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Review Article

The Interplay Between Metabolic Syndrome, Testosterone Deficiency and Erectile Dysfunction in Men's Health

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Summary

Until a decade ago the ailments of elderly men, such as atherosclerosis, hypertension, diabetes mellitus, lower urinary tract symptoms and erectile dysfunction (ED), were regarded as distinct diagnostic/therapeutic entities but there is a growing awareness that these entities are not disparate and, to improve the health of the ageing male, require an integral approach. There is an inter-dependence between the metabolic syndrome, ED and patterns of testosterone in ageing men.

The main features of the metabolic syndrome are abdominal obesity, insulin resistance, hypertension and dyslipidemia, significant factors in the etiology of erectile function. Metabolic syndrome is associated with lower-than-normal testosterone levels. A new concept of the role of testosterone in male physiology suggests that testosterone plays also a significant role in the development and maintenance of bone and muscle mass and is a determinant of glucose homeostasis and lipid metabolism. Testosterone is not only a factor in libido but exerts also essential effects on the anatomical and physiological substrate of penile erection. With these recent insights, the health problems of elderly men must be placed in a context that allows an integral approach. Treatment of testosterone deficiency is to become part and parcel of this approach.

Keywords: Metabolic Syndrome, Testosterone Deficiency, Erectile Dysfunction, Dyslipidemia, Hypertension, Diabetes Mellitus

Introduction

The introduction in 1998 of a new class of drugs, the phosphodiesterase type 5 (PDE-5) inhibitors, has been a ground-breaking event. For the first time, a class of very efficacious drugs became available for the treatment of erectile dysfunction (ED). The research into the development of this class of drugs had led to new and profound insights into the anatomical and physiological substrate of penile erection.

The introduction came with substantial funding to define the proper place of the PDE-5 inhibitors in the treatment of male sexual dysfunction. It is no exaggeration to say that the introduction of this class of efficacious drugs was hyped as a cure-all. Inevitably, there were the failures. It is, however, very fortunate that research into the causes of therapeutic failures has led to a much more comprehensible understanding of male sexual dysfunction in general and of ED in particular. There is increasing insight not to view ED as a single diagnostic and therapeutic entity. Erectile difficulties provide often a window into the presence of pathology

in these areas. Rather than a disease, ED is, particularly in elderly men who have enjoyed normal sexual function earlier in life, a manifestation of pathologies of the biological systems involved in erectile function [1]. Circulating levels of testosterone are closely related to manifestations of other etiological factors in ED, such as atherosclerotic disease and diabetes mellitus and its complications. So, it is timely to take a much broader view at ED. This is not a theoretical academic issue but a diagnostic work-up leading to the formulation of successful treatment hinges on an integral view of ED.

New Perspectives on Testosterone

In recent times, the understanding and thinking about the (patho)physiological functions of testosterone have undergone a revolutionary development. It was well known that hypogonadism in men usually resulted in loss of libido and potency which could 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 investigations [2]. Recent studies provide convincing evidence that there is a powerful effect of testosterone on the anatomical and physiological substrate of penile erection. The experience with PDE-5 inhibitors has taught that their effect is only optimal if men have normal circulating testosterone levels attesting to the essential effects of testosterone on the anatomical and physiological substrate of penile erection. While the significance of testosterone for male reproductive/sexual functioning has been obvious to most physicians, they now need to familiarize themselves with the insight that testosterone plays a significant role in the development and maintenance of bone and muscle mass, with the fact that testosterone has a positive effect on erythropoiesis and on mental functions. The latter is not limited to libido, but testosterone has a general vitalizing function on mood and energy. Even more recent are the insights that testosterone is a key player in glucose homeostasis and lipid metabolism. Physicians will have to make a change of their mindset that testosterone, rather being a dangerous companion to a man's life, bringing joy but exacting its toll, is a vital hormone for men's health, from early prenatal development to the end of a man's life. Earlier it has been questioned whether testosterone has an essential role to play in male physiology [3]. could not establish that the so-called castrati singers (boys castrated at the very beginning of their puberty to preserve the properties of their boy's voice) lived shorter than no castrated singers. But recent epidemiological studies have found that low testosterone levels are a predictor of mortality in elderly men [4-8].

Another study could not confirm this [9], but, while disagreeing on the relationship of plasma testosterone and overall mortality, the latter study agreed that a low testosterone level was predictive of mortality from ischemic heart disease.

