The Way to a Man's Heart is Through the Urologist's Office
ED, Cardiovascular Disease and Testosterone

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Testosterone is traditionally regarded as the hormone subserving male reproductive and sexual functioning. Testosterone appears to have a much wider role. It is involved in 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 aging, free testosterone levels more so than total testosterone. At least ten 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 (SHBG) predict a higher incidence of the metabolic syndrome. Administration of testosterone to hypogonadal men reverses part of the unfavorable risk profile for the development of diabetes and atherosclerosis. Urologists are in a unique position to include general aspects of men's health in their work.

Erectile dysfunction and cardiovascular disease are two faces of the same coin with androgen deficiency as the common denominator. This has recently authoritatively been reviewed.[1] One could say that ED is a local expression of the penile vasculature of generalized vascular pathology with a common pathological basis. The common underlying factor is endothelial dysfunction. Endothelial dysfunction which manifests itself clinically as impaired vasodilation 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 arteriosclerosis starts at the endothelium.[3]

The vascular endothelium is pivotal for vasodilation 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). It inhibits platelet aggregation and regulates vascular tone.[3]

Bioavailable NO can be increased by enhancing its production or reducing its inactivation. NO induces endothelial vasodilation by increasing the cyclic guanosine monophosphate (cGMP) content of vascular smooth muscle cells, resulting in relaxation. Cardiac risk factors including dyslipidemia, hypertension and type 2 diabetes, are all associated with impaired endothelial function.[3,4] Evidence is accumulating that ED is an early sign of cardiovascular disease. ED is an important marker of vascular disease throughout the arterial tree[5].

The Massachusetts Male Ageing Study, a random sample cohort study of men aged forty to seventy, investigated the relationship between baseline risk factors for coronary heart disease and subsequent ED, on the assumption that subclinical arterial disease might be manifested as ED. Overweight (defined as body mass index (BMI): >28 kg/m^2) and a composite coronary risk score also significantly predicted incident ED.[6]

Cardiovascular risk factors in mid life could predict the incidence of ED an average of twenty five years later. A study which assessed seven classic CHD risk factors in men aged thirty to sixty nine 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.[7]

Erectile function is viewed by almost all men as a significant component of quality of life[8] and erectile difficulties (ED) may be a reason to seek medical advice. As indicated above, several studies document now that there is a high concordance between the causes of ED and the causes of cardiovascular disease, this indirectly by demonstrating that there is an elevated prevalence of the metabolic syndrome and insulin resistance in a population of men with ED as compared to a general population of men.[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 may be found.[10]

The Massachusetts Male Aging Study (MMAS) equally revealed that erectile dysfunction was predictive of the metabolic syndrome. This study supports the idea that erectile dysfunction may 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 cardiovascular disease.[11]

The MMAS has also estimated the frequency of erectile dysfunction progression and remission among aging men, and assessed the relation of progression/remission to demographics, socio economic factors, comorbidities and modifiable lifestyle characteristics (Travison et al, 2007). Natural remission and progression occur in a substantial number of men with erectile dysfunction. Age and body mass index were associated with progression and remission of ED.

Interventions were non pharmacological which apparently impacted on remission and delaying progression of ED. The association of body mass index 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 improvement in sexual function in about one third of obese men with erectile dysfunction at baseline. Weight loss and increased physical activity appeared to have a favorable effect on erectile and endothelial functions in obese men.[12,13] The benefits of such interventions for overall men's health may be far reaching and support the view that ED is a portal to men's health.

Shabsigh and co-workers[14,15] have eloquently argued that ED can calculate men's health risks. Elements in the calculation of health risks (hypertension, diabetes, angina or hyperlipidemia) in men presenting with ED are: health status on a scale of 1 to 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 to 7. If the score is 1.5 to 2.5 = Medium Risk (30% to 59% probability); ≥2.5 = High Risk (≥60% probability of having the condition) and <1.5 = Low Risk (< 30% probability).[15]

A study with a similar message was conveyed by Corona et al[16] A recent paper argued that when, in the light of recent guidelines, prostate specific antigen (PSA) screening starts (≥ 40 years) to add screening for ED and hypogonadism. 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 of lipids, blood pressure, obesity and serum glucose.[10]

