The Dark Side of Testosterone Deficiency: III. Cardiovascular Disease

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ABSTRACT: A considerable body of evidence exists suggesting that androgen deficiency contributes to the onset, progression, or both of cardiovascular disease (CVD). The aim of this review is to evaluate the relationships between testosterone (T) deficiency and risk factors of CVD and to discuss the implications of androgen deficiency in men with cardiovascular risk factors. The relationship between androgen deficiency and endothelial function, lipid profiles, inflammatory responses, altered vascular smooth muscle reactivity, and hypertension are discussed with regard to CVD. A comprehensive literature search was carried out with the use of Pub Med from 1980 through 2009, and relevant articles pertinent to androgen deficiency and vascular disease were evaluated and discussed. Low T, whether attributed to hypogonadism or androgen deprivation therapy, in men with prostate carcinoma, produces adverse effects on cardiovascular health. Androgen deficiency is associated with increased levels of total cholesterol, low-density lipoprotein, increased production of proinflammatory factors, and increased thickness of the arterial wall and contributes to endothelial dysfunction. Testosterone supplementation restores arterial vasoreactivity; reduces proinflammatory cytokines, total cholesterol, and triglyceride levels; and improves endothelial function but also might reduce high-density lipoprotein levels. Testosterone is an anabolic hormone with a wide range of beneficial effects on men’s health. The therapeutic role of T in men’s health, however, remains a hotly debated issue for a number of reasons, including the purported risk of prostate cancer. In view of the emerging evidence suggesting that androgen deficiency is a risk factor for CVD, androgen replacement therapy could potentially reduce CVD risk in hypogonadal men. It should be emphasized, however, that androgen replacement therapy should be done with very thorough and careful monitoring for prostate diseases.

Key words: Androgen deficiency, endothelial dysfunction, metabolic syndrome.

J Androl 2009;30:477–494

Androgen Deficiency and Mortality in Men: An Overview

Androgens have been shown to be important for survival in that a number of studies have linked androgen deficiency to increased mortality in men. Phillips et al (1994) noted that testosterone (T) deficiency might contribute to increased cardiovascular disease (CVD). Maggio et al (2007), in the 6-year CHIANTI study, suggested that a decline in T levels is a strong independent predictor of mortality in men. Khaw et al (2007) examined the relationship between T and mortality from all causes in a nested case control study (EPIC-Norfolk) over 6–10 years with 11 606 men ranging in age between 40 and 79 years. The authors concluded that endogenous T concentrations are inversely related to mortality because of CVD, as well as all causes, and low T could be a predictive marker for those men at high risk of CVD. A study on male veterans over 5 years, in which T levels were determined twice, Shores et al (2006) reported that the survival rate decreased, as did the normal T levels; in addition, it has been found that low serum T correlates with increased mortality risk in male dialysis patients (Carrero et al, 2009). The Massachusetts Male Aging Study followed 1686 men longitudinally for over 15 years and found a weaker association. With age-adjustment, low 5α-dihydrotestosterone (5α-DHT) and sex hormone binding globulin (SHBG) levels were associated with ischemic heart disease mortality, and free T was associated with respiratory mortality (Araujo et al, 2007). In the Rancho Bernardo study, Laughlin et al (2008) followed 794 men for up to 20 years with an average of 11.8 years. Men with total T and bioavailable...
T in the lowest quartile were more likely to die than those with higher levels, independent of age and other cardiovascular mortality risks; this association was only attenuated by inflammatory cytokines such as IL-6, tumor necrosis factor alpha (TNF-α), IL-1β, and C-reactive protein (CRP). Several studies discuss the potential mechanisms pertaining to androgen deficiency and mortality. For example, reduced T levels are associated with increased cardiovascular (CV) risk factors, such as increased fat mass (Basaria and Dobs, 2001, 2007; Basaria, 2008; Laughlin et al, 2008; Montagnana and Lippi 2008; Shahani et al, 2008) and subsequent CVD, and even with death (Khaw et al, 2007). In the Caperhilly Study (South Wales), Smith et al (2005) followed more than 2500 men for a mean of 16.5 years and found that the cortisol/T ratio had a specific association to ischemic heart disease, possibly related to chronic illness, mediated through insulin resistance. The findings of the studies discussed above strongly suggest that a decline in T levels predisposes men to increased risk of CVD and mortality. Indeed, further studies on the direct action of T in vascular beds and the relationship with CV risk factors are warranted.

**Relationship Between Androgen Deficiency and Cardiovascular Disease**

**Hypogonadism (Chronic Androgen Insufficiency)** — Over the last decade, a large body of literature has emerged suggesting that a link exists between androgen deficiency and CVD. Liu et al (2003) provided an exhaustive review on androgens and CVD and concluded that T levels are consistently lower in men with CVD. Wu and Eckardstein (2003) have also reviewed the relationship between T and CVD and concluded that “based on the current evidence, the therapeutic use of T in men need not be restricted by concerns regarding cardiovascular side effects. Available data also do not justify the uncontrolled use of T or dehydroepiandrosterone (DHEA) for the prevention or treatment of coronary heart disease.”

Hak et al (2002) demonstrated that low total and bioavailable T levels were associated with increased risk of aortic atherosclerosis in elderly men, and a similar result was reported by Jones et al (2003). This association (Hak et al, 2002) was independent of age, BMI, serum binding protein, total cholesterol, high-density lipoprotein cholesterol (HDL-C), diabetes mellitus, smoking, and alcohol intake. Therefore, these data suggest that T could have a “direct” effect on CV health in the absence of other common risk factors. Phillips et al (1994) observed a significant negative correlation between a global score for coronary artery disease (CAD) and plasma free T levels. Additionally, both free and total T levels in patients with acute ischemic stroke were reported as having been significantly lower in patients who died compared with those who survived for 6 months after the stroke (Jeppesen et al, 1996). Although the link between abnormal lipid profiles and risk of CVD has been generally accepted, van Pottelbergh et al (2003) investigated the relationship of T in 715 healthy men with lipid profiles. The authors concluded that T was the most important independent hormonal determinant of HDL-C levels, and free T was the most significant predictor of HDL-C and apolipoprotein B (ApoB) concentrations.

