

## HYPOGONADISM AND METABOLIC SYNDROME: IMPLICATIONS FOR TESTOSTERONE THERAPY

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### ABSTRACT

**Purpose:** Metabolic syndrome, characterized by central obesity, insulin resistance, dyslipidemia and hypertension, is highly prevalent in the United States. When left untreated, it significantly increases the risk of diabetes mellitus and cardiovascular disease. It has been suggested that hypogonadism may be an additional component of metabolic syndrome. This has potential implications for the treatment of metabolic syndrome with testosterone. We reviewed the available literature on metabolic syndrome and hypogonadism with a particular focus on testosterone therapy.

**Materials and Methods:** A comprehensive MEDLINE review of the world literature from 1988 to 2004 on hypogonadism, testosterone and metabolic syndrome was performed.

**Results:** Observational data suggest that metabolic syndrome is strongly associated with hypogonadism in men. Multiple interventional studies have shown that exogenous testosterone has a favorable impact on body mass, insulin secretion and sensitivity, lipid profile and blood pressure, which are the parameters most often disturbed in metabolic syndrome.

**Conclusions:** Hypogonadism is likely a fundamental component of metabolic syndrome. Testosterone therapy may not only treat hypogonadism, but may also have tremendous potential to slow or halt the progression from metabolic syndrome to overt diabetes or cardiovascular disease via beneficial effects on insulin regulation, lipid profile and blood pressure. Furthermore, the use of testosterone to treat metabolic syndrome may also lead to the prevention of urological complications commonly associated with these chronic disease states, such as neurogenic bladder and erectile dysfunction. Physicians must be mindful to evaluate hypogonadism in all men diagnosed with metabolic syndrome as well as metabolic syndrome in all men diagnosed with hypogonadism. Future research in the form of randomized clinical trials should focus on further defining the role of testosterone for metabolic syndrome.

**KEY WORDS:** testis, testosterone, metabolic syndrome X, hypogonadism, obesity

### DEFINITION

Cardiovascular disease has always had a major public health impact worldwide. Risk factors for cardiovascular disease have been studied extensively. They include diabetes, dyslipidemia, hypertension and smoking. While an increasing number of Americans continue to have these comorbidities, an even larger number of people have the premorbid equivalents of impaired glucose tolerance, increased cholesterol (c) and borderline hypertension. Similarly obesity continues to be a growing problem in the United States and worldwide. It has been estimated that 47 million Americans are currently obese and have at least 2 of the 3 premorbid conditions listed.<sup>1</sup> In the last several decades there has been a paradigm shift, in which this constellation of premorbid factors has come to be recognized as a high risk medical condition known as metabolic syndrome, syndrome X or insulin resistance syndrome.

Metabolic syndrome has been defined by multiple medical groups, including the National Heart, Lung, and Blood Institute,<sup>2</sup> WHO<sup>3</sup> and the American Association of Clinical Endocrinologists (see Appendix, and tables 1 and 2).<sup>4</sup> While the exact definition of obesity varies among the groups, all 3 have in common certain requirements, including central obesity, insulin dysregulation, abnormal lipid profile and borderline or overt hypertension.

### PREVALENCE

An estimated 47 million American adults meet the criteria for metabolic syndrome. Ford et al estimated that almost half of all individuals older than 60 years may have metabolic syndrome (fig. 1).<sup>1</sup> There is a steady decrease in prevalence with decreasing age but even in teenagers as many as 4.2% may have the disorder. Prevalence rates also differ among ethnic groups. The highest overall prevalence has been found in Hispanic individuals, particularly Mexican-American individuals, followed by white, black and other ethnic groups. These differences across ethnicities persist even after adjusting for age, body mass index (BMI) and socioeconomic status. In white and other ethnicities there is little difference in the prevalence of metabolic syndrome in men and women (fig. 2). Black and Mexican-American women have a 57% and 26% higher prevalence compared with black and Mexican-American men, respectively.

