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REVIEW ARTICLE

The role of the urologist in the prevention and early detection of cardiovascular disease

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ABBREVIATIONS

ED, erectile dysfunction; CVD, cardiovascular disease; NO, nitric oxide;
MMAS, Massachusetts Male Aging Study;
CHD, coronary heart disease;
BMI, body mass index; PDE5(I), phosphodiesterase-5 (inhibitor);
SHBG, sex-hormone binding globulin

Abstract In this review we identify whether problems encountered in urology, such as erectile dysfunction, have a bearing on general health, in particular cardiovascular health. Testosterone, traditionally regarded as the hormone subserving male reproductive and sexual functioning, appears to have a much wider role. Recent findings show that testosterone is involved in the metabolic control of glucose and lipids, of strength of bone and muscle, and psychological aspects such as mood and energy. Serum testosterone levels decline with ageing, free testosterone levels more so than total testosterone. At least 10 publications have shown that low testosterone levels are associated with an increased risk of death. The metabolic syndrome is a clustering of risk factors predisposing to diabetes mellitus type 2, atherosclerosis, and cardiovascular morbidity and mortality. There is a direct correlation between plasma testosterone and insulin sensitivity, and low testosterone levels are associated with an increased risk of type 2 diabetes mellitus, dramatically illustrated by androgen deprivation in men with prostate carcinoma. Lower total testosterone and sex hormone-binding globulin levels predict a higher incidence of the metabolic syndrome. Administration of testosterone to hypogonadal men reverses part of the unfavourable risk profile for the development of diabetes and atherosclerosis, thus also improving risk factors for erectile dysfunction. We conclude that urologists diagnosing and treating erectile problems are in a unique position to include general aspects of men's health in their work, and thus contribute to general health and to cardiovascular health in particular.

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Introduction

Erectile dysfunction (ED) and cardiovascular disease (CVD) are two faces of the same coin, with androgen deficiency as common denominator; this was recently authoritatively reviewed [1]. One could say that ED is a local expression in the penile vasculature of generalised vascular pathology with a common pathological basis. The common underlying factor is endothelial dysfunction; the latter manifesting clinically as impaired vasodilatation is the hallmark of ED [2]. The endothelium is the single layer of cells lining the surface of blood vessels. It has become clear that it is not merely a histological structure, but it has several important functions in cardiovascular health and disease with regard to vascular tone, inflammation, and adhesion of thrombocytes. The process of atherosclerosis starts at the endothelium [3].

The vascular endothelium is pivotal for vasodilatation, which is the physiological basis for adequate tissue perfusion to warrant adequate oxygenization in relation to actual demands. This flexible response depends on the capacity to change the resistance of the vascular system. The underlying physiological mechanism is the production of local agents, of which the most significant is nitric oxide (NO); this inhibits platelet aggregation and regulates vascular tone [3].

Bioavailable NO can be increased by enhancing its production or reducing its inactivation. NO induces endothelial vasodilatation by increasing the cGMP content of vascular smooth muscle cells, resulting in relaxation. Cardiac risk factors (including dyslipidaemia, hypertension and type 2 diabetes mellitus) are all associated with impaired endothelial function [2]. Evidence is accumulating that ED is an early sign of CVD. ED is an important marker of vascular disease throughout the arterial tree [3].

The Massachusetts Male Aging Study (MMAS), a random-sample cohort study of men aged 40–70 years, investigated the relationship between baseline risk factors for coronary heart disease (CHD) and subsequent ED, on the assumption that subclinical arterial disease might be manifested as ED. Overweight (defined as body mass index, BMI, of $>28\ kg/m^2$) and a composite coronary risk score also significantly predicted incident ED [4].

Cardiovascular risk factors in mid-life could predict the incidence of ED an average of 25 years later. A study which assessed seven classic CHD risk factors in men aged 30–69 years, from 1972 to 1974 and then again in 1998, found that mean age, BMI, cholesterol and triglycerides were each significantly associated with an increased risk of ED [5].

