 2 diabetes. *Endocr J.* 2007;54:871–877.
- Fukui M, Tanaka M, Hasegawa G, Yoshikawa T, Nakamura N. Association between serum bioavailable testosterone concentration and the ratio of glycosylated albumin to glycosylated hemoglobin in men with type 2 diabetes. *Diabetes Care.* 2008;31:397–401.
- Ginsberg HN. Insulin resistance and cardiovascular disease. *J Clin Invest.* 2000;106:453–458.
- Giuliano FA, Leriche A, Jaudinot EO, de Gendre AS. Prevalence of erectile dysfunction among 7689 patients with diabetes or hypertension, or both. *Urology.* 2004;64:1196–1201.
- Grossman M, Thomas MC, Panagiotopoulos S, Sharpe K, Macisaac RJ, Clark S, Zajac JD, Jerums G. Low testosterone levels are common and associated with insulin resistance in men with diabetes. *J Clin Endocrinol Metab.* 2008;93(5):1834–1840.
- Guay AT, Velasquez E, Perez JB. Characterization of patients in a medical endocrine-based center for male sexual dysfunction. *Endocr Pract.* 1999;5:314–321.
- Gustafson B, Hammarstedt A, Andersson CX, Smith U. Inflamed adipose tissue: a culprit underlying the metabolic syndrome and atherosclerosis. *Arterioscler Thromb Vasc Biol.* 2007;27:2276–2283.
- Haffner SM, Miettinen H, Karhapä P, Mykkänen L, Laakso M. Leptin concentrations, sex hormones, and cortisol in nondiabetic men. *J Clin Endocrinol Metab.* 1997;82:1807–1809.
- Haffner SM, Shaten J, Stern MP, Smith GD, Kuller L. Low levels of sex hormone-binding globulin and testosterone predict the development of non-insulin-dependent diabetes mellitus in men. MRFIT Research Group. Multiple Risk Factor Intervention Trial. *Am J Epidemiol.* 1996;143:889–897.
- Haidar A, Yassin A, Saad F, Shabsigh R. Effects of androgen deprivation on glycaemic control and on cardiovascular biochemical risk factors in men with advanced prostate cancer with diabetes. *Aging Male.* 2007;10:189–196.
- Hong CY, Park JH, Ahn RS, Im SY, Choi HS, Soh J, Mellon SH, Lee K. Molecular mechanism of suppression of testicular steroidogenesis by proinflammatory cytokine tumor necrosis factor alpha. *Mol Cell Biol.* 2004;24:2593–2604.
- Hutson JC, Stocco DM, Campbell GT, Wagoner J. Sertoli cell function in diabetic, insulin-treated diabetic, and semi-starved rats. *Diabetes.* 1983;32:112–116.
- 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.
- Isidori AM, Strollo F, More M, Caprio M, Aversa A, Moretti C, Frajese G, Riondino G, Fabbri A. Leptin and aging: correlation with endocrine changes in male and female healthy adult populations of different body weights. *J Clin Endocrinol Metab.* 2000;85:1954–1962.
- Jang Y, Kim OY, Ryu HJ, Kim JY, Song SH, Ordovas JM, Lee JH. Visceral fat accumulation determines postprandial lipemic response, lipid peroxidation, DNA damage, and endothelial dysfunction in nonobese Korean men. *J Lipid Res.* 2003;44:2356–2364.
- Kalinchenko SY, Kozlov GI, Gontcharov NP, Katsiya GV. Oral testosterone undecanoate reverses erectile dysfunction associated

- with diabetes mellitus in patients failing on sildenafil citrate therapy alone. *Aging Male*. 2003;6:94–99.
- Kapoor D, Aldred H, Clark S, Channer K, Jones T. Clinical and biochemical assessment of hypogonadism in men with type 2 diabetes. *Diabetes Care*. 2007;30:911–917.
- 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.
- Kovanez I, Ferrini MG, Vernet D, Nolzco G, Rajfer J, Gonzalez-Cavadi NF. Pioglitazone prevents corporal veno-occlusive dysfunction in a rat model of type 2 diabetes mellitus. *BJU Int*. 2006;98:116–124.
