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Review Article

The Relationship between Testosterone Deficiency and Men's Health

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Testosterone is important in the physiology of various organs and tissues. The serum testosterone concentration gradually declines as one of the processes of aging. Thus, the concept of late-onset hypogonadism has gained increasing attention in the last few years. Reported symptoms of late-onset hypogonadism are easily recognized and include diminished sexual desire and erectile quality, particularly in nocturnal erections, changes in mood with concomitant decreases in intellectual activity and spatial orientation, fatigue, depression and anger, a decrease in lean body mass with associated decreases in muscle volume and strength, a decrease in body hair and skin alterations, and decreased bone mineral density resulting in osteoporosis. Among these various symptoms, sexual dysfunction has been the most common and necessary to treat in the field of urology. It is well known that a low serum testosterone level is associated with erectile dysfunction and hypoactive sexual libido and that testosterone replacement treatment can improve these symptoms in patients with hypogonadism. Recently, in addition to sexual dysfunction, a close relationship between metabolic syndrome, characterized by central obesity, insulin resistance, dyslipidemia, and hypertension, and late-onset hypogonadism has been highlighted by several epidemiologic studies. Several randomized control trials have shown that testosterone replacement treatment significantly decreases insulin resistance in addition to its advantage for obesity. Furthermore, metabolic syndrome is one of the major risk factors for cardiovascular disease, and a low serum testosterone level is closely related to the development of atherosclerosis. Presently, it is speculated that a low serum testosterone level may increase the risk for cardiovascular disease. Thus, testosterone is a key molecule in men's health, especially that of elderly men.

Key Words: Testosterone; Hypogonadism; Erectile dysfunction; Atherosclerosis; Cardiovascular diseases

INTRODUCTION

Testosterone exerts most of its biological action through binding with androgen receptors located in the nucleus of the target cells. It is well known that testosterone is important in the physiology of various organs and tissues in which androgen receptors are located, such as such as the skin, muscle, liver, bone and bone marrow, brain, and sexual organs. However, as one of the processes of aging, the serum testosterone concentration gradually declines by 1.6% per year with aging, especially after 40 years of age. Thus, the maintenance of a physiologic concentration

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of serum testosterone, even in elderly men, has received widespread attention because low serum testosterone levels have been associated with increased mortality in male veterans.[1] In this regard, the concept of late-onset hypogonadism (LOH) has come to the forefront in the last few years. LOH has been defined as 'a clinical and biochemical syndrome associated with advancing age and characterized by typical symptoms and a deficiency in serum testosterone levels' by the International Society of Andrology (ISA), the International Society for the Study of the Aging Male (ISSAM), and the European Association of Urology (EAU) in 2005.[2] The European Male Aging Study of 2,966 middle-aged and elderly men found a rate of LOH (serum total testosterone level of <3.2 ng/ml, free testosterone level of <64 pg/ml, and at least three sexual symptoms) in 2.1% of men between 40 and 79 years of age.[3] In Japan, a clinical practice manual for LOH has also been written and published by a collaborative team from the Japanese Urological Association (JUA) and the Japanese Society for the Study of the Aging Male (JSSAM) to recommend standard procedures for diagnosis, treatment, prevention, and monitoring of adverse reactions due to testosterone replacement therapy (TRT), and for post-treatment assessments.[4] Reported symptoms of LOH are easily recognized and include diminished sexual desire and erectile quality, particularly in nocturnal erections, changes in mood with concomitant decreases in intellectual activity and spatial orientation, fatigue, depression and anger, a decrease in lean body mass with associated decreases in muscle volume and strength, a decrease in body hair and skin alterations, and decreased bone mineral density resulting in osteoporosis.[5-10] Among these symptoms of LOH, sexual dysfunction has been the most common and necessary to treat in the field of urology. Recently, in addition to sexual dysfunction, the close relationship between LOH and metabolic syndrome (MS), characterized by central obesity, insulin resistance, dyslipidemia, and hypertension, has been highlighted by several epidemiologic studies. It is well known that MS is common and is associated with several lifestyle diseases, but the most important reason that MS has gained attention in the field of public health is its association with an increased risk of cardiovascular disease (CVD). Thus, it is reasonable that the relationship between testosterone and CVD has also received increased attention.