### PATHOGENESIS

To our knowledge a central unifying theory to explain the relationships among the various components of metabolic syndrome remains to be elucidated. However, the ongoing obesity epidemic in the Western world has been suggested as a major causative factor in the pathogenesis of this increasingly more prevalent disease.<sup>2</sup> In particular abdominal or central obesity has been linked to hypertension, increased serum low density lipoprotein (LDL), low serum high density lipoprotein (HDL) and hyperglycemia.<sup>5,6</sup> Focusing on normal and overweight women, Carey et al measured the association

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TABLE 1. Adult Treatment Panel III clinical identification of metabolic syndrome in men

Feature	Defining Level
Abdominal obesity (cm, in waist circumference)	Greater than 120, greater than 40
Fasting plasma triglycerides (mg/dl, mmol/l)	Greater than 150, 1.69
Fasting plasma HDLC (mg/dl, mmol/l)	Less than 40, 1.03
Fasting blood glucose (mg/dl, mmol/l)	Greater than 110, 6.1
Diastolic/systolic blood pressure (mm Hg)	Greater than 130, greater than 85
Diagnosis is metabolic syndrome if patient has 3 or more features.	

between regional adiposity, such as visceral-abdominal, subcutaneous-abdominal or peripheral-nonabdominal, and insulin sensitivity.<sup>7</sup> They found that abdominal obesity much more than peripheral obesity is a significant determinant of insulin sensitivity. Given that abdominal adipose tissue is highly responsive to lipolytic stimuli and large amounts of free fatty acids enter the portal circulation in obese subjects, it is likely that abdominal obesity impairs hepatic and peripheral insulin sensitivity in obese patients.<sup>8</sup>

Excessive hepatic gluconeogenesis, impaired peripheral glucose use and increased lipolysis leading to increased free fatty acids are the hallmarks of insulin resistance found in metabolic syndrome. Examining the multiple physiological effects of insulin in the human body helps us understand metabolic abnormalities that result from insulin resistance in metabolic syndrome. In the vascular system insulin stimulates the growth of endothelial cells and pericytes.<sup>9</sup> In the kidney insulin has a role in volume and, hence, blood pressure regulation by activating mechanisms of sodium reabsorption.<sup>10</sup> Insulin also facilitates wound healing by promoting effective platelet aggregation and fibrinolysis.<sup>11</sup>

When normal insulin regulation is disrupted, as in metabolic syndrome, abnormalities in endothelial function, blood pressure regulation and coagulation result. These abnormalities cause atherosclerosis, chronic inflammation and unstable plaque formation,<sup>12</sup> which predispose to acute thrombosis in the cardiovascular system.<sup>11</sup>

In addition to central obesity and insulin resistance, several other endocrine factors have been implicated in the pathogenesis of metabolic syndrome. It has been suggested that alterations in the peripheral metabolism of glucocorticoids, brought about by changes in the expression of 11 $\beta$ -hydroxysteroid dehydrogenase, type I, may be responsible for the abnormalities in body fat distribution seen in patients with obesity and/or hyperglycemia.<sup>13</sup> Laaksonen et al reported that low total testosterone (T), free testosterone and sex hormone-binding globulin (SHBG) correlate strongly

TABLE 2. American Association of Clinical Endocrinologists clinical criteria for diagnosis of insulin resistance syndrome

Risk Factor Components	Abnormality Cutoffs
Overweight/obesity (kg/m <sup>2</sup> )	BMI 25 or greater
Increased triglycerides	150 or Greater mg/dl (1.69 mmol/l)
Low HDL cholesterol (mg/dl, mmol/l):	
Men	Less than 40, 1.04
Women	Less than 50, 1.29
Increased diastolic/systolic blood pressure (mm Hg)	130/85 or Greater
2-Hr post-glucose challenge (mg/dl)	Greater than 140
Fasting glucose (mg/dl)	110–126

Other risk factors are family history of type 2 diabetes, hypertension or coronary vascular disease, polycystic ovary syndrome, sedentary life-style, advancing age and ethnic group at high risk for type 2 diabetes or cardiovascular disease (diagnosis depends on clinical judgment based on risk factors).

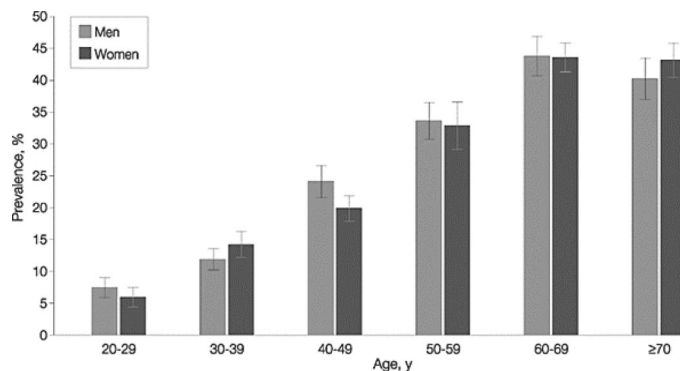


FIG. 1. Age specific prevalence of metabolic syndrome in 8,814 American adults at least 20 years old by sex according to National Health and Nutrition Examination Survey III, 1988 to 1994. Data are shown as percent  $\pm$  SE. y, years.

with metabolic syndrome.<sup>14</sup> Intuitively low SHBG should predict high free testosterone. However, the pathomechanism of the correlation of low SHBG with metabolic syndrome is not clear and may need further clarification in future research.

