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Effects of Androgen on the Cardiovascular System in the Aging Male

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= Abstract =

Testosterone decrease in men with age has become well established. As such, several modes of testosterone replacement therapy have become available, primarily for supplementation to alleviate the effects of age associated hypogonadism, as manifested by frailty, sarcopenia, poor muscle quality, decreased libido and erectile functions. Recent investigations have found significant association between hypogonadism and cardiovascular disease, type 2 diabetes, obesity and dyslipidemia. The association is more clearly presented in patients receiving androgen deprivation therapy for prostate cancer. Furthermore, testosterone supplementation restores arterial vasoreactivity, reduces proinflammatory cytokines, total cholesterol, and triglyceride levels, and improves endothelial function and insulin sensitivity. Future long term trials should be performed to identify persistent benefits and safety of this treatment.

Key Words: Androgens, Testosterone, Hormone replacement therapy, Cardiovascular diseases, Metabolic syndrome

Introduction

In recent years the interest for hypogonadism in the aging process has seen a surprising increase. The prevalence of low serum total testosterone is approximately 20% by the age of 50 years and 50% by the age of 80 years.[1] In contrast to menopause, in which all women undergo a nearly complete cessation of gonadal estrogen secretion, in men, gonadal androgen secretion decreases gradually and progressively after the age of 30 years, but does not generally cease, and androgen levels remain highly variable in older men. The prevalence of clinical androgen deficiency was recently reported to be about 6 to 12% in middle-aged and elderly men.[2] Almost two decades have passed since the first study on androgen supplementation in elderly men was published. In the United States, prescription for testosterone supplementation has increased over 500 percent since 1993.[3] Testosterone-replacement therapy has been reported to produce a wide range of benefits for men with hypogonadism that include improvement in libido, bone density, muscle mass, body composition, mood, erythropoiesis, and cognition.[4]

Despite these well known advantages, androgens in general and testosterone in particular, have been widely believed to be associated with a high risk of cardiovascular disease (CVD) in men.[5,6] There are three main observations that led previous investigators to presume on the overt effects of testosterone. First, male gender itself was viewed to be an independent risk factor for CVD. The male to female ratio of mortality from vascular disease is 3:1 throughout the world and this ratio is independent of the background prevalence of vascular disease and of other cardiovascular risk factors.[7,8] Second, large observational

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studies supported estrogen to show protective effects.[9,10] Third, abuse of synthetic androgens in high doses by athletes sometimes leads to premature CVD.[7]

However, recent literature has improved our understanding of testosterone and its effect on the cardiovascular system. Here we review the effects of low testosterone on the cardiovascular system, and the benefits of testosterone replacement therapy.

Metabolic and Cardiovascular Effects of Hypogonadism

1. Increased CVD and hypogonadism

The simple observation that there is a significant sex difference in the morbidity and mortality of CVD has made it tempting to conclude androgens are responsible for the elevated cardiovascular risk in men.[11] A related hypothesis is that the lack of estrogens in men might be the cause of the difference in cardiovascular sex risk. However, in recent years there have been significant counterarguments. A major counterargument is based on the geographic and ethnic differences in the prevalence of CVD.[12] Morbidity and mortality from CVD in Northern and Eastern Europe compared with Southern Europe and Japan varies from 5 to 10 fold.[13] This suggests that other risk factors may be more important than sex. The narrowing sex gap after middle age adds another counterargument minimizing a possible causative role of sex hormones in CVD. The multifactorial nature of the pathogenesis of atherosclerosis minimizes the importance of testosterone as a single explanatory factor of the sex difference.[11]

Androgens have been shown to be important for survival in that a number of studies have linked androgen deficiency to increased mortality in men.[14] In a comprehensive review in 2003, 39 observational studies were reported: 32 were cross sectional studies, 16 showed no association, and another 16 showed that lower testosterone was associated with high prevalence of CAD. No single study showed an association between increased testosterone level and symptoms of CAD.[12] The Massachusetts Male Aging Study followed 1,686 men longitudinally for over 15 years and found a weak association.[2] In a retrospective review

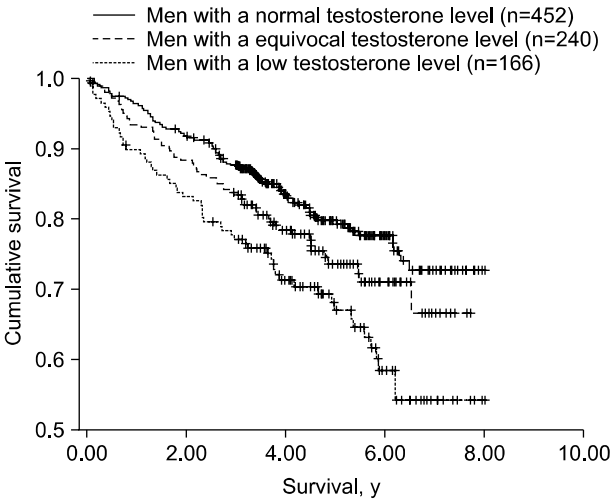

Fig. 1. Kaplan-Meier survival curves for 3 testosterone level groups.[1]