A link between hypogonadism and increased CAD has been suggested by several studies (Basaria and Dobs, 2007; Khaw et al, 2007; Maggio et al, 2007; Basaria, 2008; Laughlin et al, 2008; Mäkinen et al, 2008; Montagnana and Lippi, 2008; Shahani et al, 2008). Hypogonadism is thought to contribute to development of the metabolic syndrome (MetS), which increases CVD risk (Laaksonen et al, 2003; Traish et al, 2009a). In a study of 1896 non-diabetic middle-aged men, the authors demonstrated that men with MetS had a significantly higher waist to hip ratio, fasting glucose, triglyceride, CRP, and fibrinogen levels (and lower HDL levels), compared with controls, all of which were related to an increased risk of CVD (Laaksonen et al, 2003). Therefore, T has both a direct physiological role in maintaining CV health, independent of common risk factors as stated previously (Hak et al, 2002), as well as an indirect role by modulating cardiac risk factors such as those implicated in the MetS. Mäkinen et al (2005) showed that middle-aged men with low T have increased carotid atherosclerosis. Dunajska et al (2004) assessed sex hormone profiles in men with CAD and found that they had lower total T values and a significantly lower free androgen index and total testosterone/estradiol ratio compared with controls. Dobrzycki et al (2003) showed that patients with at least a 50% lesion of at least 1 vessel had significantly elevated systolic and diastolic blood pressure, fibrinogen, and triglyceride levels and a reduction in ejection fraction, free and total T, and HDL-C. These results are consistent with those of Dunajska et al (2004) and further highlight the combination of androgen deficiency and the MetS components in the etiology of coronary atherosclerosis.

The clinical and epidemiological studies discussed in this section make a strong association between hypogonadism (chronic androgen insufficiency) and CVD. This link between androgen deficiency and men’s vascular health is of paramount importance and should be investigated further to determine the therapeutic potential of androgens in men with vascular disease.

**Androgen Deprivation Therapy and CVD** — Men undergoing androgen deprivation therapy (ADT; induced
chronic androgen deficiency) for prostate cancer develop hyperglycemia, insulin resistance, and vascular disease (Smith et al, 2001; Basaria et al, 2006; Basaria, 2008; Shahani et al, 2008). Smith et al (2001) noted that men undergoing ADT for prostate cancer experience stiffening of large arteries, resulting in increased central arterial pressure. ADT has also been associated with increased risk of CVD, diabetes, and mortality (Smith et al, 2001; D'Amico et al, 2007; Smith, 2007a,b, 2008; Basaria, 2008; Hakimian et al, 2008; Platz, 2008). D'Amico et al (2007) found that 6 months of ADT treatment significantly shortened the amount of time leading to myocardial infarction. One observational study of 73,196 men with prostate cancer receiving gonadotropin-releasing hormone (GnRH) agonists found that these men were at an increased risk for coronary heart disease, myocardial infarction, and sudden cardiac death (Keating et al, 2006). In fact, the authors found that being on ADT for as little as 1–4 months significantly increased the odds for having an incident of coronary heart disease. Additionally, the unadjusted rates per 1000 person-years for developing coronary heart disease, myocardial infarction, or sudden cardiac death were significantly higher with GnRH agonist treatment compared with those not receiving this treatment. Lu-Yao (2008) even suggested that elderly men with T-1 to T-2 localized prostate cancer should not be given primary ADT because of reduced overall survival in these patients, which supports earlier observations made by D'Amico et al (2007). Although these studies suggest that ADT is associated with CVD, it is not clear yet whether the reduction in T levels or the resultant increase in hyperglycemia, insulin resistance, and other side effects of ADT are the main contributors to the pathophysiology of CVD in ADT patients. The effects of severe T deficiency in patients receiving ADT might not simulate the effects of moderate androgen insufficiency observed in most hypogonadal patients. Clearly, studies with a large number of subjects and reasonable durations are needed to shed light on this important aspect of androgen deficiency. Regardless, it is clear that the reduction of T is sufficient to initiate or promote this cascade of adverse events or do both.

Yialamas et al (2007) investigated the effects of acute androgen withdrawal in men who were being treated with T replacement for idiopathic hypogonadotropic hypogonadism. It was thought that insulin resistance was secondary to weight gain with androgen deprivation, but these investigators found that acute withdrawal of T quickly induced insulin resistance without any detectable change in body composition or leptin concentration. Besides an increase in fasting insulin and a decrease in the insulin sensitivity index, the trend was also toward an increase in fasting glucose and a rise in the inflammatory cytokine IL-6. This suggests a direct effect of T on insulin sensitivity.

Relationship Between Androgen Deficiency and Lipid Profiles

A host of studies have suggested that reduced T levels are associated with increased total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C; Barrett-Connor and Khaw, 1988; Barrett-Connor, 1992; Haffner et al, 1993; Simon et al, 1997; Barud et al, 2002). Testosterone replacement therapy for androgen deficiency, however, reduced TC and LDL-C (Tenover 1992; Zgliczynski et al, 1996; Tripathy et al, 1998; Howell et al, 2001; Ly et al, 2001; Saad et al, 2007, 2008; Table 1). A positive association between T and HDL-C levels was also reported (van Pottelbergh et al, 2003; Zitzmann and Nieschlag, 2007; Saad et al, 2008; Stanworth et al, unpublished). Indeed, discrepancies have been noted in relation to changes in HDL-C profiles with T therapy (Table 1). For instance, increased HDL-C with normalizing T was observed in some studies (Saad et al, 2007; Zitzmann and Nieschlag, 2007), whereas no changes (Zgliczynski et al, 1996; Uyanik et al, 1997) or reduced HDL-C levels were also noted in other studies (Thompson et al, 1989; Bagatell et al, 1994). Such discrepancies can be attributed to 1) study design, 2) doses and formulations of androgen used, 3) routes of administration, 4) patients' age and hypogonadal status, 5) body fat distribution, and 6) methods of analysis.

ADT and Lipid Profiles—Lower T levels in aging men are associated with elevated triglycerides (TGs) and reduced HDL-C levels (Zmuda et al, 1997). Testosterone suppression in men with prostate cancer results in elevated total and LDL-C after 3 months of treatment compared with baseline (Dockery et al, 2003). A longer course of T deprivation (6 months) in men with prostate cancer was shown to have a nonsignificant effect on HDL and TG levels but confirmed Dockery et al's (2003) earlier finding of elevated total cholesterol as reported by Nishiyama et al (2005) and Smith et al (2001, 2002). Smith et al (2006) showed that GnRH agonist treatment for prostate cancer for just 3 months led to significantly elevated TGs. Long-term antiandrogenic treatment for 2.5 years, as assessed by Chen et al (2005), revealed a unique lipid profile, showing significantly elevated TGs and decreased HDL values, although only HDL-C was affected. This suggests that antiandrogenic therapy contributes to CAD through changes in lipoprotein (ApoA-1 and ApoA-II) values, TG levels, and a concomitant reduction in HDL-C levels. The variability among the aforementioned studies on lipid profiles might be a consequence of variation in study design, such as the duration of treatment, method...
### Table 1. Relationships between testosterone and plasma lipid profiles in observational studies, interventional studies, and androgen deprivation therapy (ADT) studies are shown