- 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.
- Lage MJ, Barber BL, Markus RA. Association between androgen-deprivation therapy and incidence of diabetes among males with prostate cancer. *Urology*. 2007;70:1104–1108.
- Lindmark S, Burein J, Ericksson JW. Insulin resistance, endocrine function and adipokines in type 2 diabetes patients at different glycemic levels: potential impact for glucotoxicity in vivo. *Clin Endocrinol*. 2006;65:301–309.
- Luukka V, Pesonen U, Huhtaniemi I, Lehtonen A, Tilvis R, Tuomilehto J, Houlu M, Huupponen R. Inverse correlation between serum testosterone and leptin in men. *J Clin Endocrinol Metab*. 1998;83:3243–3246.
- Maggio M, Basaria S, Ceda GP, Ble A, Ling SM, Bandinelli S, Valenti G, Ferrucci L. The relationship between testosterone and molecular markers of inflammation in older men. *J Endocrinol Invest*. 2005;28(11 suppl proceedings):116–119.
- Maggio M, Blackford A, Taub D, Carducci M, Ble A, Metter EJ, Braga-Basaria M, Dobs A, Basaria S. Circulating inflammatory cytokine expression in men with prostate cancer undergoing androgen deprivation therapy. *J Androl*. 2006;27:725–728.
- Malkin CJ, Pugh PJ, Jones RD, Kapoor D, Channer KS, Jones TH. The effect of testosterone replacement on endogenous inflammatory cytokines and lipid profiles in hypogonadal men. *J Clin Endocrinol Metab*. 2004;89:3313–3318.
- Marin P. Testosterone and regional fat distribution. *Obes Res*. 1995;3 (suppl 4):S609–S612.
- Marin P, Holmang S, Gustafsson C, Jonsson L, Kvist H, Elander A, Eldh J, Sjostrom L, Holm G, Bjorntorp P. Androgen treatment of abdominally obese men. *Obes Res*. 1993;1:245–251.
- Marin P, Holmang S, Jonsson L, Sjostrom L, Kvist H, Holm G, Lindstedt G, Bjorntorp P. The effects of testosterone treatment on body composition and metabolism in middle-aged obese men. *Int J Obes Relat Metab Disord*. 1992;16:991–997.
- Marin P, Lonn L, Andersson B, Oden B, Olbe L, Bengtsson BA, Bjorntorp P. Assimilation of triglycerides in subcutaneous and intraabdominal adipose tissues in vivo in men: effects of testosterone. *J Clin Endocrinol Metab*. 1996;81:1018–1022.
- Morimoto S, Mendoza-Rodríguez CA, Hiriart M, Larrieta ME, Vital P, Cerbón MA. Protective effect of testosterone on early apoptotic damage induced by streptozotocin in rat pancreas. *J Endocrinol*. 2005;187:217–224.
- 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.
- Naharci MI, Pinar M, Bolu E, Olgun A. Effect of testosterone on insulin sensitivity in men with idiopathic hypogonadotropic hypogonadism. *Endocr Pract*. 2007;13:629–635.
- Nielsen TL, Hagen C, Wraae K, Brixen K, Petersen PH, Haug E, Larsen R, Andersen M. Visceral and subcutaneous adipose tissue assessed by magnetic resonance imaging in relation to circulating androgens, sex hormone-binding globulin, and luteinizing hormone in young men. *J Clin Endocrinol Metab*. 2007;92:2696–2705.
- Nishiyama T, Ishizaki F, Anraku T, Shimura H, Takahashi K. The influence of androgen deprivation therapy on metabolism in patients with prostate cancer. *J Clin Endocrinol Metab*. 2005;90:657–660.
- Norata GD, Tibolla G, Seccomandi PM, Poletti A, Catapano AL. Dihydrotestosterone decreases tumor necrosis factor- α and lipopolysaccharide-induced inflammatory response in human endothelial cells. *J Clin Endocrinol Metab*. 2006;91:546–554.
- Oh JY, Barrett-Connor E, Wedick NM, Wingard DL, Rancho Bernardo Study. Endogenous sex hormones and the development of type 2 diabetes in older men and women; the Rancho Bernardo study. *Diabetes Care*. 2002;25:55–60.