Given the multiple metabolic and endocrine axes involved in metabolic syndrome and the large number of complex interactions among them, it is clear that much remains to be understood about the true pathogenesis of this disease.

#### SEQUELAE

Patients with metabolic syndrome are at high risk for cardiovascular disease, diabetes mellitus and chronic renal insufficiency.<sup>14</sup> In men with any of these chronic medical illnesses their already compromised quality of life is often further decreased by erectile dysfunction (ED) or voiding dysfunction. Currently treatment modalities focus on treat-

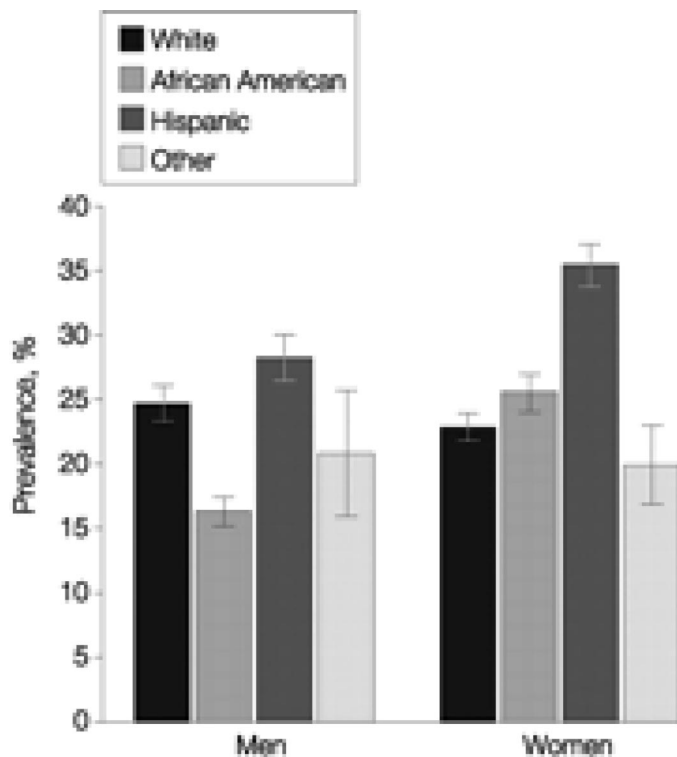


FIG. 2. Age adjusted prevalence of metabolic syndrome in 8,814 American adults at least 20 years old by sex and race or ethnicity according to National Health and Nutrition Examination Survey III, 1988 to 1994. Data are shown as percent  $\pm$  SE.

ing the primary disease, eg improving glycemic control to slow ED, or on palliating urological symptoms, eg using phosphodiesterase inhibitors for ED or anticholinergic medications for voiding dysfunction. In the remainder of this review we examine the evidence suggesting that hypogonadism is associated with metabolic syndrome and treating hypogonadism with testosterone therapy may improve not just urological sequelae, but also the other abnormal components of this multifactorial disease process.

#### OBSERVATIONAL STUDIES

Multiple cross-sectional studies have shown inverse correlations between plasma testosterone and triglycerides (TGs), total cholesterol, LDL, fibrinogen and plasminogen activator type I.<sup>15–23</sup> Other studies have shown inverse correlations between plasma testosterone and BMI, waist circumference, the waist-to-height ratio, amount of visceral fat, serum leptin, serum insulin and serum-free fatty acid concentrations.<sup>24–26</sup> In a case-control study of 50 age and race matched men segregated by testosterone levels hypoandrogenemia was associated with higher BMI, systolic blood pressure, fasting serum glucose, serum insulin and the levels of all lipids except HDL and apolipoprotein A<sub>1</sub>.<sup>27</sup> Seftel et al examined a managed care claims database containing 272,325 men with ED and found that 68% had a concurrent diagnosis of hypertension, hypercholesterolemia, diabetes or depression.<sup>28</sup>