<table>
<thead>
<tr>
<th>Study and Mode of Treatment</th>
<th>No. of Subjects in Study</th>
<th>Age, y</th>
<th>Endogenous Testosterone Levels</th>
<th>Triglycerides, mg/dL</th>
<th>Change in Triglyceride Level</th>
<th>Total Cholesterol, mg/dL</th>
<th>Change in Cholesterol Level</th>
<th>LDL-C, mg/dL</th>
<th>Change in LDL-C Level</th>
<th>HDL-C, mg/dL</th>
<th>Change in HDL-C Level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Observational studies</strong></td>
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<tr>
<td>Khaw et al, 2007</td>
<td>2314</td>
<td>42–78</td>
<td>Low quartile</td>
<td>199.3</td>
<td>↓</td>
<td>229.7</td>
<td>↑</td>
<td>146.2</td>
<td>↑</td>
<td>49.5</td>
<td>↑</td>
</tr>
<tr>
<td>van Pottelbergh et al, 2003</td>
<td>715</td>
<td>35–59</td>
<td>Low</td>
<td>160.3</td>
<td>↑</td>
<td>239.4*</td>
<td>↑</td>
<td>159.7</td>
<td>↑</td>
<td>45.24</td>
<td>↑</td>
</tr>
<tr>
<td>Simon et al, 1997</td>
<td>50</td>
<td>Low</td>
<td>Normal</td>
<td>128.42</td>
<td>↓</td>
<td>226.9</td>
<td>↓</td>
<td>167.8</td>
<td>↓</td>
<td>46.8</td>
<td>↑</td>
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<td><strong>Interventional studies</strong></td>
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<tr>
<td>Emmelot-Vonk et al, 2008</td>
<td>237</td>
<td>60–80</td>
<td>Before</td>
<td>141.7</td>
<td>↔</td>
<td>216.5</td>
<td>↔</td>
<td>150.8</td>
<td>↔</td>
<td>46.4</td>
<td>↓</td>
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<tr>
<td>Dobs et al, 2001</td>
<td>29</td>
<td>21–65</td>
<td>Before</td>
<td>122.2</td>
<td>↔</td>
<td>209.59</td>
<td>↔</td>
<td>131.5</td>
<td>↓</td>
<td>49.88</td>
<td>↓</td>
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<tr>
<td>Allan et al, 2008</td>
<td>60</td>
<td>≥75</td>
<td>Before</td>
<td>132.8</td>
<td>↔</td>
<td>197.2</td>
<td>↔</td>
<td>123.7</td>
<td>↔</td>
<td>46.4</td>
<td>↔</td>
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<td>Zitzmann and Nieschlag, 2007</td>
<td>66</td>
<td></td>
<td>Before</td>
<td>132.0 NS</td>
<td>↔</td>
<td>201 NS</td>
<td>↔</td>
<td>127.6 NS</td>
<td>↔</td>
<td>50.3 NS</td>
<td>↔</td>
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<td>Saad et al, 2008</td>
<td>27</td>
<td>61 (mean)</td>
<td>Before</td>
<td>249</td>
<td>↓</td>
<td>263</td>
<td>↓</td>
<td>168</td>
<td>↓</td>
<td>33</td>
<td>↑</td>
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<td>Saad et al, 2008</td>
<td>28</td>
<td></td>
<td>Before</td>
<td>312</td>
<td>↓</td>
<td>268</td>
<td>↓</td>
<td>164</td>
<td>↓</td>
<td>36.5</td>
<td>↑</td>
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<td>Page et al, 2005</td>
<td>70</td>
<td>71</td>
<td>Before</td>
<td>143</td>
<td>↓</td>
<td>197</td>
<td>↓</td>
<td>122</td>
<td>↓</td>
<td>43</td>
<td>↑</td>
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<td>Malkin et al, 2004a</td>
<td>27</td>
<td>36–78</td>
<td>Before</td>
<td>208</td>
<td>↓</td>
<td>188</td>
<td>↓</td>
<td>109</td>
<td>↓</td>
<td>37.5</td>
<td>↔</td>
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<td><strong>Androgen deprivation therapy studies</strong></td>
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<tr>
<td>Chen et al, 2005</td>
<td>24</td>
<td>60</td>
<td>Before</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>148</td>
<td>↑</td>
<td>44.7</td>
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* Indicates significant change from baseline.
of androgen suppression, or sample size. Regardless, each study revealed an increase in lipid concentrations and an unfavorable lipid profile in response to ADT.

Yannucci et al (2006) explored the concurrent therapy of hyperlipidemia in patients receiving ADT and statin therapy. The authors found a differential effect of various forms of ADT on changes in total cholesterol levels from baseline up to 2 different time points (day 85 and day 169) and characterized the role of simultaneous statin therapy in these patients. The various forms of ADT included 1) leuprolide acetate (LA), a gonadotropin releasing hormone agonist; 2) LA + bicalutamide (B), an antiandrogen; and 3) Abarelix (A), a gonadotropin-releasing hormone antagonist. First, the authors found that statin therapy did not significantly improve lipid profiles in patients receiving 85 days of ADT. Second, lipid parameters were more likely to be elevated when given LA or A, as opposed to LA + B. These data suggest that the nature of the ADT agent used could lead to a difference in observed lipid profiles and that these profiles are also dependent on the time from baseline at which they are measured. It is also interesting that statin therapy did not significantly improve lipid profiles, suggesting that regulation of 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase activity might not be involved in the dyslipidemia seen in patients with ADT. Haidar et al (2007) found that in 29 diabetic prostate cancer patients with ADT, total cholesterol, LDL, and TGs increased, whereas HDL levels decreased, as T levels declined. Prostate cancer patients who are also diabetic and receiving ADT exhibited similar lipid profiles to nondiabetic cancer patients receiving ADT. The studies discussed above suggest that ADT alters the lipid profile because of androgen deficiency and that this pathophysiology is not corrected by statin therapy. Physicians need to weigh the risks and benefits before making decisions on the use of ADT as a treatment.

**Androgen Supplementation Therapy and Lipid Profiles**—Testosterone treatment in hypogonadal men typically has been shown to lower serum cholesterol and TGs (Márin et al, 1993; Márin, 1995) and total cholesterol and LDL (Page et al, 2005). Tan et al (1998) observed a reduction in HDL, but this was mainly a decrease in HDL₃-C and apolipoprotein particles (LpA-1 and LpA-1:A-II) mediated by T on hepatic lipase activity. Hepatic lipases and hormone-sensitive lipases hydrolyze triacylglycerides in lipoproteins, releasing free fatty acids, and they play an important role in lipid and lipoprotein metabolism and contribute to vascular disease. Swerdloff and Wang (2003) analyzed total cholesterol, LDL, HDL, and TGs in 52 older men (60 and over), as well as in 119 younger men (under 60), all of whom were hypogonadal and received T gel
treatment for 180 days. Treatment of men ages 60 and over resulted in a greater reduction of total cholesterol, LDL, and TGs than that observed in men under the age of 60. Thus, there may be a relationship between age and the body’s physiological capacity to lower serum lipids.