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. It was 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.[17] But 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.[18-21] There are androgen receptors in the human corpus cavernosum.[22]

Several studies show that testosterone plays a critical role in restoring and maintaining the penile trabecular smooth muscle structure and function[23-25] as well as regulating the cell apoptosis.[26] In line with this, Aversa et al[27] 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 emphasized the potential mechanism for veno occlusive dysfunction in androgen deficiency[28] (for review:18). A study by Corona et al[29] shows that pulse pressure as an index of arterial stiffness is associated with androgen deficiency and impaired penile blood flow in men with ED. Testosterone has a positive impact on hemodynamic processes and the veno occlusive properties in the penile trabecular tissues. Testosterone may repair venous leakage in hypogonadal patients and subjects with metabolic syndrome. The impact of a hormonal factor on veno occlusive properties of the corpora cavernosa indicates that restoration of testosterone to normal may repair mechanical damage of the corpora cavernosa.[30,31] This has also been found to be the case in laboratory animals.

In a well designed intervention study, Aversa et al[22] provided support for this mechanism of action of testosterone on the erectile tissues of the penis. They assessed the effects of androgen administration in twenty patients with arteriogenic ED (confirmed with dynamic colour duplex ultrasound), not responding to treatment with sildenafil 100mg. 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 PDE-5 inhibitors.

In line with the above, Foresta et al[32] have documented that normal plasma testosterone is required for erectile function. In severely hypogonadal men (plasma testosterone (<2.0 ng/mL) the nocturnal penile tumescence, ultrasound measurement of arterial carvernous inflow and visually stimulated erection in response to sildenafil 50mg or apomorphine 3mg were minimal. The responses to these pharmacological stimuli normalized after six months of administration of testosterone patches evidencing the significant role of normal levels of testosterone for erectile function.
The phosphodiesterase type 5 inhibitors (PDE5-Is) have revolutionized treatment of erectile dysfunction (ED). But 30% to 35% of patients fail to respond. Associated testosterone deficiency, not properly diagnosed, has been proposed as one of the reasons for failure. A number of studies suggest that the activity of PDE5-Is as a treatment of ED is androgen dependent. In rodents, castration reduces protein expression and activity of PDE 5, and testosterone treatment is capable of upregulation.[23,33] In addition, medical or surgical castration prevents the enhancing effect of PDE 5-Is on erections induced by electro stimulation of the cavernous nerves.[23,34] The expression of nitric oxide (NO) synthesis[35,36] is regulated by androgens. The expression of PDE 5 has been found to be androgen dependent, as well, in humans.[33]

In addition, several clinical studies suggest that testosterone deficiency is a risk factor for poor response to sildenafil.[20,37-42] Five uncontrolled studies have also reported beneficial effects of a combination therapy with testosterone and PDE 5-Is in men with ED and low or low to normal testosterone who previously had not responded to 100mg sildenafil[37,39,43,44] or 20mg tadalafil.[45,46]

In a well designed randomized placebo controlled trial, Rochira et al demonstrated that sildenafil is able to restore nocturnal erections of men with almost undetectable levels of testosterone to the same extent as testosterone replacement therapy though the combination was more powerful than either alone [47].

Testosterone and cardiovascular health

Until a decade ago, it was a widely held belief that androgens have an atherogenic effect and thus led to cardiovascular disease, and androgen administration was regarded as adding to the risk of developing cardiovascular disease. Over the last decade several papers have examined the relationship of androgens with cardiovascular disease and concluded that it is no longer tenable to regard testosterone as a culprit in the etiology of cardiovascular disease.[48-52] Recent epidemiological studies have found that low testosterone levels are a predictor of mortality in elderly men[53-56 57], particularly cardiovascular mortality.[58-60]

Over the last two years a large number of review papers have highlighted the significance of depressed levels of testosterone and cardiovascular disease.[16, 61-63] Both cross sectional and longitudinal epidemiological studies have convincingly established that low plasma testosterone/low SHBG are correlated with/predict the metabolic syndrome.[64-71] Testosterone deficiency afflicts approximately 30% of men ages forty to seventy nine years.[72] Numerous studies have found inverse associations between the severity of features of the metabolic syndrome and plasma testosterone.[73,74 75-78]