of 858 patients with multiple testosterone measurements, 40 years or older, without history of prostate or testicular cancer or anti androgen treatment, Shores et al.[1] found an increased mortality [hazard ratio 1.88] in men with low testosterone (Fig. 1). Several studies discuss the potential mechanisms pertaining to androgen deficiency and mortality. Reduced T levels are associated with increased cardiovascular risk factors, such as increased fat mass and subsequent death. Hypogonadism is thought to contribute to development of the metabolic syndrome, which increases CVD risk (Fig. 2).[15] In a study of 1896 nondiabetic middle-aged men, patients with metabolic syndrome had a significantly higher waist to hip ratio, fasting glucose, triglyceride, C-reactive protein (CRP), fibrinogen levels, and lower high density lipoprotein (HDL) levels, compared with controls, all of which were related to an increased risk of CVD.[16]

2. Insulin resistance and hypogonadism

Studies of healthy population have shown inverse relationship between testosterone and insulin levels.[17,18] Low plasma testosterone levels are commonly observed in men with type 2 diabetes and insulin resistance.[19] Hypogonadism and type 2 diabetes are often diagnosed in the same patient.[20] Hypogonadism was more prevalent in diabetic patients with increasing body-mass index (BMI), or those who were severely

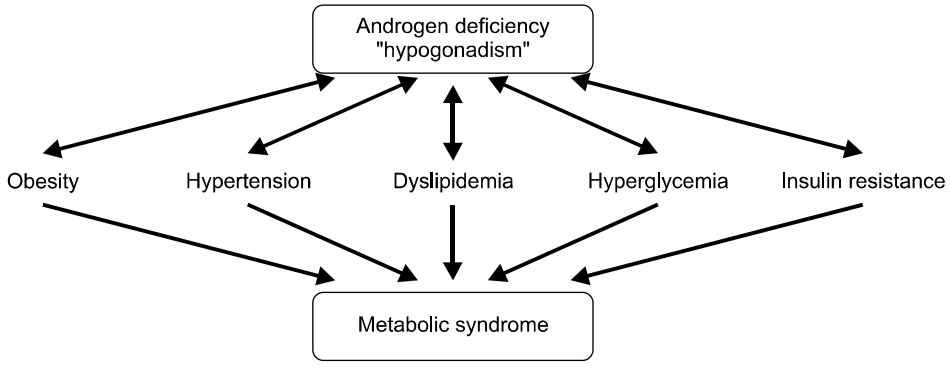

Fig. 2. The interrelationships between metabolic syndrome and hypogonadism with chronic illnesses and cardiovascular risks are shown and do appear to be quite interwoven.[14]

obese (BMI＞40). Insulin is an important regulator of sex hormone binding globulin (SHBG) production by the liver. *In vitro* studies have shown that insulin in physiologic concentrations was a potent inhibitor of SHBG production by cultured hepatoma cells.[18] Pasquali[21] elucidated these relationships by inducing glucose abnormalities with diazoxide in healthy human subjects and in men with obesity but no diabetes. They found that insulin was capable of stimulating testosterone production in vivo and simultaneously reducing SHBG concentrations in both normal and obese men. The effect of insulin on SHBG and testosterone is more pronounced in comparison of type 1 diabetes, in which patients have low insulin and normal testosterone levels, and type 2 diabetes, in which patients have high insulin and low testosterone levels.[22] While the association between SHBG and insulin resistance has been known for some time,[23] recent findings suggest that this is a secondary mechanism mediated by high levels of monosaccharides in serum which reduce SHBG production in hepatocytes.[24] Other studies have shown association between CAG repeats of androgen receptor (AR) and serum insulin levels.[25] While further investigation is required to elucidate the nature of association between hypogonadism and insulin resistance, current conclusions indicate both testosterone and SHBG are predictive of development of diabetes and metabolic syndrome.[26]

3. Obesity and hypogonadism

Obesity is the most common cause of insulin resistance.[18] Certain patterns of fat distribution are more closely related to increased incidence of diabetes and CVD. Abdominal or central obesity, as assessed by waist/hip ratio, is an essential component of metabolic syndrome and more strongly linked to the development of impaired glucose tolerance. Visceral fat, which constitutes a significant proportion of the intra-abdominal fat, has certain characteristic anatomical and metabolic features.[18] In men there is an inverse relationship between serum testosterone levels and visceral fat mass. The prevalence of obesity in ageing men has increased and is a strong predictor for testosterone deficiency seen in ageing males. Hypogonadal men also have a reduced lean body mass and an increased fat mass. Changes in total and free testosterone concentrations are reversible with weight loss.[27]