Obviously, epidemiological studies cannot unravel cause-relationships, but the evidence is convincing that the decline in testosterone levels with ageing is accounted for rather by (age-related) disease than the calendar age of men. Intervention studies provide potential answers to the causality of the relationship. It is no exaggeration to say that in modern medicine and endocrinology testosterone is no longer a marginal hormone. The following sections will deal with recent information on the relationship between testosterone and metabolic syndrome.

The Metabolic Syndrome and Its Relationship with Testosterone

The main components of the metabolic syndrome are abdominal obesity, insulin resistance, hypertension and dyslipidemia. There is a debate in the literature whether combining these components or conditions has an added diagnostic or prognostic value. Metabolic syndrome is not a disease by itself, but it is rather a pathway to disease. A clinical investigation analyzing 11 prospective European cohort studies of 6156 men with a median follow- up of 8.6 years found that nondiabetic persons with the metabolic syndrome had increased risk of death of all causes as well as cardiovascular disease [10]. The West of Scotland Coronary Prevention Study followed 6000 men for periods over 5 years and found that men with four or five features of the metabolic syndrome had a 3.7-fold increase in coronary heart disease events and, even more strikingly, a 24.5-fold increase in new onset diabetes [11]. Atherosclerosis and diabetes mellitus are significant etiological factors in ED.

Until recently, it was a widely held belief that androgens have an atherogenic effect and thus lead 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 [12-16]. Indeed, cross-sectional studies of middle-aged men have found a direct, rather than an inverse, relationship between plasma testosterone and plasma HDL cholesterol, as well as an inverse relationship between plasma testosterone and visceral fat volume [17-21]. This relationship appears to be independent of age [22]. Furthermore, earlier cohort studies linked low testosterone levels to increased cardiovascular risk and type 2 diabetes [23]. There are also several long-term observational studies showing that lower blood levels of testosterone in men are associated with accelerated atherosclerosis in carotid arteries and aorta using noninvasive imaging techniques, which further supports the notion that low testosterone level is pro-atherogenic [24-26]. After these initial cross-sectional studies, the number of longitudinal studies were able to confirm that low testosterone levels and of SHBG were predictive of the metabolic syndrome, not only in obese men but also in men with a BMI <25 kg m)2 [27-29]. The same applied to the risks of developing diabetes mellitus type 2 [30-32]. In conclusion, the scientific evidence that there is

association between low testosterone/low SHBG levels, and the metabolic syndrome is beyond any reasonable doubt now. The cause-and-effect relation remains, however, a subject of further study.

Effects of Testosterone on the Metabolic Syndrome

Testosterone inhibits the expression of the activity of lipoprotein lipase, the main enzymatic regulator of triglyceride uptake in the fat cell, preferentially in abdominal fat. Several studies have indeed confirmed that testosterone treatment reduces the waist circumference which, in its simplicity, appears to be a valid parameter of the degree of visceral obesity [33,34]. A study of testosterone administration restoring testosterone levels to mid-normal values with a duration of 8–9 months found a decrease of the visceral fat mass, a decrease of fasting glucose and lipid levels and an improvement of insulin sensitivity; in addition, a decrease in diastolic blood pressure was observed [35]. In a study by [36], testosterone administration improved body composition (reduction in trunk fat, increase in lean body mass, improvement of plasma triglycerides, total cholesterol and LDL, no impairment of HDL). Testosterone therapy reduced insulin resistance and improved glycemic control in hypogonadal men with type 2 diabetes, with improvements of cholesterol and visceral adiposity which together represent an overall reduction in cardiovascular risk, confirming an earlier study [37]. As indicated above, also in our own studies, signs and symptoms of the metabolic syndrome had improved substantially following administration of long-acting testosterone undecanoate (TU) [38-41].

While these effects of testosterone might be indirect (via an improvement of body composition: less adipose tissue, more lean body mass), there is also evidence that testosterone directly improves insulin sensitivity [42,43].