There is an inverse relationship between waist circumference, a reliable indicator of visceral obesity, and testosterone levels over all age groups.[79]

Adiposity with its associated hyperinsulinism suppresses SHBG synthesis and therewith the levels of circulating testosterone.[80,81] It also may affect the strength of LH signaling to the testis.[82] Further, insulin[83] and leptin[84] have a suppressive effect on testicular steroidogenesis. Visceral fat cells secrete a large number of cytokines which impair testicular steroidogenesis.[81,85,86] So, 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 induces the metabolic syndrome.[87,88] Low testosterone and SHBG levels appeared strongly associated not only with components of the metabolic syndrome, but also with the metabolic syndrome itself, independently of body mass index. Furthermore, sex hormones were associated with inflammation and body iron stores. Even in the absence of late stage consequences such as diabetes and cardiovascular disease, subtle derangements in sex hormones are present in the metabolic syndrome, and may contribute to its pathogenesis.[89]

The relative contributions of each of the individual National Cholesterol Education Program Adult Treatment Panel III components of the metabolic syndrome to low serum testosterone in aging men has been examined using multiple linear regression modeling. Based on these analyses the presence of diabetes or fasting serum glucose greater than 110 mg/dl, body mass index 30 kg/m^2 or greater, and triglycerides 150 mg/dl or greater each appeared to have a clinically relevant association with low serum testosterone.[75]

The issue of androgen deficiency and cardiovascular health and diabetes mellitus type 2 is very pressing for the urologist treating men with prostate cancer. The risks of development of atherosclerosis of androgen deprivation for prostate cancer have been addressed in a number of reviews[90-92], in particular the advisory of the American Heart Association[93]. Studies in men undergoing androgen deprivation treatment in prostate cancer show that within three months significant metabolic changes have occurred (a 43% increase in fat mass and a 26% increase in insulin levels)[94], confirmed in another study[95], and again in a more recent study finding that visceral fat accumulation was more closely linked to testosterone than to estradiol with insulin resistance as a secondary effect.[96]

In a ten week study of healthy lean men (23.2± 0.5 years), suppression of testosterone by a GnRH analog was associated with a marked decrease in measures of whole body protein anabolism, decreased strength, decreased fat oxidation, and increased adiposity.[97] 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 seven to ten[10] years. The odds ratio for future diabetes was 1.58 for a decrease of 1SD in free testosterone (4 ng/dl).[87]

In another study, the association of low levels of testosterone with the development of the metabolic syndrome and diabetes in men was studied. After eleven years of follow up, 147/702 men had developed the metabolic syndrome and fifty seven men, diabetes. Men with total testosterone, calculated free testosterone, and SHBG levels in the lower fourth had several fold increased risk of developing the metabolic syndrome and diabetes after adjustment for age.[88] Similar findings were found in a recent report.[98] These studies indicate that the degree of suppression of serum testosterone may 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[99] and strongly impairs glycemic control of men with diabetes mellitus.[100]

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

It is clear now that low testosterone levels are a factor in the etiology of common ailments of elderly men such as the metabolic syndrome and its associated diseases such as diabetes mellitus and atherosclerotic disease. The question arises then whether testosterone treatment has a role to play in the treatment of the metabolic syndrome and its sequels such as diabetes mellitus type 2 and cardiovascular disease.