Zgliczynski et al (1996) studied 22 men, 11 of whom had hypopituitarism (first group) and 11 who were otherwise healthy elderly men with low T levels (second group), and treated them with 200 mg of T enanthate every 2 weeks for 1 year. The reduction in total cholesterol and LDL was significant. Men with hypopituitarism after 12 months of treatment showed a greater reduction in these lipid values, compared with men with other forms of hypoandrogenism. The physiological efficiency of T in lowering the lipid profile in men aged 60 and above seems to be affected by whether men present with primary or secondary hypogonadism. The mechanism by which T exerts its effect, particularly its role in reducing adipose tissue in the abdominal region, was highlighted by Márin et al (1995). The authors measured TG uptake and lipoprotein lipase (LPL) activity both before and after 9 months of treatment with transdermal T and found a significant effect of T on these processes. Testosterone significantly reduced TG uptake and LPL activity. One year later, Márin et al (1996) further specified that T exerted its most significant effect by reducing labeled TG uptake in omental and retroperitoneal adipose tissues.

The interrelationships between HDL, BMI, and T treatment in hypogonadal men appear complex at first. However, Dobs et al (2001) investigated hypogonadal men who were treated for 1 year with a T patch to set up simple correlations. The authors found the BMI to have a strong negative correlation with both HDL and T concentrations. Isidori et al (2005), in a meta-analysis on the metabolic effects of T treatment, suggested that reduction of HDL cholesterol was mainly noted in studies in which the T levels were supraphysiological. This was noted more with the older long-acting T esters rather than with the T patches, gels, or intramuscular (IM) T undecanoate. This could be explained by the older T esters used in the studies producing supraphysiological levels for the first few days after injection.

The aforementioned studies suggest that T replacement has a favorable effect on the lipid profile in T-deficient men. In fact, one study showed that regular treatment with intramuscular T undecanoate kept LDL levels low and HDL levels high in hypogonadal individuals for up to 9.5 years (Zitzmann and Nieschlag, 2007). Although this long-term effect of T is very important for some individuals suffering from an unfavorable lipid profile, another recent study suggested that incorporating lifestyle modifications alongside androgen treatment could have a synergistic effect in raising HDL levels and reducing TG levels (Heufelder, unpublished data; Heufelder et al, in press), a result that was found in newly diagnosed type 2 diabetic subjects. In summary, ADT results in unfavorable lipid profiles, and androgen supplementation therapy in hypogonadal men improves lipid profiles and body composition, suggesting a reduction in risk factors for CVD related to dyslipidemia and the MetS.

Potential Mechanisms of Testosterone Action on Vascular Beds

Androgen Action on the Endothelium—Clinical and preclinical evidence exists linking endothelial dysfunction to androgen deficiency (Akishita et al, 2007; Lu et al, 2007; Miller and Mulvagh, 2007; Foresta et al, 2008). In a clinical study, Akishita et al (2007) assessed 187 men with coronary risk factors and found that the percent flow-mediated vasodilation (FMD) in men in the lowest quartile of free T was 1.7 times less than percent FMD of men in the highest quartile. Total and free T were related to percent FMD, independent of other risk factors such as age, body mass index, hypertension, hyperlipidemia, and diabetes mellitus. The authors discussed mechanisms by which T might regulate vasomotor function and suggested different mechanisms depending on the mode of T administration. The authors cite studies suggesting that the benefits of short-term intracoronary administration of T and supraphysiologic doses in vitro could be mediated by smooth muscle cell membrane ion channels, and not through endothelial or androgen receptor mechanisms. Conversely, they report studies that have found that acute and chronic supplementation of T benefit patients by increasing the percent FMD without increasing basal brachial artery diameter, suggesting that T acts through an endothelium-dependent mechanism.

Testosterone might improve parameters relating to CVD through mediation of endothelial progenitor cell activity. Foresta et al (2006) investigated the effects of T on the role that endothelial progenitor cells play in endothelial repair in 10 young idiopathic patients with hypogonadotrophic hypogonadism. They observed that the number of endothelial progenitor cells in hypogonadal men was fewer than the number in healthy control subjects. The authors further found that treating idiopathic hypogonadotrophic hypogonadism with T gel therapy, at 50 mg/d for 6 months, increased the number of circulating endothelial progenitor cells in these men. These findings point toward a decreased number of circulating endothelial progenitor cells as being a potential risk factor for CVD seen in patients with hypogonadism. Interestingly, Foresta et al (2008) presented clinical data demonstrating that androgens...
can stimulate endothelial progenitor cells. Because all of the effects were abolished after flutamide (androgen receptor blocker) pretreatment, it was concluded that the effects were mediated via the androgen receptor. The levels of T used in these studies were calculated to be in the normal physiological range (Foresta et al, 2008).

In preclinical studies, Lu et al (2007) examined the endothelium from castrated rats by transmission electron microscopy and demonstrated significant endothelial damage, in which the cell surface appeared crumpled, rough, adhesive, and ruptured. This pathology was partially restored by treatment of castrated rats with T or DHT. These observations strongly suggested that low concentrations of T or DHT were associated with ultrastructural damage to the aortic endothelium.

Liu and Dillon (2002, 2004) demonstrated through in vitro studies with endothelial cell culture that physiological concentrations of DHEA acutely increase NO release from intact vascular endothelial cells by a plasma membrane–dependent mechanism. This action of DHEA is mediated by a steroid-specific, G protein–coupled receptor mechanism that activates endothelial nitric oxide synthase (eNOS) in both bovine and human endothelial cells. DHEA restored aortic eNOS levels and eNOS activity, suggesting that DHEA could have direct genomic and nongenomic effects on the vascular wall. This cellular mechanism might underlie some of the cardiovascular protective effects proposed for androgens, as reviewed recently by Simoncini et al (2004) and Simoncini and Genazzani (2007).

The relationship between androgen deficiency, endothelial dysfunction, and vascular disease is very complex (Figure) and is the subject of several reviews. Insulin resistance, which is exacerbated by androgen deficiency, might mediate endothelial dysfunction and vascular disease (Traish et al, 2009b). Clinical consequences of insulin resistance include dyslipidemia (Ginsberg, 2000), hyperglycemia (Haffner, 2000; Haffner et al, 2000), hypertension, and abnormal vascular behavior (Reaven et al, 1996) and also include vascular inflammation and thrombotic risk inflammation (Calles-Escandon et al, 1998; Sobel, 1999).