Taken together the findings of these observational studies support the hypothesis that low testosterone is a component of a multidimensional metabolic syndrome characterized by obesity, diabetes mellitus, hypertension, dyslipidemia and a procoagulant/antifibrinolytic state. A large European population based study recently showed that hypogonadism is associated not just with individual components of metabolic syndrome, but also with the entire syndrome itself, as defined by WHO criteria.<sup>14</sup> Given their findings, the group suggested that mild hypogonadism should be considered an element of metabolic syndrome. More recently Laaksonen et al reported that hypogonadism can predict the subsequent development of diabetes and metabolic syndrome in middle-aged men.<sup>29</sup> They also hypothesized that, in addition to being an early marker of metabolic syndrome or overt diabetes, hypogonadism may also be involved in the pathogenesis of these disease processes. However, while obesity, insulin resistance and hypogonadism are certainly thought to be linked, currently the exact causal relationships among them remain unclear. There is evidence in the literature individually supporting each of the 3 factors as the sentinel condition in the development of metabolic syndrome.

*Obesity as the sentinel factor in metabolic syndrome.* Morbidly obese and insulin resistant men frequently have low serum testosterone and increased estradiol.<sup>26,30</sup> Weight loss has been shown to lead to an increase in testosterone and a corresponding decrease in estradiol.<sup>31,32</sup> Furthermore, it is known that aromatase, the enzyme necessary for the conversion of testosterone to estradiol, is found in abundance in adipose tissues. From these findings it has been suggested that obesity causes hypogonadism by the increased aromatization of testosterone to estradiol in adipose tissue. An alternate explanation is that obesity increases glucocorticoid turnover and production, resulting in dysregulation of the hypothalamic-pituitary-adrenal axis and mild hypoandrogenism.<sup>13,33</sup> Hence, there are multiple feasible mechanisms by which obesity may induce hypogonadism as well as the other elements of metabolic syndrome. In a cohort of men with obesity and ED Esposito et al recently observed that even in the absence of hypertension, insulin resistance and dyslipidemia significant improvements in erectile function could be achieved by weight loss.<sup>34</sup>

*Insulin resistance as the sentinel factor in metabolic syn-*

*drome.* It has been shown that the reactive hyperinsulinemia associated with insulin resistance has a negative regulatory effect on SHBG production.<sup>35,36</sup> Furthermore, inhibition of insulin secretion by diazoxide leads to an increase in SHBG, suggesting that insulin is a negative regulator of hepatic SHBG production.<sup>37</sup> This has been confirmed by in vitro hepatocyte cell culture studies showing the inhibition of SHBG production by insulin and the stimulation of SHBG production by testosterone.<sup>38</sup> These experiments show how men who have no abnormalities except insulin resistance may have hypogonadism on the stepwise progression to metabolic syndrome.

*Hypogonadism as the sentinel factor in metabolic syndrome.* Experimental rats have been shown to have marked insulin resistance after orchiectomy with insulin sensitivity restored by the administration of physiological doses of testosterone.<sup>39</sup> The loss of testosterone leads to a decrease in skeletal muscle mass and an increase in circulating nonesterified fatty acids.<sup>40,41</sup> Tsai et al reported that low testosterone is also a predictor of increased visceral fat in Japanese-American men.<sup>24</sup> This evidence offers a plausible mechanism as to how men who are initially only hypogonadal may progress to insulin resistance and central obesity.

The studies mentioned show how any of the 3 factors, namely obesity, insulin resistance or hypogonadism, may be the initial condition leading to metabolic syndrome. The exact order of the conditions is not important. The critical point is to realize that the various components are clearly intertwined and multiple complex interactions are necessary for the development of metabolic syndrome.

#### INTERVENTIONAL STUDIES

Since the concept of hypogonadism as a critical component of metabolic syndrome is only in its infancy, testosterone as a treatment option for metabolic syndrome has not been thoroughly studied. However, numerous studies of the individual metabolic and endocrine effects of testosterone on the human body exist. They suggest a promising role for this agent for the treatment of metabolic syndrome (table 3).