In this review, we focus on the relationship between the serum testosterone level and three diseases - sexual dysfunction, metabolic disease, and CVD - in terms of men's health.

SEXUAL DYSFUNCTION

In general, sexual dysfunction significantly affects men's quality of life. Sexual dysfunction, in particular hypoactive sexual dysfunction, reduced nocturnal and morning erections, erectile dysfunction (ED), delayed ejaculation, and reduced semen volume, are prominent and often the presenting symptoms in men with low testosterone level. Among several sexual symptoms, erectile function has gained the most attention and has been considered to be most associated with the serum testosterone level. It is also known that a low serum testosterone level is rarely the major cause of ED in the aging male, although hormonal alterations may play a subsidiary role in many cases of ED. However, it is generally accepted in the clinical setting that castrated men have impaired erectile function and that normal erection depends on testosterone, as many animal studies have provided evidence of the role of testosterone in erectile function.[11-14] Furthermore, it was reported that nocturnal erection is also substantially weaker in patients with a low serum testosterone level than in men with a normal serum testosterone level,[15] although where and how testosterone acts in the erection process remain to be elucidated in humans. We previously reported that the International Index of Erectile Function-5 score for erectile function increased significantly with increases in serum testosterone in a study of 130 men with symptoms of sexual dysfunction.[10] The fundamental importance of testosterone at most levels of the pathways that serve penile erection, from the cortex through the midbrain and spinal cord to the smooth muscle cells and endothelial function, gives the consideration of testosterone status a significant place in the management of most patients with ED. With respect to the mechanism of testosterone in the improvement of erectile function, an animal study showed that testosterone has a clear and major role in maintaining nitric oxide synthase activity peripherally.[16] In humans, it was also reported that admin-

istration of testosterone undecanoate resulted in a restoration of plasma testosterone levels in hypogonadal ED patients and improved sexual attitudes and performance in 61% of subjects.[17] A significant improvement of erectile function in comparison to a placebo was found in a meta-analysis of 17 randomized controlled trials (RCTs) of middle-aged and elderly men with low testosterone levels.[18] In general, the first choice of treatment for ED has been administration of a selective inhibitor of phosphodiesterase type 5 (PDE5-I) since the introduction of sildenafil citrate. Although oral PDE5-Is are a well-tolerated treatment for ED, the specific patient population considered challenging to treat with respect to PDE5-I therapy includes patients with severe neurologic damage such as that resulting from radical prostatectomy, diabetes mellitus, and severe vascular disease.[19] Therefore, additional therapeutic strategies are needed to overcome this problem. In this regard, it has been reported that TRT can restore erections in men who had originally showed no response to PDE5-I[20,21] and that it is especially beneficial only in hypogonadal men with a baseline total testosterone level of <3 ng/ml, as found in a RCT.[22] At present, there is no doubt that a testosterone preparation may be an additional tool in the treatment of ED, together with PDE5-I.