Endothelial dysfunction is also associated with dyslipidemia, obesity, and diabetes (McVeigh and Cohn, 2003). Mechanisms underlying lipotoxicity include oxidative stress and proinflammatory signaling, whereas the mechanisms underlying glucotoxicity include oxidative stress, advanced glycation end product formation, the hexosamine pathway, and proinflammatory signaling (Kim et al, 2006). Pharmacological intervention should target these overlapping mechanisms that contribute to the etiology of insulin resistance and endothelial dysfunction. LDL cholesterol seems to be the most important fraction that affects the endothelial function and promotes atherosclerosis. In a clinical study, Barud et al (2002) showed an inverse relationship between low T and elevated LDL antibody levels and, after multiple regression analyses, that only T was independently associated. Current drugs to improve endothelial function in patients with diabetes include folic acid, HMG-CoA reductase inhibitors, ACE inhibitors, Niaspan, l-arginine, insulin and insulin sensitizers, and possibly phosphodiesterase type 5 inhibitors (Fonseca and Jawa, 2005). Some clinical studies have also reported that simple modifications in nutrition and exercise can positively alter endothelial function and reduce inflammation (Esposito et al, 2006).

A clinical study by Malkin et al (2004b) found a reduction in proinflammatory cytokines, total cholesterol, and triglyceride levels in 27 hypogonadal men treated with T. Specifically, TNF-α and IL-1β levels were significantly reduced after 4 weeks of treatment compared with baseline measurements. The authors reported that these proinflammatory factors are associated with the development of atheromatous plaque, and the T-induced reduction of these factors is certainly beneficial to those at risk for CVD. In a different study, the authors further reported that total cholesterol and TNF-α are significantly reduced with T therapy in 10 hypogonadal men with angina (Malkin et al, 2004a). Ischemic thresholds were also improved in these men receiving T therapy.

Testosterone has been shown to produce positive effects on endothelial function, as measured via brachial arterial vasoreactivity in men with CAD (Kang et al, 2002). Men were either given placebo or 160 mg of oral T undecanoate. Those patients receiving T treatment for 12 weeks had a significantly greater percentage of flow-mediated and nitroglycerin-mediated dilation compared with the response seen in controls receiving placebo.

In animal model studies with dogs (Chou et al, 1996) and rabbits (Yue et al, 1995), the authors attributed T’s positive effects on the vasculature to the direct stimulation of endothelium-derived NO or vascular smooth muscle K+ channels. Geary et al (2000) analyzed cerebral artery myogenic tone in male rats and found this to correlate with the presence of T. This effect of T was negated by removal of the endothelium or by the combined inhibition of the cyclooxygenase pathway and K+ channels. Geary et al (2000) suggests that myogenic tone is independent of NOS activity, but is an endothelium-dependent process mediated through cyclooxygenase or K+ channel inhibition, or both, in that this inhibition eliminates any differences between orchiectomized groups of animals treated with or without T.

A study by Nakao et al (1981), who used a cell culture system, suggested that T inhibits endothelial cyclooxy-
genase, suppressing prostacyclin production in arterial smooth muscle cells in culture. The authors suggested that "testosterone may stimulate thrombus formation and accelerate atherosclerosis by suppressing prostacyclin production in arterial smooth muscle." These studies were performed in cultured cells that might have lost their phenotype, with T concentrations far above the physiological levels.

In a clinical study, Polderman et al (1993) suggested that plasma T levels modulate endothelin levels and these were found to be higher in men than in women, suggesting sex hormone differential regulation. Because
endothelin is a powerful vasoconstrictor, it might influence myogenic tone through changes in intracellular Ca\(^{2+}\) ([Ca\(^{2+}\)]\(i\)) and other second messenger systems, which could contribute to CVD. On the contrary, Kumanov et al (2002) concluded that hypogonadism significantly increased plasma endothelin levels compared with healthy male controls. Furthermore, castration of male rats also increased endothelin levels, suggesting that androgens down-regulate endothelin synthesis (Ajayi et al, 2004). Thus, the limited data on the potential role of T in regulating endothelin function does warrant definitive conclusions.

In a clinical study, Fu et al (2008) found that in male patients with coronary heart disease, free T was inversely correlated with vascular cell adhesion molecule-1 (VCAM-1) and intima media thickness (IMT), both indicators of endothelial dysfunction. VCAM-1 is produced by endothelial cells and could be an important step in the atherosclerotic and inflammatory process because it facilitates the adherence and migration of circulating monocytes through the dysfunctional endothelium. Interestingly, however, a more recent study conducted by Webb et al (2008) did not find T treatment to influence endothelial function. The difference in global endothelial function has not been reported in men with coronary heart disease and low T compared with placebo after being treated with T undecanoate for 8 weeks. Clearly, further studies are needed to determine whether free T and VCAM-1 directly interact and the nature of any possible relationship between T and some aspects of endothelial function. Although the physiological or biochemical mechanisms remain poorly understood, the clinical and basic science evidence from the data reported to date is ample to support an association between androgen deficiency and endothelial dysfunction.

Androgen Action on Vascular Smooth Muscle Function—Clinical studies. Clinical studies have demonstrated that T could have beneficial effects in men with CVD. A series of reports by Malkin et al (2003a,b,c) suggested that men with low T levels are at increased risk of CAD and T could be a protective factor against atherosclerosis. The authors further noted that T treatment reduced the QT dispersion in men with heart failure (Malkin et al, 2003a) and advanced the hypothesis that T immunomodulating properties inhibit atheroma formation and progression to acute coronary syndrome (Malkin et al, 2004a,b). In a subsequent commentary, Malkin et al (2003c) noted that endogenous levels of T are inversely related to the severity of aortic atheroma and to the progression of aortic atheroma when assessed radiologically. Testosterone replacement therapy in hypogonadal men was shown to delay time to ischemia and improve mood and was associated with a reduction in total cholesterol and TNF-\(\alpha\) (Malkin et al, 2004a). Furthermore, the authors (Malkin et al, 2007) presented data suggesting that physiological T therapy improved insulin sensitivity in men with moderate to severe congestive heart failure.

In clinical studies, Malkin et al (2006b) reported that T therapy in men with moderately severe heart failure is safe, with no excess of adverse events, and that T improves functional capacity and symptoms of patients with moderately severe heart failure. Similarly, Webb et al (2008) demonstrated that oral T undecanoate had selective and modest enhancing effects on perfusion in myocardium supplied by unobstructed coronary arteries and suggested that the T undecanoate–related decrease in basal arterial stiffness might partly explain the effects of exogenous T on signs of exercise-induced myocardial ischemia.