*Effects of testosterone on the cardiovascular system.* Testosterone has been shown in vitro and in vivo to have direct vasodilatory effects on coronary arteries. Yue et al observed that testosterone administered to rabbits induces relaxation of the coronary arteries and aorta.<sup>42</sup> They proposed that the site of action of testosterone may be an adenosine triphosphate insensitive potassium channel. In a study of elderly men with coronary artery disease Webb et al reported coronary artery dilatation and improved coronary blood flow with the direct intracoronary infusion of physiological amounts of testosterone for 3 minutes.<sup>43</sup> In a randomized, double-blind, placebo controlled study of men with chronic stable angina English et al noted short-term improvements in electrocardiographic changes, as manifested by time to 1 mm ST segment depression in the electrocardiogram, after the daily application of a low dose transdermal testosterone patch for several weeks.<sup>44</sup> Patients with lower baseline testosterone showed responses of greater magnitude.

In studies of obese, hypogonadal and diabetic men treated with oral<sup>45,46</sup> or transdermal<sup>40</sup> testosterone blood pressure was shown to decrease favorably. Conversely men treated with androgen deprivation therapy for prostate cancer have been found to have increased arterial stiffness.<sup>47,48</sup> In 1 of these studies an interval improvement in arterial compliance was noted during a period when androgen deprivation therapy was halted.<sup>47</sup>

*Effects of testosterone on glucose homeostasis.* At physiological doses testosterone is known to have beneficial effects on glucose regulation. In experimental nondiabetic rats exposed to subtherapeutic or supratherapeutic doses of testosterone marked insulin resistance developed.<sup>39</sup> When serum testos-

TABLE 3. *Interventional studies*

References	Study Design	No. Pts.	Hypogonadism Criteria	Pt. Status at Study Entry	Treatment	Followup (mos)	Effects				Comments
							Obesity Parameters	Lipid Panel	Cardiovascular Status	Diabetic Parameters	
Wang et al <sup>49</sup>	Randomized	227	Single morning serum T at screening 10.4 nmol/l or less (300 ng/dl)	Hypogonadism	1% T gel, permeation enhanced T patch	3	Increased lean mass, decreased fat mass + %	Decreased LDL, HDL, TG			Dose response treatment effect in T gel group
Katznelson et al <sup>51</sup>	Open label	29	Serum T less than 10.4 nmol/l	Hypogonadism	Oral T enanthate	18	Decreased subcutaneous fat, increased lean muscle mass				
Li et al <sup>46</sup>		86		Hypogonadism	Oral T undecanoate	2	Decreased waist/hip ratio	No total or TG change	Decreased blood pressure		
Boyanov et al <sup>46</sup>	Randomized	48	Total serum T less than 15.1 nmol/l	Hypogonadism, type 2 diabetes mellitus, visceral obesity	Oral T undecanoate	3	Decreased body wt, waist/hip ratio + % body fat	No change	Decreased blood pressure	HbA1c	
Wittert et al <sup>50</sup>	Randomized	76	Total T less than 8 nmol/l	Healthy, age 70 yrs or older	Oral T undecanoate	12	Increased lean body mass, decreased fat mass	No change in plasma TG, total + LDL HDL	No change		
Marin <sup>40</sup>	Double-blind		Not available	Abdominal obesity	Transdermal T dihydrotestosterone	9	Decreased visceral fat mass (T)	Decreased LP/L activity + plasma c, TG (T)	Decreased diastolic blood pressure		No change in femoral adipose tissue
Hislop et al <sup>58</sup>		9	Not available	9 Bodybuilders with anabolic-androgenic steroids (AAS), 10 healthy men on triptolein for 5 wks, normal control group	AAS	1.5		AAS decreased HDLc, Lp(a) + postprandial TG, no LDLc + total change, triptolein increased HDLc, total + Lp(a), no LDLc, PPT change	Decreased diastolic blood pressure		Compare with triptorelin
Zgliczynski et al <sup>59</sup>	Open label	22	Serum T less than 3.5 ng/ml	22 Hypogonadal elderly men (11 hypopituitary, 11 healthy, hypogonadic)	Intramuscular T enanthate	12		Decreased total c, LDL, TG + HDL			Same results in 2 groups with different hypogonadism etiologies
Dobs et al <sup>60</sup>	Open label, multicenter	29	Serum T 8.7 nmol/l or less	Hypogonadism	Permeation enhanced T transdermal system	12		Decreased HDL, increased c/HDL ratio + TG, slight decrease in LDL + total c			
Smith et al <sup>47</sup>		22	Not available	Prostate Ca	Androgen deprivation therapy	6	Decreased lean body mass, increased fat mass	No Lp change	Increased large artery stiffening, no peripheral blood pressure change		Increased serum insulin, no serum glucose change