Hypoactive sexual desire is another prominent and often the presenting symptom along with ED. Low or absent libido might be due to a decreased testosterone level, but it could also be a consequence of psychogenic factors, other substances, or chronic illness. Indeed, urologists are familiar with the rapid disappearance of the libido in men treated with medical or surgical castration, although there are some men in whom sexual interest is preserved. Several cross-sectional studies have shown a significant association between serum testosterone concentration and the level of sexual desire in aging outpatients[23,24] and men with ED.[25,26] A longitudinal study also showed a close relationship between the serum testosterone level and sexual desire.[27] The Olmsted County Study, with its large number of subjects, showed an association between a higher testosterone level and an increase in sexual desire.[28] When reduced sexual desire is primarily due to hypogonadism, two meta-analyses of RCTs demonstrated a significant improvement in sexual desire after TRT.[25,26] Therefore, it is believed that a physiological serum testosterone level is essential for normal sexual desire. Another sexual symptom associated with testosterone other than ED and hypoactive sexual desire is ejaculatory dysfunction. However, the relationship between testosterone and ejaculatory function remains mostly speculative,[29] although it is well known in the clinical setting that testosterone contributes to the volume of ejaculate and the quality of the emission. Ejaculatory dysfunction such as delayed ejaculation or anejaculation is the least studied and least understood of sexual dysfunctions because of the relative rarity of the condition and the absence of effective treatments. A testosterone preparation may be the only tool for treatment. Indeed, regarding the efficacy of TRT in treating ejaculatory dysfunction, a significant improvement in ejaculatory ability was found in depressed men with low testosterone levels who continued to take serotonergic antidepressants. Taken together, testosterone is closely related to several kinds of sexual dysfunction such as ED, hypoactive sexual desire, ejaculatory dysfunction, and orgasmic dysfunction.[30]

METABOLIC DISEASES

MS is characterized by central obesity, insulin resistance, dyslipidemia, and hypertension and is another disease syndrome affecting quality of life that is receiving increased attention in the fields of medicine and public health.[31] The pathogenesis of MS is multifactorial, but the first step may be central obesity because this has been linked to hypertension, increased serum low-density lipoprotein (LDL), low serum high-density lipoprotein (HDL), and hyperglycemia.[31] A close inverse relation was reported to exist between serum testosterone levels and the degree of obesity in men.[32,33] In particular, it was emphasized that central obesity is inversely related to serum testosterone level.[34-36] It was previously reported that in elderly men, lean body mass and muscle mass correlate with the serum free testosterone level.[37-39] Furthermore, it is accepted clinically that obesity contributes to the onset of diabetes mellitus, which is one of the diagnostic factors for MS.

Regarding diabetes, it is well known in urology that androgen deprivation therapy for patients with prostate cancer increases insulin resistance,[40,41] and indeed, the serum

total testosterone level is inversely related to the insulin concentration and insulin resistance in men.[42] Several epidemiological studies in men have shown that a close association between a low serum testosterone level and type 2 diabetes mellitus (T2DM) has been reported.[43-45] Recently, it was reported that about a third of men with T2DM present with LOH.[46] However, the more interesting finding than that of a close relationship between low serum testosterone level and T2DM in cross-sectional studies is the fact that a low serum testosterone level is a precursor for the incidence of insulin resistance and T2DM, as shown in longitudinal studies of healthy men.[47-49] When the efficacy of TRT for diabetes is considered, three recent large RCTs consistently showed a significant decrease in insulin resistance,[50-52] although testosterone-induced changes in glucose metabolism still appear inconsistent and less pronounced than would be expected.

As for an association between a low serum testosterone level and lipids, an increase in serum cholesterol, LDL cholesterol, and triglycerides, and a decrease in HDL cholesterol were found in men with prostate cancer receiving androgen ablation treatment.[53] The efficacy of TRT for lipid metabolism as well as for insulin resistance has been reported by recent meta-analyses of RCTs with middle-aged and elderly men such that exogenous testosterone reduced the serum level of total cholesterol and LDL cholesterol.[18,54]

With regard to hypertension, it has also been argued that an inverse relationship between the serum testosterone level and blood pressure exists, although the effect of testosterone on blood pressure is still unclear. It was first reported that transdermal testosterone showed a significant reduction in the diastolic blood pressure in abdominally obese men.[55] Another study showed a significant reduction in both systolic and diastolic blood pressure by TRT for men with osteoporosis.[56] Furthermore, TRT combined with diet and exercise was more effective for antihypertensive activity than was treatment with diet and exercise alone in men with MS.[57] A prospective study demonstrated that a low serum testosterone level at baseline predicts the development of high blood pressure.[58] The European Male Aging Study of 2,966 middle-aged and elderly men showed that men with LOH had a higher Body Mass Index (BMI), higher waist circumference, lower HDL cholesterol, higher triglycerides, higher systolic blood pressure, and higher glucose, insulin, and homeostasis model assessment-estimated insulin resistance (HOMA-IR) values.[59] Conversely, the odds ratios of having a low serum testosterone level were significantly higher in men with hypertension (1.84), hyperlipidemia (1.47), diabetes (2.09), and obesity (2.38) in a study with more than 2,000 men aged at least 45 years old.[60] Taken together with the other studies reviewed in this article, it is strongly speculated that a low serum testosterone level is associated with several metabolic factors individually, including obesity, hyperglycemia, hyperlipidemia, and hypertension, although the mechanism for this association has not been sufficiently elucidated.