Erectile function is viewed by almost all men as a significant component of quality of life and erectile difficulties (e.g. ED) might be a reason to seek medical advice. As indicated above, several studies documented that there is a high concordance between the causes of ED and the causes of CVD [6], this indirectly by showing that there is an elevated prevalence of the metabolic syndrome and insulin resistance in a population of men with ED compared with a general population of men [7–9]. The authors argue that the ultimate goal therefore must be not only to treat the erectile problem but also to diagnose and adequately (aggressively) treat any cardiac risk factors that might be found.

The MMAS also showed that ED was predictive of the metabolic syndrome. This study supports the idea that ED might provide a warning sign and, at the same time, an opportunity for early intervention in men otherwise considered at lower risk for the metabolic syndrome and subsequent CVD.

The MMAS also estimated the frequency of the progression of ED and remission among ageing men, and assessed the relation of progression/remission to demographics, socioeconomic factors, comorbidities and modifiable lifestyle characteristics [10]. Natural remission and progression occur in a substantial number of men with ED. Age and BMI were associated with the progression and remission of ED. Interventions were non-pharmacological and apparently influenced remission and delayed progression of ED. The association of BMI with remission and progression, and the association of smoking and health status with progression, offer potential avenues for facilitating remission and delaying progression using non-pharmacological intervention. Lifestyle changes are associated with an improvement in sexual function in about a third of obese men with ED at baseline. Weight loss and increased physical activity appeared to have a favourable effect on erectile and endothelial functions in obese men.

The benefits of such interventions for overall men's health might be far-reaching and support the view that ED is a portal to men's health.

Shabsigh et al. [11] eloquently argued that ED can be used to calculate men's health risks. Elements in the calculation of health risks (hypertension, diabetes, angina or hyperlipidaemia) in men presenting with ED are: health status on a scale of 1–7 (1 = excellent, 7 = poor), waist size, severity of ED, presence/absence of a sexual partner). The calculation produces scores within the range of 1–7; a score of 1.5–2.5 is 'medium risk' (30–59% probability), of >2.5 is 'high risk' ($\geqslant 60\%$ probability of having the condition) and <1.5 is 'low risk' ($<30\%$ probability) [11]. A study with a similar message was conveyed by Corona et al. [12]. A recent paper argued that when, in the light of recent guidelines, PSA screening starts (aged $\geqslant 40$ years) screening for ED and hypogonadism should be added. ED and hypogonadism are signals of future all-cause mortality and overall health status, and thus move these evaluations into the broader arena of public health. Screening for ED and hypogonadism provide determinants to assess general metabolic and cardiovascular health risks in men, and in addition to PSA, should include screening tests for lipids, blood pressure, obesity and serum glucose.

The relevance of the age-related decline of testosterone for sexual functioning

The understanding of the (patho) physiological functions of testosterone with regard to sexual functioning has undergone a revolutionary development. There are now insights that endocrine conditions are often associated with ED [13]. It is well-known that hypogonadism in men usually results in loss of libido and potency, which can be restored by androgen administration. The original insights into the mechanisms of action of androgens on sexual function indicated a prominent role of testosterone on sexual interest, while the effects of testosterone on erectile function were less apparent from these early investigations. However, new research has presented convincing evidence that testosterone has profound effects on tissues of the penis involved in the mechanism of erection, and that testosterone deficiency impairs the anatomical and

physiological substrate of erectile capacity, at least in part reversible upon androgen replacement [14]. There are androgen receptors in the human corpus cavernosum. Several studies show that testosterone plays a critical role in restoring and maintaining the penile trabecular smooth muscle structure and function, as well as regulating the cell apoptosis. In line with this, Aversa et al. [15] reported that the circulating levels of free testosterone, independently of age, positively correlated with the degree of relaxation of the corporal smooth muscle cells and the cavernous endothelial cells, giving support to the potential role of androgens in regulating smooth muscle function in the penis.

Adipocyte accumulation in penile subtunical area of the corpus cavernosum emphasised the potential mechanism for veno-occlusive dysfunction in androgen deficiency (for review, see Yassin et al. [16]). Testosterone has a positive effect on haemodynamic processes and the veno-occlusive properties of the penile trabecular tissues. Testosterone may repair venous leakage in hypogonadal patients and men with metabolic syndrome. The effect of a hormonal factor on the veno-occlusive properties of the corpora cavernosa indicates that restoration of testosterone to normal might repair mechanical damage of the corpora cavernosa [17]. This has also been found to be the case in laboratory animals.