Underlying mechanism responsible for the reduced testosterone levels in obese men is unknown. The reduction in free testosterone seen in massive obesity is not accompanied by a reciprocal increase in luteinizing hormone (LH), suggesting a form of hypogonadotropic hypogonadism.[28] In women, SHBG decrease with obesity. Central obesity has lower SHBG concentration than peripheral obesity. Central obesity has a higher testosterone production rate. Percentage free testosterone fraction tends to be higher in women with central obesity.[21] In the obese male total and free testosterone blood concentration levels progressively decrease with increasing body weight. The reduction is associated with progressively decreasing levels of SHBG concentrations. LH and follicle-stimulating hormone (FSH) levels are usually normal or slightly reduced, as are gonadotropin responses following luteinizing hormone releasing hormone (LHRH) stimulation. Both SHBG and testosterone are negatively correlated with insulin

levels. Such an inverse relationship is due to the ability of insulin to inhibit hepatic SHBG synthesis in the liver.[21] Obese males usually express a characteristic hormonal profile described as "hyperestrogenic hypogonadotropic hypogonadism".[29] The origin of hypoandrogenism in obese males is multifactorial. It is primarily attributable to an increase in circulating estrogens that appear to result in relative hypogonadotropism, although the diminished levels of SHBG in obese individuals will by itself result in reduced total testosterone levels. Weight correlates negatively with blood testosterone levels and testosterone/estradiol ratio.[29] Both estrone and estradiol are increased in obese males compared to controls.[30] Aromatization of C19 androgens like testosterone and androstenedione is a key step in estrogen biosynthesis and is catalyzed by the aromatase enzyme. Increase in estrogens in obese males is due to increased conversion of adrenal and testicular androgens owing to the increased available aromatase enzyme in fatty tissue.[29] Aromatase inhibition increases testosterone levels and decreases estradiol in non obese males, and such "correction" of hypoandrogenism in obese males during aromatase inhibition is an extension of a general effect of such medications.[29]

However, the concept that increased estrogen availability in human obesity may play a role in determining abnormalities of androgens contradicts the emerging role of estrogens in the regulation of adipose fat function and morphology.[21] Male patients with estrogen resistance caused by a mutation of the estrogen receptor gene[31] or estrogen deficiency due to aromatase gene mutation[32] tend to be overweight and to present with glucose intolerance and insulin resistance.[21] Recent studies on animal models have provided clear evidence of the importance of estrogens and estrogen receptor α signaling in the regulation of fat mass. In fact, aromatase-deficient mice and male and female estrogen receptor α-knockout (αERKO) mice become obese with aging. Given the emerging evidence on the regulatory effects of estrogens on adipose tissue, much more convincing studies should therefore be performed to support the concept that increased estrogen production rate may be responsible for disparate sex-dependent alterations of androgen secretion and metabolism in obesity.

4. Lipid profile change in hypogonadism

Khaw et al[33] followed 11,606 men aged 40 to 79 years in a nested case-control study found mean testosterone concentrations were lower in men who died of any cause, CVD, or cancer than in control subjects. Men who died of cardiovascular causes also had significantly higher mean body mass index, serum cholesterol, and low density lipoprotein (LDL): HDL cholesterol ratios. Testosterone concentrations were significantly inversely related to body mass index, waist-hip ratio, triglycerides, and prevalence of diabetes mellitus and were positively related to total cholesterol, LDL cholesterol, and HDL cholesterol concentrations and to cigarette smoking habit. In a cross sectional study of 715 healthy middle aged men, Van Pottelbergh et al[34] found positive association between physiological free testosterone and HDL-Cholesterol, which was independent of estradiol, the aromatization product of testosterone. In a nested case-control study between normal and low testosterone groups of 25 men each, Simon et al[17] found low testosterone was associated with significantly higher serum triglycerides, LDL cholesterol and lower HDL cholesterol. These results imply potential disadvantage of low testosterone in cardiovascular (CV) events.

5. Androgen deprivation therapy

Androgen deprivation therapy (ADT) is widely used in patients with prostate cancer. ADT improves cancer related symptomatology and quality of life. Clearly established consequences of ADT include sexual dysfunction, decreased lean body mass, decreased quality of life, and osteoporosis.[4] In addition, ADT has been found to induce a series of detrimental changes in metabolic status. A 48 week study of 40 men treated with ADT for prostate cancer demonstrated an average body mass increase of 2.4%, fat mass increase of 9.4% and lean body mass increase of 2.7%.[35] A follow up study by this group showed combined androgen blockade of leuprolide and bicalutamide for 12 weeks led to a 63% increase in insulin levels and decreased in-

sulin sensitivity.[36] Similar findings were observed from a 12 month follow up of 20 patients undergoing ADT for prostate cancer. Compared with 18 age matched localized prostate cancer patients not receiving ADT and 20 age matched controls, the ADT group showed increased abdominal obesity and hyperglycemia, along with elevated triglycerides and an overall higher prevalence of metabolic syndrome.[37] This group also studied the effects of ADT on insulin resistance with a similar component of patients.[38] After 12 months follow up, patients showed increased insulin resistance (as represented by HOMA index), elevated baseline glucose and hyperinsulinemia. In a large population based study of 14,597 men being treatment with ADT, treatment with gonadotropin releasing hormone (GnRH) agonists was associated with increased incidence of diabetes, coronary artery disease (CAD), myocardial infarction and sudden cardiac death.[39] However a recent review notes that long term follow up data almost entirely consist of cross sectional studies, suggesting long term prospective trials are required to establish a causative relationship.[40]

Testosterone Replacement Therapy

While, during the past decade, several studies have shown an association between hypogonadism and metabolic or cardiovascular dysfunctions, whether testosterone replacement can reverse these effects requires further evaluation. Recent studies, however, have presented promising results.