Jones et al (2004b) reviewed the role of T on vascular reactivity in men and cited studies suggesting that T replacement is associated with an improvement in vascular reactivity in men with CAD and improves endothelial FMD. The authors suggested that this might be true only in diseased vessels. Interestingly, the authors suggested that the data from animal studies are inconclusive and cited a number of references with positive, negative, and neutral results. Thus, the exact molecular mechanism of androgen action on the vasculature remains to be investigated further.

In vitro studies. Several in vitro studies investigated the physiological mechanisms of androgen-mediated vasodilation in various blood vessels from animals and humans. For instance, several studies have demonstrated vasorelaxing effects of T and 5\(\alpha\)-DHT on vascular and nonvascular smooth muscle, probably via inhibition of L-type calcium channels (Sochorová et al, 1991; Scrugg et al, 2004, 2007; Perusquia et al, 2005; Hall et al, 2006; Er et al, 2007; Montaño et al, 2008). In some studies, 5\(\alpha\)-DHT was more potent than T in relaxing KCl-induced contractions. Testosterone at nanomolar concentrations was a powerful antagonist for L-type voltage–operated Ca\(^{2+}\) channels (L-VOCCs). The data showed that 5\(\alpha\)-DHT–induced vasorelaxation is attributed to its selective blockade on L-VOCCs, but T-induced vasorelaxation involved concentration-dependent additional mechanisms involving L-VOCC antagonists at low concentrations and increasing [Ca\(^{2+}\)]\(i\) and cAMP production at high concentrations. Similar data were noted in porcine coronary arteries in which T caused vasodilation (Hutchison et al, 2005). Similarly, Cairrão et al (2008) demonstrated that T induced relaxation of human umbilical arteries via a nongenomic-dependent mechanism. The relaxation is thought to be partially mediated by activation of large-conductance Ca(2+)-activated potassium channels (BK[Ca])
and voltage-sensitive potassium channels (Kv). The involvement of these channels in a T-relaxant mechanism is dependent on the pathways activated by the contractile agent used.

Furthermore, Navarro-Dorado et al (2008) showed that T and the nonaromatizable metabolite 5α-DHT evoked a concentration-dependent relaxation on nor-epinephrine precontracted small-artery aortic rings in an endothelium-independent manner. The authors suggested that T induced a direct vasodilatory action in small arteries independent of the endothelium by blockade of extracellular Ca\(^{2+}\) entry through L-VOCCs and non-L-VOCCs. Studies in human umbilical arteries showed that T and 5α-DHT caused vasodilation via a non–androgen receptor pathway (Perusquia et al, 2007). Similarly, isolated radial arteries were relaxed by supraphysiological doses of T, presumably via activation of ATP/potassium channels (Seyrek et al, 2007). A similar vasodilation was also observed in internal mammary arteries (Yıldız et al, 2005). Testosterone induced a vasodilatory response in rabbit tracheal smooth muscle; this effect was attributed to eNOS (Kouloumenta et al, 2006).

It should be noted that T caused vasodilation in denuded vessels (Yue et al, 1995; Murphy and Khalil, 1999), suggesting an endothelium-independent mechanism. Webb et al (1999) showed that T treatment into the left coronary artery caused vasodilation and increased flow. Tep-Areenan et al (2003) investigated the effects of T on vasodilation in the rat aorta in an organ bath and demonstrated that T induced acute vasorelaxation, which is likely mediated via inhibition of extracellular calcium influx and via the action of endothelium-derived prostanoids. Similarly, Jones et al (2004a) suggested that T-induced vasodilation via nongenomic mechanisms is independent of the androgen receptor and of the vascular endothelium. The authors postulated that the action of androgens is mediated via direct calcium antagonism in the vascular smooth muscle. Malkin et al (2006a) demonstrated that T facilitated vasodilation in subcutaneous resistance arteries from patients with heart failure in a concentration-dependent manner. Interestingly, T therapy reduced the vasodilation response to acetylcholine and sodium nitroprusside and increased contractile responses to norepinephrine. The authors postulated that the benefits of T in vascular function could be offset by a decline in vascular reactivity. However, the authors did not comment on the fact that the doses of T used in the in vitro studies are of pharmacological nature and not of physiological function, in that micromolar levels of T were used, which are far above any physiological level known in vivo. Furthermore, the resistance arteries were obtained from patients with vascular disease, which could have skewed the outcome of the study. In addition, the remodeling of tissue in response to sex steroid hormones is a long-term process and cannot be ignored in interpreting data from in vitro studies. It is our view that the data in this study do not negate the observed benefits of T in vascular function in vivo and cannot be explained purely on the contractility response data obtained in vitro.

Yıldız and Seyrek (2007) hypothesized that because denuded vasculature produced the same result in response to T as the intact blood vessels, the major effect of T is likely mediated directly by the vascular smooth muscle. The postulated mechanism suggests that T either activates K\(^+\) channels to increase efflux, inhibits Ca\(^{2+}\) channels, or both, causing hyperpolarization and subsequent vasodilation. Because these changes occur in seconds to minutes, it is suggested that this action is likely to be mediated via the interactions with receptors on the membrane (nongenomic effect) rather than by interaction with the nucleus (genomic effect). Furthermore, other studies have shown the presence of the androgen receptor on the membrane of vascular smooth muscle cells (Fujimoto et al, 1994; Benten et al, 1999), suggesting that the proposed mechanism is likely. The data from in vitro studies suggest that T-induced relaxation of the arterial wall was mediated via inhibition of Ca\(^{2+}\) entry into the smooth muscle (Crews and Khalil, 1999; Giannattasio et al, 1999). On the basis of the data reported to date, the exact mechanisms underlying the physiological effect of T on vascular reactivity remain unclear and might involve activation of K+ channels and antagonism of Ca\(^{2+}\) channels, are likely to be of nongenomic signaling, and might not require the endothelium.

Relation of T to IMT and to Atheroma Formation—Carotid atherosclerosis is assessed as a function of maximum common carotid IMT as well as maximum IMT of the carotid bulb (Mäkkinen et al, 2005). The values of these 2 parameters were greater in men who had low T compared with controls. Barrett-Connor (2005) noted that lower T levels correlate with increased IMT. De Pergola et al (2003) found that free T plasma levels are negatively associated with IMT of the common carotid artery in overweight and obese glucose-intolerant young adult men, independent of age, total body fat, central fat accumulation, and fasting glucose concentrations. These observations suggest that hypotestosteronemia might accelerate the onset of atherosclerosis and the risk for congestive heart disease in obese patients. Muller et al (2004) found a similar result in 195 elderly men between the ages of 77 and 96, in which IMT was measured after a 4-year interval. During this period, a drop in free T levels was related to an increase in IMT of the common carotid artery,
independent of BMI, the waist to hip ratio, the presence of hypertension and diabetes, smoking, and serum cholesterol levels. Fukui et al (2003) measured serum free and total T concentrations in 253 men with type 2 diabetes and found serum free T concentration to be inversely related to atherosclerosis as determined by IMT and plaque score through ultrasonographic methods. The author cited coronary angiographic studies aimed to detect atheroma, suggesting a significant inverse correlation between T concentration and presence and severity of CAD.