TABLE 3. Continued

References	Study Design	No. Pts.	Hypogonadism Criteria	Pt Status at Study Entry	Treatment	Followup (mos)	Effects			Comments
							Obesity Parameters	Lipid Panel	Cardiovascular Status	
Dockery et al <sup>48</sup>		16	Not available	16 Men with prostate Ca, 15 with arterial stiffness	Gonadotropin-releasing hormone analogues	3	No BMI change	Increased total c + HDLc, no LDLc + TG change	Decreased systemic arterial compliance, increased central pulse wave velocities	Increased serum insulin, no serum glucose change
Webb et al <sup>43</sup>		13	Not available	Coronary artery disease	Intracoronary 3-min T infusion	Not available			Coronary artery dilatation + increased coronary blood flow	
English et al <sup>44</sup>	Randomized, double-blind, placebo controlled	46	Not available	Chronic stable angina	Transdermal T patch	3			Decreased exercise induced myocardial ischemia	
Ozata et al <sup>55</sup>	Open label	22	"Severely retarded sexual maturation and failure to undergo puberty spontaneously before 18 yrs of age and was confirmed by a decreased serum T concentration below the normal range for adults, FSH and LH levels within or below the normal range"	Idiopathic hypogonadotropic hypogonadism	Human chorionic gonadotropin/human menopausal gonadotropin	3		No TG, LpA-I/A-II, HDLc, HDL3, apo A-I + apo B change, increased total c, LDLc, LpA-I + HDL2		
		9	Not available	Klimfelter syndrome	T enanthate	3		No TG, LpA-I/A-II, HDLc, HDL3 + apo A-I change, increased total c, LDLc, LpA-I, HDL2 + apo B		
Tan et al <sup>54</sup>	Open label	11	Not specified	Hypogonadism	Intramuscular T enanthate	3		No total c, TG, apo B, apo(a), LpA-I + LpL activity change, decreased HDL3c, LDLc, TG, apoA-I + LpA-I/A-II, increased HDL2c + hepatic lipase		
Kenny et al <sup>61</sup>	Randomized, controlled	44	Bioavailable T less than 4.44 nmol/l	Hypogonadism	Transdermal T	12		No total c, TG + LDLc change, decreased HDL2		No vascular reactivity change
Denti et al <sup>62</sup>	Randomized, controlled	13	Not available	Benign prostatic hypertrophy	Finasteride	6	No body composition change	Increased HDL3c + Lp(a)		

terone was normalized, insulin sensitivity was fully restored. In human studies of obese, diabetic and hypogonadal men testosterone administration resulted in decreased fasting glucose, increased insulin sensitivity and decreased glycosylated hemoglobin A<sub>1c</sub>.<sup>45,40</sup> In studies of patients with prostate cancer undergoing androgen deprivation therapy increased serum insulin has been noted despite no change in glucose.<sup>47,48</sup> This suggests an underlying resistance to insulin and a subsequent need for higher serum levels to achieve euglycemia.

*Effects of testosterone on body composition.* The age related decrease in testosterone normally seen in aging men is associated with a progressive loss of muscle mass and increase in body fat. The principle of testosterone therapy in hypogonadal elderly men is based on the supposition that correcting testosterone levels should result in an increase in muscle mass and a decrease in fat mass. Wang et al treated 227 hypogonadal men with testosterone therapy in the form of a gel (50 or 100 mg daily) or a permeation enhanced patch (5 mg daily).<sup>49</sup> After 90 days of treatment all groups demonstrated an increase in lean body mass. Notably the group of men treated with 100 mg testosterone gel daily showed more than a 2-fold increase in muscle mass relative to the other groups ( $p = 0.0002$ ), suggesting a possible dose-response relationship between testosterone therapy and muscle mass. This dose-response relationship was not observed in changes in fat mass. The 2 groups of men receiving the different concentrations of testosterone gel showed similar decreases in body fat mass and the group receiving the testosterone patch showed no decrease in body fat mass after 90 days.