1. Testosterone replacement therapy in CVD: improvement of cytokine milieu, body composition and ischemic threshold

The improvements in short term cardiovascular function has been attributed to various effects either directly by testosterone, or indirectly through aromatization.[41] Older studies indicate testosterone therapy relieved symptoms of angina and peripheral vascular disease.[42] Recent animal studies also show testosterone having acute effect in dilatation of the coronary and pulmonary arteries.[43] It is believed that testosterone causes both endothelium dependent and endothelium independent vasodilatation. The former is achieved by an increased release of nitric oxide from endothelium, whereas the latter by blocking of calcium channels and/or opening of potassium channels.[44] Recent in vitro studies have demonstrated that testosterone inhibits L-type calcium channels which is the same site of action as the dihydropyridine calcium antagonist nifedipine.[45] More direct evidence was shown by Webb et al[46] by infusing testosterone to 13 men with CAD. Testosterone, administered acutely at physiological concentrations, induced coronary artery dilatation up to 4.5% and increases coronary blood flow up to 17.4% in men with coronary atherosclerosis.

Significant evidence has also accumulated to show beneficial effects of testosterone on the improvement of the cytokine milieu. Patients with CAD have elevated circulating levels of cytokines and C-reactive protein, with higher levels present in those with unstable angina or acute myocardial infarction.[47,48] Angiographic studies have shown that infarcts are reported in even vessels with stenosis of less than 70%.[49] Clinical manifestations of coronary atheroma are not directly related to the local burden of atheroma but to the amount of plaque inflammation.[50] The initial process of atheroma formation involves chemotaxis of monocyte chemoattractant protein-1 (MCP-1) by endothelial cells reacting to accumulation of cholesterol in the arterial wall (Fig. 3). As a result monocytes and macrophages infiltrate the vessel wall and produce inflammatory cytokines, including tumor necrosis factor (TNF). The stability of the fibrin cap in affected by the continuing inflammation, as T-lymphocytes produce γ-interferon, reducing the production of fibrin and inhibiting smooth muscle proliferation. Activated macrophages produce matrix metalloproteinases, digesting and breaking down the plaque matrix. TNF and interleukin-1β promote the release of these digestive enzymes, while anti-inflammatory cytokines such as interleukin (IL)-4 and -10 reduce matrix metalloproteinase (MMP) activity. The balance of stimulatory and inhibitory cytokines is crucial to the stability of the plaque.[50]

There is evidence from several studies that androgens possess immune-modulating properties. Androgens

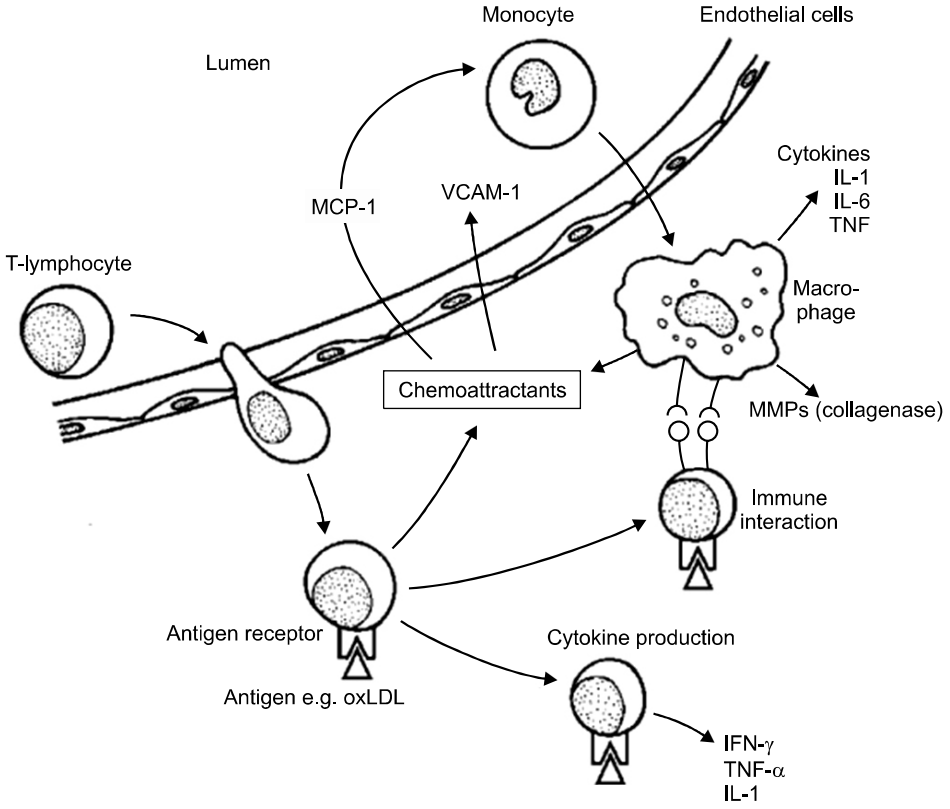

Fig. 3. Immune and inflammatory reaction.[50]