Effects of Testosterone-Only Therapy to Elderly Men with Erectile Dysfunction

In a recent study [44], investigated the effects of restoring testosterone levels to normal with long-acting TU, in 22 hypogonadal men (mean age:58 years) with complaints of low sexual desire and ED. TU is a novel parenteral testosterone preparation and its clinical use and safety are now well documented. Fifteen patients had low serum testosterone and there were significant co-morbidities. In all patients, serum testosterone levels were restored to normal within 6–8 weeks following administration of TU. Twelve patients reported significant improvement in the sexual desire domain of the International Index of Erectile Function (IIEF) following treatment with this long-acting testosterone. In 9 of 12 patients this occurred only after at least 12–24 weeks, so there is a latency before the beneficial effects of TU become manifest. The remaining 10 patients reported an improvement of sexual desire but no significant improvement in erectile function. No changes in serum prostate specific antigen (PSA) or prostate volume were noticed in patients receiving this long-acting testosterone preparation [45]. So, it appeared that restoring testosterone levels to normal in men with proven subnormal testosterone levels improves libido in most subjects and erectile function in more than 50% of these men. An important clinical observation was that it may take 12–24 weeks before the effects of testosterone become manifest, so treatment with testosterone must not be regarded as unsuccessful after too short periods of administration [44]. This encouraged the authors to extend their observation to a larger group of 771 patients consulting for ED [44,46]. The average period they had suffered from ED was 3.6 years. A total of 141 turned out to be hypogonadal men (18.3%, mean age: 56 years). Of these 141 men, 122 received i.m. injections of long-acting TU at day 1, again after 6 weeks and thereafter every 3 months and were prospectively evaluated for a mean of 5 months (3– 11 months). Digital and sonographic examinations of the prostate were performed every 3 months. Following treatment for at least 12 weeks of the total of 122 patients, 71 patients reported significant improvement in the sexual desire domain, and in the erectile function domain. The remaining 51 patients who had suffered from ED longer than 7 years reported an improvement of sexual desire but no significant improvement in the erectile function domain, even though their testosterone values were normalized [46, 38]. Not only sexual functions had improved following treatment with long-acting TU but also several features of the metabolic syndrome had improved, such as waist circumference, lipid profiles, glycemic control and blood pressure [38]. No significant alterations in prostate parameters have been noticed so far.

These results confirmed that testosterone-only therapy restored erectile function in the majority of the hypogonadal patients of this group, particularly in patients whose complaints of ED had not been longstanding. The success of testosterone treatment is less in men with co-morbidities, but also in the latter men significant improvements are observed. These results suggest that testosterone should be considered more often as first-line therapy in hypogonadal men, also in elderly men [46,47]. In case the treatment with testosterone is not successful, PDE-5 inhibitors or the combination of PDE-5 inhibitors with testosterone might be helpful [16, 48]. Within the observation period, we did not see any side-effects of testosterone administration.

Erectile Dysfunction is a 'Portal' to Men's Health

The above has demonstrated a close relationship between ailments frequently occurring in the ageing male (visceral obesity, cardiovascular disease, diabetes mellitus and ED) on the one hand and hypogonadism on the other. In view of this close relationship late-onset hypogonadism is probably an expression of poor health with a high-risk profile for debilitating diseases. Men usually are in denial of ailments at all ages, but certainly also when they are ageing. Erectile function is viewed by almost all men as a significant component of quality of life [49] and erectile

difficulties may be a reason to seek medical advice. 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 with a general population of men [50]. The 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. The prestigious Massachusetts Male Aging Study (MMAS) equally revealed that ED was predictive of the metabolic syndrome. This study supports the idea that ED 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 [51].

Shabsigh et al. (16,2006, 2008) [16, 52] have eloquently argued that ED can calculate men's health risks. The men's health calculator is intended to raise awareness about cardiovascular disease and diabetes risk. It is intended to be easy, short, quick and suitable for both print and Internet. The four questions address different aspects of body functions and health. These questions were derived from the MALES study that included many subjects in eight countries. Elements in the calculation of health risks (hypertension, diabetes, angina or hyperlipidemia) in men presenting with ED are health status on a scale of 1–7 (1 = excellent, 7 = poor), waist circumference, severity of ED, presence/absence of a sexual partner. The calculation produces scores of ranges 1–7. A score of 1.5–2.5 indicates medium risk (30–59% probability); ‡ 2.5 high risk (60% probability of having the condition) and < 1.5 low risk (< 30% probability).

Conclusion

Sexual health may be a portal to men's health. Hypogonadism and ED are epidemiologically associated and may predict metabolic syndrome and type 2 diabetes. More interventional studies are needed to determine the relationship between testosterone and diabetes mellitus and the metabolic syndrome and to assess the benefit/risk ratio of testosterone therapy in men with hypogonadism, diabetes and the metabolic syndrome. Treatment of ED may entail testosterone administration [53] and these interventional studies may provide an opportunity to determine therapeutic and preventive feasibility, benefits and justification of testosterone administration on the closely interrelated ailments of ED and the metabolic syndrome of which epidemiological hypogonadism is a correlation.

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