Mäkinen et al (2005) have shown that middle-aged men with symptoms of androgen deficiency are at risk of increased carotid IMT and have suggested that normal T levels might offer protection against the development of atherosclerosis. Malkin et al (2003b, 2004a) hypothesized that the immune-modulating properties of T are important in inhibiting atheroma formation and progression to acute coronary syndrome. The authors demonstrated that significant reduction in total cholesterol was recorded with T therapy and demonstrated a shift in the cytokine balance to a state of reduced inflammation. The aforementioned studies support an inverse relationship between IMT and androgen levels.

Androgen Deficiency and Hypertension

Endogenous T levels decline with age, and Swartberg et al (2004a,b) found that men greater than 25 years old presenting with hypertension had lower total T values, independent of age. Smith et al (2001) assessed the effects of induced hypogonadism (3 months of GnRHa) on hypertension by analyzing large artery stiffening in men with prostate cancer. With the use of peripheral and central arterial waveforms, the authors found that, after 3 months of treatment with GnRHa, diastolic pressure was elevated, along with mean pulse pressure.

Hypertension, dyslipidemia, and obesity coupled with insulin resistance are manifest components of the MetS contributing to CVD risk. When hypertension, dyslipidemia, and IR are present in the same subject, it often leads to hyperglycemia and visceral obesity, which are characteristic of the MetS. The relationship between obesity, insulin resistance, hypertension, and dyslipidemia is complex, making it difficult to dissect the pathophysiology of each component alone without considering them in a comprehensive framework. In addition, the effects of androgen deficiency on hypertension, insulin resistance, and dyslipidemia underscore the need to understand how androgens influence each of these components (Figure).

Märin et al (1993) have shown that T gel treatment for abdominally obese men for 9 months reduced diastolic blood pressure significantly. Another recent study by Zitzmann and Nieschlag (2007) observed a similar result, in which both resting systolic and diastolic blood pressure were significantly lowered during treatment with intramuscular T undecanoate in 66 hypogonadal men for up to 9.5 years, with the most significant reductions in both pressures occurring by the fifth injection between the 40th and 44th week. Anderson et al (1996) demonstrated significant favorable changes in diastolic blood pressure in eugonadal men with osteoporosis treated for 6 months with androgen therapy. A similar observation was noted by Phillips et al (1993) in obese men with hypogonadism in which T levels correlated positively with blood pressure. The relationship between hypertension and androgen deficiency is complex in relationship to cardiovascular risk because multiple other risk factors are involved. However, the data in the above studies do suggest that T replacement therapy reduces blood pressure.

Potential Therapy of Hypogondal Men With T to Reduce Risk of Vascular Disease

One of the fears of therapy with T is the purported link between T and the development of prostate cancer. Recent epidemiological and clinical studies suggested that there is no association between T levels and risk of prostate cancer (Stattin et al, 2004; Travis et al, 2007; Roddam et al, 2008). There is no evidence to date to suggest that low plasma T levels are protective against prostate cancer and that physiological levels of T increase the risk of prostate cancer. Interestingly, T levels decline with age, and prostate cancer incidence increases with age, suggesting that low T might contribute to the development of cancer and normal physiological T levels could be protective against prostate cancer (Prehn, 1999). This concept is difficult to grasp in light of the myriad studies linking prostate cancer growth to T on the basis of the interpretation of data in which androgen deprivation results in regression of metastatic prostate disease.

English et al (2000) reported on the beneficial effects of T in men with exercise-induced myocardial ischemia during an exercise stress test, as assessed by time to ST depression, suggesting that androgen therapy could mediate vasodilation. However, in this study, English et al (2000) did not specifically select for patients with low T, although they reported in a different study that T replacement therapy was beneficial in hypogonadal men with angina, in that the time to ischemia had been lengthened. Chronic T therapy has been shown to reduce arterial calcification (Hak et al, 2002), improve lipid profiles (Haffner et al, 1993, 1994), and reduce inflammatory cytokine levels (Malkin et al, 2004a,b; Maggio et al, 2006). Malkin et al (2004a) also found that patients with lower baseline T levels experienced the
greatest benefit with regard to T supplementation on ischemia. These aforementioned studies suggest that androgen deficiency could contribute to a number of clinical pathologies related to the cardiovascular system, and that T therapy might ameliorate some of these conditions.

To reduce the risk of CVD, cardiologists have recommended making lifestyle modifications, such as cessation of smoking, weight loss, and controlling blood pressure, as well as monitoring blood glucose and lipids (Nesto, 2008). Because many of the risk factors associated with CVD are shared by patients with erectile dysfunction (ED), it was not surprising to learn that modifying such risk factors improved erectile function in men with ED (Khatana et al, 2008). The Mediterranean diet, which was shown to be inversely associated with the incidence of the MetS (Tortosa et al, 2007), has been shown to improve erectile function as well (Esposito et al, 2006).

Acute T supplementation has been shown to increase cardiac output and reduce systemic vascular resistance in men with chronic heart failure (Pugh et al, 2003). More recently, Webb et al (2008) have shown that 8 weeks of oral T undecanoate in men with coronary heart disease and low T helped to increase perfusion in the myocardium supplied by unobstructed arteries and increase left ventricular ejection fraction. There was no effect, however, on global myocardial perfusion, global endothelial function, quality of life, or angina symptoms compared with placebo. Testosterone treatment has also been shown to improve the amount of exercise tolerated in men with chronic heart failure, measured as the distance walked during a shuttle walk test (Pugh et al, 2004). In fact, the average distance walked by those patients receiving T was 91 m compared with an average of 26 m in patients receiving placebo. Another benefit of T has been its ability to increase the angina threshold in men with chronic stable angina (English et al, 2000). In this study, one group of men received T therapy (5 mg of T patch per day for 3 months) while the other received placebo, and the threshold to reach myocardial ischemia increased with prolonged T supplementation up through 14 weeks. It should be noted that the patients were not selected for low T. In a subsequent study, the authors investigated the potential mechanism of T on the vasculature in vitro and concluded that T acts as a vasodilator by primarily inhibiting the calcium-dependent elements of vascular contraction (English et al, 2002).