have been shown to suppress the activity of pro-inflammatory cytokines while enhancing that of anti-inflammatory factors. Investigating changes of inflammatory cytokines in 29 patients with idiopathic hypogonadotropic hypogonadism (IHH), patients showed greater degree of inflammatory activity compared to healthy control, while testosterone therapy resulted in decreased overall circulating cytokines.[51] Inverse relationship has also been found between testosterone and plasminogen activator inhibitor I, fibrinogen and factor VII.[52] Cell culture studies also show testosterone to reduce expression of pro-inflammatory cytokines such as TNF-α, interleukin 1 and interleukin 6 in human vascular endothelium, monocytes and fibroblasts.[53]

While most studies agree that testosterone replacement therapy improves body composition, with increased muscle mass and decreased central obesity,[54-56] several discrepancies have been reported concerning changes in serum lipid profiles. Alterations in HDL-cholesterole under testosterone therapy are usually described as a slight decline.[57-59] Wang et al. investigated the effect of testosterone gel on 142 patients for 42 months, reporting no significant change in serum LDL and cholesterol, but a slight increase in serum HDL levels. Despite the modicum changes in lipid profile, patients showed significant improvements in body composition. Zitzmann et al[25] also showed an increased HDL and decreased LDL and cholesterol levels with intramuscular injections in 66 patients, further noting that the discrepancy may develop following longer observational periods where the lipid profile adopts the changes to body composition. These results are further compounded by the various routes of administration, patient selection and duration of these studies. Further investigation is required to make a definite statement on these matters.

A short term study of testosterone of twelve men with CAD or proven myocardial infarction showed significant changes in improvement in ischemic threshold parameters, presented as increase in time to 1 mm ST depression during Bruce protocol exercise treadmill testing.[41] Furthermore, this study showed concurrent evidence of total cholesterol and serum tumor necrosis

factor α reduction. A more recent trial studied the effects on ischemia for 12 months with a randomized parallel group control trial.[60] At the end of follow up, the testosterone group showed increased time to ischemia, assessed as 1 mm ST depression during Bruce protocol, and decreased serum triglycerides and BMI, with no significant effects on serum HDL. Serum CRP was lower in the treatment group, but without statistical significance.

2. Testosterone replacement therapy in diabetes: decrease in insulin levels and improved insulin sensitivity

As mentioned earlier, men with type 2 diabetes have a higher prevalence of hypogonadism. Testosterone is an important modulator of insulin sensitivity. However, surprisingly few studies have dealt with improvement in glycemic control with testosterone replacement therapy. Boyanov et al[61] performed a non blinded study of 48 men with mild androgen deficiency and type 2 diabetes. Twenty-four men receiving oral testosterone showed significant reduction in body weight, body fat, blood glucose and mean glycated hemoglobin compared to the other patients on placebo. Moon et al. also showed improvement of serum glucose in men with higher baseline glucose, after administration of testosterone for 24 weeks (Fig. 4).[62] Kapoor et al[54] performed a double blind cross over study on 24 men with hypogonadism and type 2 diabetes. Treatment periods lasted approximately 3 months. Testosterone therapy improved fasting insulin sensitivity, reduced glycated hemoglobin, fasting blood glucose, and total cholesterol as well as visceral adiposity as assessed by waist circumference and waist/hip ratio. A 12 month study of patients with hypogonadotropic hypogonadism on oral testosterone by Hong et al[59] showed a trend toward improvement in overall insulin levels and insulin sensitivity, as well as decreased abdominal fat, as measured by abdominal CT. With both the increase in accumulative data of both observational and interventional studies, there is a changing view that testosterone is not limited to being a marginal hormone catering to men seeking eternal youth, but a central element in glucose and lipid metabolism (Table 1).[63]

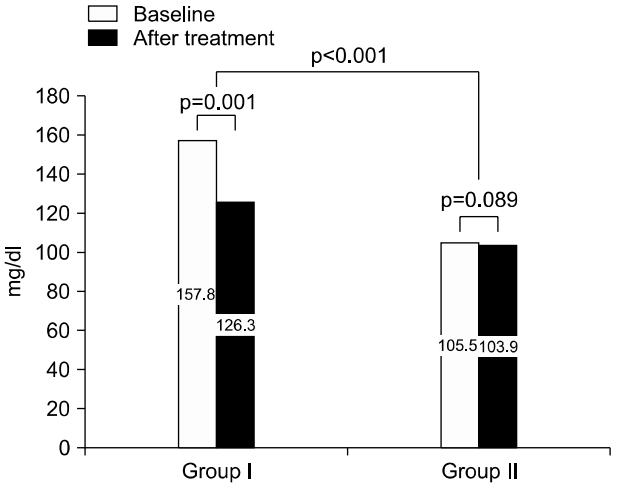

Fig. 4. Group I: high initial fasting glucose, Group II: low initial fasting glucose. Glucose level of group I decreased more than that of group II.[62]

Conclusion

Androgen deficiency and the possible cardiovascular risks it pertains is a developing field of investigation.