Although TRT was expected to be a new strategy for the treatment for MS, concern exists regarding the change in the serum adiponectin level that might be caused by TRT. Adiponectin is the most abundant of the adipocytokines and exerts profound anti-diabetic, anti-atherogenic, and anti-inflammatory effects, and is also believed to be a key molecule in the etiology of MS.[61,62] Worryingly, the serum adiponectin level is inversely related to the testosterone level in rodents.[63] It was reported in a relatively young population that serum adiponectin levels in hypogonadal men are significantly higher than those in eugonadal men and that at 6 months after initiation of TRT, which increased the serum testosterone levels to the normal range, the adiponectin levels were significantly reduced in the hypogonadal men.[64] Thus, the advantage of TRT for MS has been controversial because TRT may worsen MS as a result of decreased levels of adiponectin. Regarding this point, we reported previously that no inverse relation exists between adiponectin and testosterone levels in symptomatic older patients with LOH and that TRT does not affect adiponectin levels in older men.[65] Thus, TRT, particularly in patients with LOH, does not appear to pose a large risk of inducing MS as a result of a decrease in serum adiponectin levels. At present, TRT may be one optional treatment for MS, although additional studies with larger numbers of patients will be necessary to confirm its safety and efficacy.

Low serum testosterone is associated not only with the individual components of MS but also with MS itself. Low serum testosterone levels have been reported to be directly

associated with MS in cross-sectional[66] and longitudinal studies.[67] Several recent studies have shown that the serum testosterone level is significantly lower in those with MS than in those without MS.[68,69] A recent meta-analysis of studies comprising a large number of subjects with MS also showed that the serum testosterone level was lower in men with MS than in men without MS (mean difference, −2.64 nmol/L; 95% confidence interval [CI], −2.95 to −2.32).[70] Similar findings were reported not only in studies with Caucasian men but also in studies with Asian men. A study of middle-aged Japanese men who underwent general health checks showed that the serum testosterone level was also significantly lower in the group with MS than in that without MS, and the testosterone level decreased significantly in accord with an increase in the number of MS components present.[71] That study further showed that after adjustment for age, BMI, and waist circumference, the testosterone level was still significantly correlated with MS. Another study with middle-aged Japanese men also showed that a low serum testosterone level was significantly related to each of the individual factors of MS by age-adjusted regression analyses.[72] We also found that a higher probability of MS was clearly associated with a lower level of serum total testosterone in an age-adjusted logistic model comprising 1,150 healthy middle-aged men. Interestingly, a clinical value of serum testosterone as a predictive factor for the development of MS was recently reported; a meta-analysis of longitudinal studies showed that the baseline testosterone level was 2.17 nmol/L lower in men with incident MS compared with controls ($p < 0.0001$).[73] At present, it is well accepted that a low serum testosterone level has emerged as a reliable prognosticator of MS in men whose testosterone deficiency is genetic or iatrogenic following surgery,[67,74,75] or pharmacologically induced by gonadotropin-releasing hormone during prostate cancer treatment.[76]

CARDIOVASCULAR DISEASE

In the past, testosterone was believed to have adverse effects on cardiovascular function. However, a cross-sectional epidemiological meta-analysis has shown that the serum testosterone level is low in patients with CVD.[77] Interestingly, the association between a low serum testosterone level and CVD in that study did not lessen in a logistic regression model after adjusting for age, BMI, diabetes, and hypertension. Recent review papers have also highlighted the significance of a decreased serum testosterone level and CVD.[78,79]