In a well-designed intervention study, Aversa et al. [18] provided support for this mechanism of action of testosterone on the erectile tissues of the penis. They assessed the effects of androgen administration in 20 patients with arteriogenic ED (confirmed with dynamic colour duplex ultrasonography), not responding to treatment with sildenafil 100 mg. The patients' testosterone levels were in the lower quartile of the normal range. In this placebo-controlled study, treatment with transdermal testosterone raised plasma testosterone levels and led to an increase of arterial inflow into the cavernous tissue, and to an improvement of ED, thus enhancing the response to treatment with phosphodiesterase-5 inhibitors (PDE-5Is). In line with this latter study, Foresta et al. [19] reported that normal plasma testosterone levels are required for erectile function. In severely hypogonadal men (plasma testosterone < 2.0 ng/mL) the nocturnal penile tumescence, ultrasonographic measurement of arterial cavernous inflow and visually stimulated erection in response to sildenafil 50 mg or apomorphine 3 mg were minimal. The responses to these pharmacological stimuli normalised after 6 months of administration of testosterone patches, showing the significant role of normal levels of testosterone for erectile function.

The PDE5-Is have revolutionized the treatment of ED, but 30–35% of patients fail to respond [14,20]. Associated testosterone deficiency, not properly diagnosed, has been proposed as one of the reasons for failure. Several studies suggest that the activity of PDE5-Is as a treatment for ED is androgen-dependent. In rodents, castration reduces protein expression and activity of PDE5, and testosterone treatment is capable of upregulating them [21]. In addition, medical or surgical castration prevents the enhancing effect of PDE5-Is on erections induced by electrostimulation of the cavernous nerves. The expression of NO (NO synthesis) is regulated by androgens. The expression of PDE5 has been found to be androgen-dependent also in humans [21]. As a result, androgens promote the formation of a substrate that the PDE5-Is can act upon. In addition, several clinical studies suggest that testosterone deficiency is a risk factor for a poor response to sildenafil [3]. Several uncontrolled studies have also reported beneficial effects of a combined therapy with testosterone and PDE5-Is in men with ED and low or low-normal testosterone levels, and who previously had not responded to 100 mg sildenafil or 20 mg tadalafil [22].

Testosterone and cardiovascular health

Until a decade ago, it was a widely held belief that androgens have an atherogenic effect and thus led to CVD, and androgen administration was regarded as adding to the risk of developing CVD. Over the last decade several papers have examined the relationship of androgens with CVD and concluded that it is no longer tenable to regard testosterone as a culprit in the aetiology of CVD. Recent epidemiological studies have found that low testosterone levels are a predictor of mortality in elderly men, particularly cardiovascular mortality [23].

Over the last 2 years many review papers have highlighted the significance of depressed levels of testosterone in CVD. Both cross-sectional and longitudinal epidemiological studies have convincingly established that low plasma testosterone/low sex-hormone binding globulin (SHBG) levels are correlated with or predict the metabolic syndrome [24]. Testosterone deficiency afflicts $\approx$30% of men aged 40–79 years [25]. Numerous studies have found inverse associations between the severity of features of the metabolic syndrome and plasma testosterone level [26]. There is an inverse relationship between waist circumference, a reliable indicator of visceral obesity, and testosterone levels over all age groups.

Adiposity with its associated hyperinsulinism suppresses SHBG synthesis and therewith the levels of circulating testosterone. It also might affect the strength of LH signalling to the testis. Further, insulin and leptin [27] have a suppressive effect on testicular steroidogenesis. Visceral fat cells secrete many cytokines which impair testicular steroidogenesis. Thus there are reasons to believe that adiposity is a significant factor in lowering circulating levels of testosterone.