There is increasing evidence of a beneficial effect of testosterone treatment on visceral fat and other elements of the metabolic syndrome.[101,102] Changes in visceral fat appeared to be a function of changes in serum

total testosterone[103] and have recently been reviewed.[104] A number of 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 100mg i.m. there was significant increase in lean body mass and a decline of serum cholesterol.[105] In an eight months study of twenty three middle aged abdominally obese men, a decrease of visceral fat mass (without a change in body mass, subcutaneous fat mass or lean body mass) was observed. Insulin resistance improved and blood glucose, diastolic blood pressure and serum cholesterol decreased with testosterone treatment.[106]

In a study of one hundred eight men, over sixty five years of age, fat mass decreased and lean mass increased upon testosterone treatment.[107] The beneficial effects of androgens on (visceral) fat have been confirmed in other studies,[108,109] the latter also finding an improvement of insulin sensitivity. Testosterone treatment increased lean body mass, decreased fat mass, decreased total cholesterol, low density lipoprotein, and leptin in a study of seventy men over thirty six months.[110]

Testosterone therapy reduced insulin resistance and improved glycemic control in hypogonadal men with type 2 diabetes.[111] Testosterone treatment reduced fat mass and abdominal adipose tissue and increased fat free mass in a one year study.[112] Testosterone treatment selectively lessened visceral fat accumulation without 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, over fifty five years of age, over fifty two weeks.[103] A study of testosterone administration to a total of two hundred seven men over six months reported an increase in lean body mass and a decrease in fat mass.[113] In a study of thirty two 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 (n=16) or to diet and exercise in combination with testosterone gel 50mg once daily (n=16) and treated for fifty two weeks, testosterone significantly improved glycemic control, waist circumference and other parameters of the metabolic syndrome compared to diet and exercise alone.[114]

In a recent study of hypogonadal men, with the metabolic syndrome, a reduction in waist circumference and visceral fat mass, and improvement in insulin sensitivity measured with HOMA-IR and reduced fasting glucose without changes in body mass index were observed.[115] Another recent study found significant decreases in weight, body mass index, and waist circumference in one hundred eighty four men between thirty five to seventy years of age, with lower than normal testosterone values, of whom one hundred thirteen were treated with testosterone. Levels of leptin, insulin and some inflammatory markers also decreased.[116]

A number of observational studies have confirmed the findings in the above blinded placebo controlled studies. Testosterone therapy given to adult men with acquired hypogonadism decreases subcutaneous fat and increases lean muscle mass.[117] In a study over thirty months, of men receiving treatment with testosterone gel, a decrease in fat mass and an increase in lean body mass was found.[118] In a recent Thai study of testosterone administration to one hundred sixty one hypogonadal men, over fifty four weeks, a decrease in body fat and waist circumference was found.[119] Another recent study found an improvement of all elements of the metabolic syndrome, of liver steatosis and of C-reactive protein in one hundred seventeen men treated over one year with testosterone.[120]

Furthermore, testosterone reduces insulin levels and insulin resistance in men with obesity. A study in hypogonadal men with type 2 diabetes has shown that testosterone replacement also improves glycemic control although this study was non blinded.[121] Testosterone substitution in hypogonadal men improves insulin sensitivity.[122] In a recent Korean study, glucose levels were significantly reduced after twenty four weeks of testosterone treatment in men with baseline glucose > 110 mg/dl while there was no change in men with baseline glucose < 110 mg/dl.[123]

By contrast, two studies replacing testosterone in men with diabetes type 2 and hypogonadism found little or no effect on glycemic control[124,125] but another study analyzing the effects of testosterone administration to twenty four hypogonadal men (10 treated with insulin) over the age of thirty years with type 2 diabetes found that testosterone replacement therapy reduced insulin resistance (as measured by homeostatic model index) and improved glycemic control in hypogonadal men with type 2 diabetes.[111]

The above referenced study of Heufelder et al[114] also found an additional effect of testosterone to exercise and diet on glycemic control in men with newly diagnosed diabetes mellitus type 2. So, while the evidence for powerful effects of normalization of circulating

levels of testosterone on glucose homeostasis so far is limited, there are studies to prove that administration of testosterone may have favorable effects on glycemic 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 erectile dysfunction, were regarded as distinct diagnostic/therapeutic entities but there is a growing recognition that these entities are not disparate but interdependent in their etiology. To improve the health of the aging male, they require an integral diagnostic and therapeutic approach.

Measurement of testosterone is pivotal to adequate health care in most of the ailments of aging men. While this may be obvious in cases of ED, it should include conditions such as cardiovascular disease and diabetes mellitus type 2. This may at first sight seem unorthodox to physicians treating patients with these conditions.

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