Table 1. Cardiovascular disease and type 2 diabetes

	Hypogonadism	Testosterone replacement therapy
Cardiovascular disease	- Increased mortality - Obesity - Poor lipid profile: higher triglycerides, lower HDL	- Short term relief: angina, vasodilatory effects - Beneficial cytokine profile: suppress proinflammatory cytokines - Improved ischemic threshold
Type 2 diabetes	- Concomitant association increased with high BMI - Increased insulin associated with reduced SHBG concentrations - Increased insulin resistance	- Improved glycemic control: reduced blood glucose and glycated hemoglobin

The past decade has seen explosive amount of interest toward both the detriments of hypogonadism as well as the benefit of testosterone replacement therapy.

Current results propound the association of the hypogonadal state with increased risk of cardiovascular and metabolic dysfunctions. Results have shown obesity, dyslipidemia and insulin resistance was also associated with hypogonadism, as well as a significant increase in the risk of cardiovascular mortality. These effects are all the more succinctly presented in ample amounts in patients with prostate cancer undergoing androgen deprivation therapy. Studies into the molecular mechanism of androgens on vascular endothelial cells and atheroma development have also shown hypogonadism was associated with a change in the cytokine milieu towards pro-inflammatory configurations.

In parallel to these findings, recent development of alternative methods of testosterone delivery to avoid the hepatic comorbidities of earlier methods have gleaned upon the benefits of testosterone replacement therapy. Studies have shown testosterone replacement not only to improve lean body mass, libido and sexual function, but also to improve insulin sensitivity, lower fasting glucose levels in type 2 diabetics, improve ischemic threshold and lower the risk of mortality in patients with CVDs. These benefits have been found to be brought about by improving the lipid profile and abating inflammatory cytokine production.

However, most of the intervention studies had too few patients observed across too short a study period. It is evident that long term data is still lacking. Further long term, double blind, randomized, placebo controlled clinical trials must be carried out to validate hypogonadism as an important and significant risk of cardiovascular and metabolic dysfunctions, as well as to elucidate the role of testosterone replacement therapy in these patients.

REFERENCES

1) Shores MM, Matsumoto AM, Sloan KL, Kivlahan DR. Low serum testosterone and mortality in male veterans. Arch Intern Med 2006;166:1660-5
2) Araujo AB, O'Donnell AB, Brambilla DJ, Simpson WB, Longcope C, Matsumoto AM, et al. Prevalence and incidence of androgen deficiency in middle-aged and older men: estimates from the Massachusetts Male Aging Study. J Clin Endocrinol Metab 2004; 89:5920-6
3) Rhoden E, Morgentaler A. Risks of testosterone-replacement therapy and recommendations for monitoring. N Engl J Med 2004;350:482-92
4) Bain J. Testosterone and the aging male: to treat or not to treat? Maturitas 2010;66:16-22
5) Foreman MD. Cardiovascular disease. A men's health hazard. Nurs Clin North Am 1986;21:65-73
6) Kalin M, Zumoff B. Sex hormones and coronary disease: a review of the clinical studies. Steroids 1990; 55:330-52
7) Assmann G, Lewis B, Mancini M. The recognition and management of hyperlipidaemia in adults: a policy statement of the European Atherosclerosis Society. Eur Heart J 1988;9:571-600
8) Njølstad I, Arnesen E, Lund-Larsen PG. Smoking, serum lipids, blood pressure, and sex differences in myocardial infarction: a 12-year follow-up of the Finnmark Study. Circulation 1996;93:450-6
9) Gordon T, Kannel W, Hjortland M, McNamara P. Menopause and coronary heart disease. The Framingham Study. Ann Intern Med 1978;89:157-61
10) Stampfer M, Colditz G, Willett W, Manson J, Rosner B, Speizer F, et al. Postmenopausal estrogen therapy and cardiovascular disease: ten-year follow-up from the Nurses' Health Study. N Engl J Med 1991;325:756-62
11) Shabsigh R, Katz M, Yan G, Makhsida N. Cardiovascular issues in hypogonadism and testosterone therapy. Am J Cardiol 2005;96:67M-72M
12) Wu FC, von Eckardstein A. Androgens and coronary artery disease. Endocr Rev 2003;24:183-217
13) Levy D, Kannel WB. Searching for answers to ethnic disparities in cardiovascular risk. Lancet 2000; 356:266-7
14) Traish AM, Saad F, Feeley RJ, Guay A. The dark side of testosterone deficiency: III. Cardiovascular disease. J Androl 2009;30:477-94
15) Traish AM, Guay A, Feeley R, Saad F. The dark side of testosterone deficiency: I. Metabolic syndrome and erectile dysfunction. J Androl 2009;30:10-22
16) Makinen J, Jarvisalo MJ, Pollanen P, Perheentupa A, Irjala K, Koskenvuo M, et al. Increased carotid athe-