- Oltmanns KM, Fruehwald-Schultes B, Kern W, Born J, Fehm HL, Peters A. Hypoglycemia, but not insulin, acutely decreases LH and T secretion in men. *J Clin Endocrinol Metab*. 2001;86:4913–4919.
- Osuna JA, Gomez-Perez R, Arata-Bellarbarba 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.
- Pagotto U, Gambineri A, Pelusi C, Genghini S, Cacciari M, Otto B, Castaneda T, Tschop M, Pasquali R. Testosterone replacement therapy restores normal ghrelin in hypogonadal men. *J Clin Endocrinol Metab*. 2003;88:4139–4143.
- Parazzini F, Menchini Fabris F, Bortolotti A, Calabro A, Chatenoud L, Colli E, Landoni M, Lavezzari M, Turchi P, Sessa A, Mirone V. Frequency and determinants of erectile dysfunction in Italy. *Eur Urol*. 2000;37:43–49.
- Parikh NI, Pencine MJ, Wang TJ, Lanier KJ, Fox CS, d'Agostino RB, Ramachandran SV. Increasing trends in incidence of overweight and obesity over 5 decades. *Amer J Med*. 2007;120:242–250.
- Park K, Ku JH, Kim SW, Paick JS. Risk factors in predicting a poor response to sildenafil citrate in elderly men with erectile dysfunction. *BJU Int*. 2005;95:366–370.
- Pasquali R, Casimirri F, Cantobelli S, Melchionda N, Morselli Labate 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.
- Pasquali R, Casimirri F, De lasio R, Mesini P, Boschi S, Chierici R, Flaminia R, Biscotti M, Vicennata V. Insulin regulates testosterone and sex hormone-binding globulin concentrations in adult normal weight and obese men. *J Clin Endocrinol Metab*. 1995;80:654–658.
- Pasquali R, Macor C, Vicennati V, Novo F, De Lasio R, Mesini P, Boschi S, Casimirri F, Vettor R. Effects of acute hyperinsulinemia on testosterone serum concentrations in adult obese and normal-weight men. *Metabolism*. 1997;46:526–529.
- Pitteloud N, Dwyer AA, DeCruz S, Lee H, Boepple PA, Crowley WF Jr, Hayes FJ. Inhibition of luteinizing hormone secretion by testosterone in men requires aromatization for its pituitary but not its hypothalamic effects: evidence from the tandem study of normal and gonadotropin-releasing hormone-deficient men. *J Clin Endocrinol Metab*. 2008;93:784–791.
- Pitteloud N, Hardin M, Dwyer AA, Valassi E, Yialamas 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.
- Ponholzer A, Temml C, Mock K, Marszalek M, Obermayr R, Madersbacher S. Prevalence and risk factors for erectile dysfunction in 2869 men using a validated questionnaire. *Eur Urol*. 2005;47:80–86.
- Rader DJ. Effect of insulin resistance, dyslipidemia, and the intra-abdominal adiposity on the development of cardiovascular disease and diabetes mellitus. *Amer J Med*. 2007;120:512–518.
- Rhoden EL, Ribeiro EP, Riedner CE, Teloken C, Souto CA. Glycosylated haemoglobin levels and the severity of erectile dysfunction in diabetic men. *BJU Int*. 2005b;95:615–617.
- Rhoden EL, Ribeiro EP, Teloken C, Souto CA. Diabetes mellitus is associated with subnormal serum levels of free testosterone in men. *BJU Int*. 2005b;96:867–870.
- Romeo JH, Seftel AD, Madhun ZT, Aron DC. Sexual function in men with diabetes type 2: association with glycemic control. *J Urol*. 2000;163:788–791.
- Saez JM. Leydig cells: endocrine, paracrine, and autocrine regulation. *Endocr Rev*. 1994;15:574–626.
- Schroeder ET, Zheng L, Ong MD, Martinez C, Flores C, Stewart Y, Azen C, Sattler FR. Effects of androgen therapy on adipose tissue and metabolism in older men. *J Clin Endocrinol Metab*. 2004;89:4863–4872.