While it is clear that disease, and in the context of this contribution, in particular the metabolic syndrome, suppresses circulating testosterone levels, it has also been documented that low testosterone levels induce the metabolic syndrome. Low testosterone and SHBG levels appeared to be strongly associated not only with components of the metabolic syndrome, but also with the metabolic syndrome itself, independently of BMI. Furthermore, sex hormones were associated with inflammation and body iron stores. Even in the absence of late-stage consequences such as diabetes and CVD, subtle derangements in sex hormones are present in the metabolic syndrome, and might contribute to its pathogenesis.

The relative contributions of each of the components of the National Cholesterol Education Program Adult Treatment Panel III for metabolic syndrome to low serum testosterone in ageing men has been examined using multiple linear regression modelling. Based on these analyses the presence of diabetes or a fasting serum glucose level of > 110 mg/dL, BMI $\geqslant 30$ kg/m^2 and triglyceride level of $\geqslant 150$ mg/dL each appeared to have a clinically relevant association with low serum testosterone level [28].

The issue of androgen deficiency and cardiovascular health and diabetes mellitus type 2 is very important for the urologist treating men with prostate cancer. The risks of developing atherosclerosis on androgen deprivation for prostate cancer

have been addressed in several reviews [29], in particular the advisory report of the American Heart Association [30]. Studies in men undergoing androgen deprivation treatment in prostate cancer show that within 3 months significant metabolic changes have occurred (a 43% increase in fat mass and a 26% increase in insulin levels) [31]. This has been confirmed in another study [32], and again in a more recent study finding that visceral fat accumulation was more closely linked to testosterone than to oestradiol, with insulin resistance as a secondary effect [33]. In a study over 10 weeks of healthy lean men (aged 23.2 ± 0.5 years), suppression of testosterone by a GnRH analogue was associated with a marked decrease in measures of whole-body protein anabolism, decreased strength, decreased fat oxidation, and increased adiposity [34]. Epidemiological prospective studies of men with low testosterone levels have examined the association between low testosterone levels and the subsequent development of diabetes type 2 over 7–10 years. The odds ratio for future diabetes was 1.58 for a decrease of 1 sd in free testosterone level (4 ng/dL) [35]. In another study the association of low levels of testosterone with the development of the metabolic syndrome and diabetes in men was studied. After 11 years of follow-up, 147/702 men had developed the metabolic syndrome and 57 men developed diabetes. Men with total testosterone, calculated free testosterone, and SHBG levels in the lower quartile had a several-fold increased risk of developing the metabolic syndrome and diabetes after adjusting for age. Findings were similar in a more recent report [36]. These studies indicate that the degree of suppression of serum testosterone level might be an element in the development of the metabolic syndrome and diabetes mellitus, and that incomplete suppression of testosterone may slow the occurrence of side-effects of androgen deprivation.

Other studies showed convincingly that acute androgen deprivation reduces insulin sensitivity in young men and strongly impairs glycaemic control in men with diabetes mellitus [37].

Testosterone administration to men with the metabolic syndrome and diabetes mellitus type 2