Testosterone might exert its beneficial effects on the vasculature through modulation of cardiovascular risk factors, such as hypertension (Dubey et al, 2002), hypercholesterolemia (Lichtenstein et al, 1987; Zmuda et al, 1997; Gyllenborg et al, 2001), diabetes (Oh et al, 2002), and obesity (Haffner et al, 1994). However, T could negatively affect the vasculature by directly affecting endothelial and smooth muscle function. Sader et al (2001) investigated the effects of T and T + estradiol in young healthy men and found that estradiol but not testosterone improved FMD, an endothelium-dependent function. In a subsequent study, Sader et al (2003) administered 800 mg of T depot preparation into 9 hypogonadal men and assessed as percent FMD and arterial reactivity 2–4 weeks before and after T replacement. The authors concluded that physiological T replacement in hypogonadal men is associated with decreased endothelium-dependent dilation, but not with any alteration in lipid profiles or blood pressure. Although these studies suggested that T had a negative effect on vascular function, they have limitations, such as the small number of patients studied, the short study duration, and T levels before treatment that were in the normal range and not the hypogonadal range (13 nM). Thus, data from such studies should be interpreted with great caution.

The common effects of T on various physiological processes were noted long ago in the area of increased energy, decreased fatigue, increased lean body and muscle mass, and decreased fat mass. More recently, T’s effects on functional mobility and cognition were reported, although the subjects in that study did not have symptoms of androgen deficiency and most were not hypogonadal (Emmelot-Vonk et al, 2008).

As the link between cardiovascular risk and visceral obesity became clearer, it was also found that T therapy prevented gain in visceral adipose tissue (Allan et al, 2008). Recently, cardiologists have become more aware that hypogonadism may be deleterious to cardiac health, especially since the link between hypogonadism and the MetS has been made (Jackson, 2006). Svartberg (2007) reviewed the current literature and found that because of strong associations between low levels of T and the different components of the MetS, T might have a protective role against them and cardiovascular risk. In a study by Muller et al (2005), it was shown that men with higher levels of T had increased insulin sensitivity and a reduced risk of the MetS, independent of insulin levels and body composition, reinforcing the notion that T might protect against the development of the MetS. Pitteloud et al (2005) showed that insulin resistance, the core of the MetS, is associated with decreasing T production by the Leydig cells.

It is logical to speculate that treating men with hypogonadism and the MetS with T might ameliorate some of its components, especially if hypogonadism is a fundamental component of the MetS (Makhshida et al, 2005; Traish et al, 2009a,b). Treatment of hypogonadism with T replacement reduces symptoms of sexual dysfunction as well as features of the MetS after 9
months (Saad et al, 2008). Interestingly, both oral and injection therapy reduced waist circumference and improved lipid profiles. Kapoor et al (2006) also noted improvement in the MetS parameters in 24 men for 3 months with T replacement with injection therapy. Testosterone therapy improved insulin resistance and glycemic control and reduced visceral adiposity, waist circumference, and total cholesterol. Heufelder et al (in press) studied hypogonadism in men with type 2 diabetes mellitus and found that modifying risk factors improved many parameters related to the MetS, but that the improvement was enhanced after T administration. This included improvement in fasting glucose, hemoglobin A1c, insulin levels, waist circumference, triglycerides, HDL cholesterol, CRP, leptin, and blood pressure.

It is promising that components of the MetS can be improved by T in hypogonadal men. It makes the

Table 2. The salient features of the relationship between testosterone and cardiovascular disease

<table>
<thead>
<tr>
<th>The Salient Features of the Review</th>
<th>Cited Literature</th>
<th>Our Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>7. Testosterone deficiency reduced FMD</td>
<td>Akishita et al, 2007, Saad et al, 2008</td>
<td>T deficiency decrease FMD</td>
</tr>
<tr>
<td>8. Testosterone deficiency increases the synthesis of inflammatory cytokines</td>
<td>Malkin et al, 2004a,b</td>
<td>T therapy reduces production of proinflammatory cytokines</td>
</tr>
<tr>
<td>11. Testosterone deficiency is associated with metabolic syndrome</td>
<td>Laaksonen et al, 2003, Kapoor et al, 2006, Traish et al, 2009a</td>
<td>Hypogonadism and ADT are thought to contribute to the development of the MetS</td>
</tr>
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Abbreviations: ADT, androgen deprivation therapy; CV, cardiovascular; CVD, cardiovascular disease; ED, erectile dysfunction; FMD, flow-mediated vasodilation; IMT, intima media thickness; MetS, metabolic syndrome; T, testosterone.
assessment and diagnosis of hypogonadism in men with, or at risk for, the MetS important in the primary care setting. The answer as to whether correcting components of the MetS will decrease cardiovascular morbidity and mortality is unknown at present and will require larger clinical studies for longer periods of time. The possibilities, however, remain very exciting.

Summary and Conclusions

The relationship between androgen deficiency and CVD is an evolving area of investigation. To date, the largest studies are of epidemiological nature, and controlled clinical studies are urgently needed in this field. Androgen deficiency is often associated with many pathophysiological states and has adverse effects on men’s health. Androgen deficiency might be the underlying cause for a variety of common clinical conditions, such as diabetes, ED, the MetS and CVD. Table 2 summarizes the salient features of androgen deficiency as it relates to vascular disease. The relationship between insulin resistance and androgen deficiency has been discussed recently by Traish et al (2009b), and a link between insulin resistance and androgen deficiency with vascular disease was postulated. Abnormal lipid profiles, elevation of proinflammatory factors, hypertension, insulin resistance, and endothelial dysfunction are common features in men with androgen deficiency. Early identification of patients with androgen deficiency might help reduce the likelihood that these aforementioned clinical features progress. To further elucidate the role of androgen deficiency in vascular disease, large, long-term, double-blind, randomized, placebo-controlled clinical trials must be carried out. In androgen-deficient men provided with androgen therapy, determination of appropriate clinical outcomes will need to be considered. The degree to which patients improve, the point at which androgen therapy is delivered, the specific vascular disease, possible family genetic components, and many other variables will have to be considered in the overall analysis of androgen’s therapeutic effects on vascular disease. Although challenges might lie ahead regarding how data from such clinical trials are to be properly interpreted and whether longer-term safety can be established with T supplementation, findings such as those described herein warrant definite investigation into the beneficial role that androgens might have in preventing or ameliorating cardiovascular risk in androgen-deficient men.

References


Montaño LM, Calixto E, Figueroa A, Flores-Soto E, Carbajal V, Perusquia M. Relaxation of androgens on rat thoracic aorta: testosterone concentration dependent agonist/antagonist L-type Ca2+ channel activity, and 5beta-dihydrotestosterone restricted to... 1999;31:61–74.