rosclerosis in andropausal middle-aged men. J Am Coll Cardiol 2005;45:1603-8
17) Simon D, Charles MA, Nahoul K, Orssaud G, Kremski J, Hully V, et al. Association between plasma total testosterone and cardiovascular risk factors in healthy adult men: The Telecom Study. J Clin Endocrinol Metab 1997;82:682-5
18) Kapoor D, Malkin CJ, Channer KS, Jones TH. Androgens, insulin resistance and vascular disease in men. Clin Endocrinol (Oxf) 2005;63:239-50
19) Grossmann M, Thomas M, Panagiotopoulos S, Sharpe K, MacIsaac R, Clarke S, et al. Low testosterone levels are common and associated with insulin resistance in men with diabetes. J Clin Endocrinol Metab 2008;93:1834-40
20) 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;30:911-7
21) Pasquali R. Obesity and androgens: facts and perspectives. Fertil Steril 2006;85:1319-40
22) Chandel A, Dhindsa S, Topiwala S, Chaudhuri A, Dandona P. Testosterone concentration in young patients with diabetes. Diabetes Care 2008;31:2013-7
23) Phillips G. Relationship between serum sex hormones and glucose, insulin and lipid abnormalities in men with myocardial infarction. Proc Natl Acad Sci USA 1977;74:1729-33
24) Selva D, Hogeveen K, Innis S, Hammond G. Monosaccharide-induced lipogenesis regulates the human hepatic sex hormone-binding globulin gene. J Clin Invest 2007;117:3979-87
25) Zitzmann M, Gromoll J, Von Eckardstein A, Nieschlag E. The CAG repeat polymorphism in the androgen receptor gene modulates body fat mass and serum concentrations of leptin and insulin in men. Diabetologia 2003;46:31-9
26) Laaksonen D, Niskanen L, Punnonen K, Nyyssönen K, Tuomainen T, Valkonen V, et al. Testosterone and sex hormone-binding globulin predict the metabolic syndrome and diabetes in middle-aged men. Diabetes Care 2004;27:1036-41
27) Strain GW, Zumoff B, Miller LK, Rosner W, Levit C, Kalin M, et al. Effect of massive weight loss on hypothalamic-pituitary-gonadal function in obese men. J Clin Endocrinol Metab 1988;66:1019-23
28) Zumoff B. Hormonal abnormalities in obesity. Acta Med Scand Suppl 1988;723:153-60
29) Hammoud AO, Gibson M, Peterson CM, Hamilton BD, Carrell DT. Obesity and male reproductive potential. J Androl 2006;27:619-26
30) Schneider G, Kirschner MA, Berkowitz R, Ertel NH. Increased estrogen production in obese men. J Clin Endocrinol Metab 1979;48:633-8
31) Smith EP, Boyd J, Frank GR, Takahashi H, Cohen RM, Specker B, et al. Estrogen resistance caused by a mutation in the estrogen-receptor gene in a man. N Engl J Med 1994;331:1056-61
32) Carani C, Qin K, Simoni M, Faustini-Fustini M, Serpente S, Boyd J, et al. Effect of testosterone and estradiol in a man with aromatase deficiency. N Engl J Med 1997;337:91-5
33) Khaw KT, Dowsett M, Folkerd E, Bingham S, Wareham N, Luben R, et al. Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men: European prospective investigation into cancer in Norfolk (EPIC-Norfolk) Prospective Population Study. Circulation 2007;116:2694-701
34) Van Pottelbergh I, Braeckman L, De Bacquer D, De Backer G, Kaufman JM. Differential contribution of testosterone and estradiol in the determination of cholesterol and lipoprotein profile in healthy middle-aged men. Atherosclerosis 2003;166:95-102
35) Smith MR. Changes in body composition during hormonal therapy for prostate cancer. Clin Prostate Cancer 2003;2:18-21
36) Smith MR, Lee H, Nathan DM. Insulin sensitivity during combined androgen blockade for prostate cancer. J Clin Endocrinol Metab 2006;91:1305-8
37) Braga-Basaria M, Dobs AS, Muller DC, Carducci MA, John M, Egan J, et al. Metabolic syndrome in men with prostate cancer undergoing long-term androgen-deprivation therapy. J Clin Oncol 2006;24:3979-83
38) Basaria S, Muller D, Carducci M, Egan J, Dobs A. Hyperglycemia and insulin resistance in men with prostate carcinoma who receive androgen deprivation therapy. Cancer 2006;106:581-8
39) Keating NL, O'Malley AJ, Freedland SJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy: observational study of veterans with prostate cancer. J Natl Cancer Inst 2010;102:39-46