So it is clear now that low testosterone levels are a factor in the aetiology of common ailments of elderly men, such as the metabolic syndrome and its associated diseases like diabetes mellitus and atherosclerotic disease. The question arises then whether testosterone treatment has a role in the treatment of the metabolic syndrome and its sequels, e.g. diabetes mellitus type 2 and CVD. There is increasing evidence of a beneficial effect of testosterone treatment on visceral fat and other elements of the metabolic syndrome. Changes in visceral fat appeared to be a function of changes in serum total testosterone, and this was recently reviewed [38]. Several randomized controlled trials have confirmed the beneficial effects of testosterone on body composition and variables of the metabolic syndrome. In a study of weekly administration of testosterone enanthate 100 mg intramuscular there was significant increase in lean body mass and a decline of serum cholesterol level [39]. In an 8-month study of 23 middle-aged abdominally obese men, there was a decrease of visceral fat mass (with no change in body mass, subcutaneous fat mass or lean body mass). Insulin resistance improved and blood glucose, diastolic blood pressure and serum cholesterol level decreased with testosterone treatment. In a study of 108 men aged > 65 years, fat mass decreased and lean mass increased upon testosterone treatment [40]. The beneficial effects of androgens on (visceral) fat have been confirmed in other studies. Testosterone treatment increased lean body mass, decreased fat mass, decreased total cholesterol, low-density lipoprotein, and leptin in a study of 70 men over 36 months [41]. Testosterone therapy reduced insulin resistance and improved glycaemic control in hypogonadal men with type 2 diabetes [42]. Testosterone treatment selectively lessened visceral fat accumulation with no change in total body fat mass, and increased total-body fat-free mass and total body and thigh skeletal muscle mass in a study of men aged > 55 years assessed over 52 weeks [43]. A study of testosterone administration to a total of 207 men over 6 months reported an increase in lean body mass and a decrease in fat mass [44]. In a study of 32 hypogonadal (plasma testosterone < 12 nmol/L) men with the metabolic syndrome, with newly diagnosed type 2 diabetes mellitus, single-blindly randomized to diet and exercise alone (16 men) or to diet and exercise in combination with testosterone gel 50 mg once daily (16 men), and treated for 52 weeks, testosterone significantly improved glycaemic control, waist circumference and other variables of the metabolic syndrome, compared to diet and exercise alone [45]. In a recent study of hypogonadal men with the metabolic syndrome, there was a reduction in waist circumference and visceral fat mass, and improvement in insulin sensitivity measured with the 'homeostatic model assessment of insulin resistance', and reduced fasting glucose, with no changes in BMI [46]. Another recent study found significant decreases in weight, BMI and waist circumference in 184 men aged 35–70 years with lower-than-normal testosterone values, of whom 113 were treated with testosterone. Levels of leptin, insulin and some inflammatory markers also decreased [47].

Several observational studies confirmed the findings in the cited blinded placebo-controlled studies. Testosterone therapy given to adult men with acquired hypogonadism decreases subcutaneous fat and increases lean muscle mass. In a study over 30 months of men receiving treatment with testosterone gel, there was a decrease in fat mass and an increase in lean body mass [48]. Another recent study found an improvement in all elements of the metabolic syndrome, of liver steatosis and of C-reactive protein in 117 men treated over 1 year with testosterone [49].

Furthermore, testosterone reduces insulin levels and insulin resistance in men with obesity. A study in hypogonadal men with type 2 diabetes showed that testosterone replacement also improves glycaemic control, although this study was not blinded [3]. Testosterone substitution in hypogonadal men improves insulin sensitivity. In a recent Korean study, glucose levels were significantly reduced after 24 weeks of testosterone treatment in men with baseline glucose levels of ⩾110 mg/dL, while there was no change in men with baseline glucose levels of < 110 mg/dL [50]. By contrast, two studies replacing testosterone in men with diabetes type 2 and hypogonadism found little or no effect on glycaemic control [51,52], but another study analysing the effects of testosterone administration to 24 hypogonadal men (10 treated with insulin) aged > 30 years and with type 2 diabetes, found that testosterone replacement therapy reduced insulin resistance (as measured by the homeostatic model index) and improved glycaemic control in hypogonadal men with type 2 diabetes [42]. The cited study of Heufelder et al. [45] also reported an additional effect of testosterone to exercise and diet on glycaemic control in men with newly diagnosed diabetes

mellitus type 2. Two studies were unable to detect beneficial effects of administration of testosterone on glycaemic control [52,53]. So, while the evidence for powerful effects of normalisation of circulating levels of testosterone on glucose homeostasis so far is limited, there are studies showing that administration of testosterone can have favourable effects on glycaemic control and the metabolic sequels of diabetes mellitus.

Conclusion

Until a decade ago the ailments of elderly men, such as atherosclerosis, hypertension, diabetes mellitus, and ED, were regarded as distinct diagnostic/therapeutic entities, but there is a growing recognition that these entities are not disparate but interdependent in their aetiology. To improve the health of the ageing male, they require an integral diagnostic and therapeutic approach. Measurement of testosterone levels is pivotal to adequate health care in most of the ailments of ageing men. While this may be obvious in cases of ED, it should include conditions such as CVD and diabetes mellitus type 2. This might at first sight seem unorthodox to physicians treating patients with these conditions.

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