- Selvin E, Feinleib M, Zhang L, Rohrmann S, Rifai N, Nelson W, Dobs A, Basaria S, Golden S, Platz E. Androgens and diabetes in men. *Diabetes Care*. 2007;30:234–238.
- Shabsigh R, Perelman MA, Lockhart DC, Lue TF, Broderick GA. Health issues of men: prevalence and correlates of erectile dysfunction. *J Urol*. 2005;174:662–667.
- Shahani S, Braga-Basaria M, Basaria S. Androgen deprivation therapy in prostate cancer & metabolic risk for atherosclerosis. *J Clin Endocrinol Metab*. In press.
- Shores MM, Matsumoto AM, Sloan KL, Kivlahan DR. Low serum testosterone and mortality in male veterans. *Arch Intern Med*. 2006;166:1660–1665.
- Simon D, Charles MA, Nahoul K, Orssaud G, Kremiski J, Hully V, Joubert E, Papoz L, Eschwege E. Association between plasma total testosterone and cardiovascular risk factors in healthy adult men: the Telecom Study. *J Clin Endocrinol Metab*. 1997;82:682–685.
- Smith JC, Bennett S, Evans LM, Kynaston HG, Parmar M, Mason MD, Cockcroft JR, Scanlon MF, Davies JS. The effects of induced hypogonadism on arterial stiffness, body composition, and metabolic parameters in males with prostate cancer. *J Clin Endocrinol Metab*. 2001;86:4261–4267.
- Steinbrook R. Facing the diabetes epidemic—mandatory reporting of glycosylated hemoglobin values in New York City. *N Engl J Med*. 2006;354:545–548.
- Stellato RK, Feldman HA, Hamdy O, Horton ES, McKinlay JB. Testosterone, sex hormone-binding globulin, and the development of type 2 diabetes in middle-aged men: prospective results from the Massachusetts male aging study. *Diabetes Care*. 2000;23:490–494.
- Sun P, Cameron A, Seftel A, Shabsigh R, Niederberger C, Guay A. Erectile dysfunction—an observable marker of diabetes mellitus? A large national epidemiological study. *J Urol*. 2006;176:1081–1085.
- Traish AM, Guay AT, Feeley R, Saad F. The dark side of testosterone deficiency: I. Metabolic syndrome and erectile dysfunction. *J Androl*. 2009;30(1):10–22.
- Wabitsch M, Blum WF, Mucbe R, Braun M, Hube F, Rascher W, Heinze E, Teller W, Hauner H. Contribution of androgens to the gender difference in leptin production in obese children and adolescents. *J Clin Invest*. 1997;100:808–813.
- Weyer C, Funahashi T, Tanaka S, Hotla K, Matsuzawa Y, Pratley RE, Tataranni A. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. *J Clin Endocrinol Metab*. 2001;86:1930–1935.
- Yamasaki H, Ogawa K, Sasaki H, Nakao T, Wakasaki H, Matsumoto E, Furuta H, Nishi M, Ueda K, Iwo K, Nanjo K. Prevalence and risk factors of erectile dysfunction in Japanese men with type 2 diabetes. *Diabetes Res Clin Pract*. 2004;66S:S173–S177.
- Yannucci J, Manola J, Garnick MB, Bhat G, Bubley GJ. The effect of androgen deprivation therapy on fasting serum lipid and glucose parameters. *J Urol*. 2006;176:520–525.
- Yialamas MA, Dwyer AA, Hanley E, Lee H, Pitteloud N, Hayes FJ. Acute sex steroid withdrawal reduces insulin sensitivity in healthy men with idiopathic hypogonadotropic hypogonadism. *J Clin Endocrinol Metab*. 2007;92:4254–4259.
- Zhang XH, Filippi S, Morelli A, Vignozzi L, Luconi M, Donati S, Forti G, Maggi M. Testosterone restores diabetes-induced erectile dysfunction and sildenafil responsiveness in two distinct animal models of chemical diabetes. *J Sex Med*. 2006;3:253–266.
- Zirkin BR, Chen H. Regulation of Leydig cell steroidogenic function during aging. *Biol Reprod*. 2000;63:977–981.