Multiple other studies of oral testosterone therapy in men have documented increased lean body mass, weight loss, a decreased percent of body fat and a decrease in the waist-to-height ratio.<sup>45,46,50,51</sup> In a double-blind study of men with central obesity treated with transdermal testosterone Marin found a decrease in visceral fat but not in femoral fat in men treated with testosterone.<sup>40</sup>

Rajan et al hypothesized that testosterone may regulate body composition by preferentially inducing pluripotent mesenchymal cell differentiation toward a myogenic lineage and away from an adipogenic lineage.<sup>52</sup> When this group treated pluripotent mouse C3H 10T1/2 mesenchymal cells with testosterone for 14 days, they noted an increase in myogenic differentiation and a decrease in adipogenesis. Similarly Dieudonne et al observed an anti-adipogenic effect on preadipocytes exposed to androgens in vitro.<sup>53</sup>

*Effect of testosterone on lipid regulation.* While observational studies have shown a consistent association between low testosterone and high cholesterol, studies of testosterone therapy have yielded inconsistent results. It has been suggested that testosterone may actually decrease HDL concentrations and have a potentially atherogenic effect. However, as reported by Tan et al, the testosterone induced decrease in HDL is specifically in HDL3c, which is thought to be the least anti-atherogenic subfraction.<sup>54</sup> Concentrations of HDL2c and lipoprotein (Lp) A1, 2 molecules with high anti-atherogenic activity, have actually been found to increase with testosterone administration.<sup>54,55</sup> In studies focusing only on elderly men it has been found that androgen administration is associated with only a slight decrease or no change in serum HDL.<sup>56</sup> Apart from lowering serum HDL concentrations, no other effects of testosterone, whether atherogenic or anti-atherogenic, were noted in the literature.

#### CONCLUSIONS

Metabolic syndrome is a highly prevalent condition. Given increasing physician awareness of the disease, an ongoing obesity epidemic and a growing elderly population, the prevalence of metabolic syndrome will only continue to increase. While multiple observational studies support a clear associ-

ation between hypogonadism and metabolic syndrome, the exact relationship has yet to be elucidated. It is conceivable that the definition of metabolic syndrome may be expanded in the future to include hypogonadism as an additional diagnostic parameter.

Screening for hypogonadism may be prudent in patients with metabolic syndrome and in men with 1 or more of its components. Until a global definition is agreed on the individual clinician may choose one of the common definitions of hypogonadism.<sup>57</sup> Testosterone therapy is a known, effective option for treating hypogonadism. If the strength of the association between hypogonadism and metabolic syndrome is confirmed, the potential exists for the use of testosterone as a novel treatment option for metabolic syndrome. Although no formal research on testosterone for metabolic syndrome yet exists, numerous studies have documented the beneficial effects of testosterone on body mass composition, insulin sensitivity and blood pressure regulation, which are 3 key components of metabolic syndrome. Future research should endeavor to delineate the exact usefulness of testosterone for the treatment of men with metabolic syndrome. The focus should be not only on the potential efficacy of testosterone therapy, but also on its short-term and long-term safety. Given that women are at similar or increased risk for metabolic syndrome, research efforts should also be directed toward elucidating the mechanisms by which the condition develops in women with a particular focus on the role of sex hormones.

Furthermore, if hypogonadism in middle-aged men can predict the development of metabolic syndrome later in life, this may have public health implications for improved screening and early prevention strategies. If caught in its earliest stages, a diagnosis of metabolic syndrome may motivate young, affected men toward effective preventive measures, such as diet, exercise, weight reduction and other lifestyle modifications. Testosterone administration in these early stages may possibly also prove beneficial.

#### APPENDIX: WHO CLINICAL CRITERIA FOR METABOLIC SYNDROME IN MEN

Insulin resistance identified by 1 of the following:

- Type 2 diabetes
- Impaired fasting glucose
- Impaired glucose tolerance

Or for those with normal fasting glucose levels (less than 110 mg/dl), glucose uptake below the lowest quartile for background population under investigation under hyperinsulinemic, euglycemic conditions

Plus any 2 of the following:

- Abdominal obesity (BMI greater than 30 and/or waist-to-hip ratio greater than 0.9)
- Dyslipidemia (serum triglycerides greater than 150 mg/dl or HDLC less than 35 mg/dl)
- Hypertension (blood pressure greater than 140/90 mm Hg or patient on medication)
- Urinary albumin excretion rate greater than 20  $\mu\text{g}/\text{minute}$  or albumin, creatinine ratio greater than 30 mg/gm

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