Atherosclerosis is known to be major risk factor for CVD. To assess atherosclerosis, flow-mediated dilation (FMD) of the brachial artery and intima media thickness (IMT) of the carotid artery have been used clinically as measurable markers because it is difficult to routinely measure the presence of calcified aortic plaques.[80] An association of a low testosterone level with decreased FMD in men with high risk factors for CVD was already reported from a Japanese research group.[81] Several other studies of men have shown similar findings, in that lower serum total and/or free testosterone levels are significantly associated with decreased FMD.[82,83] An inverse association of IMT with the serum testosterone level has also been reported in a study of several specific types of subjects such as very old men,[84] men with T2DM,[85] and obese men with glucose intolerance.[86] Recently, a large population-based study of men also showed the serum total testosterone level to be inversely associated with age-adjusted IMT.[87] In that study, a logistic regression model adjusted for the confounding effect of CVD risk factors showed that men with testosterone levels in the lowest quintile had an independent odds ratio (1.51) of being in the highest IMT quintile.[87] Another recent study of middle-aged men with testosterone deficiency reported that IMT correlated inversely with the serum testosterone level in multivariate models adjusted for age and several lifestyle and metabolic factors.[80] We also found that a lower serum free testosterone level was associated with a higher level of IMT in middle-aged Japanese men and that this association did not attenuate in the multivariate model adjusted for age and several clinically relevant factors.[88] Interestingly, a longitudinal study also found men with a low serum testosterone level to have elevated IMT during a 4-year follow-up period.[89] Other than the FMD and IMT findings, it is known that men with a low serum testosterone level have low levels of circulating endothelial progenitor cells, which play a key role in repairing and maintaining endothelial function and are reduced in men with CVD.[90,91] Interestingly, it was reported that TRT can increase the lev-

el of circulating endothelial progenitor cells in men with hypogonadism.[92] Thus, at present, it is believed that testosterone is a molecule important in the development of atherosclerosis.

It is speculated that testosterone can improve cardiac ischemia by acting as a coronary vasodilator because it was already proven that acute administration of testosterone at even physiological concentrations directly into coronary vessels in men undergoing cardiac catheterization increases coronary blood flow and coronary vasodilatation in a dose-dependent manner.[93] RCTs have shown that TRT prolongs the time to 1-mm ST depression during exercise testing[94] and improves the time to ST depression in hypogonadal men with chronic stable angina.[95,96] In middle-aged Japanese men with coronary risk factors, a follow-up study also showed that a low serum testosterone level is associated with cardiovascular events.[97] An RCT has shown that a physiological level induced by chronic administration of a testosterone preparation improves both cardiac condition in men with congestive heart failure and exercise tolerance in men with coronary heart disease.[98] Indeed, it has been reported that low serum testosterone levels are associated with increased cardiovascular mortality in men.[99-101] To estimate the predictive value of the serum testosterone level for all types of CVD morbidity and mortality, a meta-analysis of 19 prospective studies of elderly men was conducted in which testosterone was found to have a weak independent protective effect with an estimated relative risk of 0.89 (CI 0.83~0.96) for a change of 1 standard deviation in serum testosterone level.[102] Thus, nowadays, the concepts that a low serum testosterone level may increase the risk of developing CVD and that TRT may have a beneficial effect on CVD are widespread because several interventional studies have shown favorable results. At least, it has gradually become accepted that testosterone deficiency is a marker of early death in men and is closely associated with the presence and degree of atherosclerosis, although it is still unclear whether testosterone deficiency is a cause or consequence of atherosclerosis.

CONCLUSIONS

There is no doubt that testosterone is one important factor for men's health in this aging society. Special care must be taken with regard to MS and CVD in elderly men with a low serum testosterone level, although prospective, long-term, placebo-controlled interventional studies are required to confidently conclude that TRT is truly effective in the treatment of MS and CVD as well as of sexual dysfunction.

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