40) Shahani S, Braga-Basaria M, Basaria S. Androgen deprivation therapy in prostate cancer and metabolic risk for atherosclerosis. J Clin Endocrinol Metab 2008;93:2042-9
41) Malkin CJ, Pugh PJ, Morris PD, Kerry KE, Jones RD, Jones TH, et al. Testosterone replacement in hypogonadal men with angina improves ischaemic threshold and quality of life. Heart 2004;90:871-6
42) Lesser M. Testosterone propionate therapy in one hundred cases of angina pectoris. J Clin Endocrinol Metab 1946;6:549-57
43) Chou TM, Sudhir K, Hutchison SJ, Ko E, Amidon TM, Collins P, et al. Testosterone induces dilation of canine coronary conductance and resistance arteries in vivo. Circulation 1996;94:2614-9
44) Jones RD, Pugh PJ, Jones TH, Channer KS. The vasodilatory action of testosterone: a potassium channel opening or a calcium antagonistic action? Br J Pharmacol 2003;138:733-44
45) Hall J, Jones RD, Jones TH, Channer KS, Peers C. Selective inhibition of L-type Ca2+ channels in A7r5 cells by physiological levels of testosterone. Endocrinology 2006;147:2675-80
46) Webb CM, McNeill JG, Hayward CS, de Zeigler D, Collins P. Effects of testosterone on coronary vasomotor regulation in men with coronary heart disease. Circulation 1999;100:1690-6
47) Ikonomidis I, Andreotti F, Economou E, Stefanadis C, Toutouzas P, Nihoyannopoulos P. Increased proinflammatory cytokines in patients with chronic stable angina and their reduction by aspirin. Circulation 1999;100:793-8
48) Manten A, de Winter RJ, Minnema MC, ten Cate H, Lijmer JG, Adams R, et al. Procoagulant and proinflammatory activity in acute coronary syndromes. Cardiovasc Res 1998;40:389-95
49) Falk E, Shah PK, Fuster V. Coronary plaque disruption. Circulation 1995;92:657-71
50) Malkin CJ, Pugh PJ, Jones RD, Jones TH, Channer KS. Testosterone as a protective factor against atherosclerosis--immunomodulation and influence upon plaque development and stability. J Endocrinol 2003; 178:373-80
51) Yesilova Z, Ozata M, Kocar IH, Turan M, Pekel A, Sengul A, et al. The effects of gonadotropin treatment on the immunological features of male patients with idiopathic hypogonadotropic hypogonadism. J Clin Endocrinol Metab 2000;85:66-70
52) Hak AE, Witteman JC, de Jong FH, Geerlings MI, Hofman A, Pols HA. Low levels of endogenous androgens increase the risk of atherosclerosis in elderly men: the Rotterdam study. J Clin Endocrinol Metab 2002;87:3632-9
53) Hatakeyama H, Nishizawa M, Nakagawa A, Nakano S, Kigoshi T, Uchida K. Testosterone inhibits tumor necrosis factor-alpha-induced vascular cell adhesion molecule-1 expression in human aortic endothelial cells. FEBS Lett 2002;530:129-32
54) 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
55) Kalinchenko SY, Tishova YA, Mskhalaya GJ, Gooren LJG, Giltay EJ, Saad F. Effects of testosterone supplementation on markers of the metabolic syndrome and inflammation in hypogonadal men with the metabolic syndrome: the double blinded placebo controlled Moscow study. Clin Endocrinol (Oxf) 2010;73:602-12
56) Wang C, Cunningham G, Dobs A, Iranmanesh A, Matsumoto AM, Snyder PJ, et al. Long-term testosterone gel (AndroGel) treatment maintains beneficial effects on sexual function and mood, lean and fat mass, and bone mineral density in hypogonadal men. J Clin Endocrinol Metab 2004;89:2085-98
57) Isidori AM, Giannetta E, Greco EA, Gianfrilli D, Bonifacio V, Isidori A, et al. Effects of testosterone on body composition, bone metabolism and serum lipid profile in middle-aged men: a meta-analysis. Clin Endocrinol (Oxf) 2005;63:280-93
58) Dobs AS, Bachorik PS, Arver S, Meikle AW, Sanders SW, Caramelli KE, et al. Interrelationships among lipoprotein levels, sex hormones, anthropometric parameters, and age in hypogonadal men treated for 1 year with a permeation-enhanced testosterone transdermal system. J Clin Endocrinol Metab 2001;86:1026-33
59) Hong ES, Kim SY, Choi YJ, Kim SW, Shin CS, Park KS, et al. The effects on visceral fat and cardiovascular risk factors of testosterone replacement in secondary hypogonadal men. Endocrinol Metab 2005;20:252-60
60) Mathur A, Malkin C, Saeed B, Muthusamy R, Jones

TH, Channer K. Long-term benefits of testosterone replacement therapy on angina threshold and atheroma in men. Eur J Endocrinol 2009;161:443-9
61) 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
62) Moon du G, Park MG, Lee SW, Park K, Park JK, Kim SW, et al. The efficacy and safety of testosterone undecanoate (Nebido®) in testosterone deficiency syndrome in Korean: a multicenter prospective study. J Sex Med 2010;7:2253-60
63) Saad F, Gooren LJ. The role of testosterone in the etiology and treatment of obesity, the metabolic syndrome, and diabetes mellitus type 2. J Obes 2011; 2011. pii: 471584. Epub 2010 Aug 10.