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Testosterone: clinical relevance in ageing men

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Summary

Testosterone production declines with age in men. The decline is associated with several risk factors and diseases, including obesity and cardiovascular and metabolic diseases, diminished muscular, cognitive and sexual function and changes in body composition. Androgen treatment in elderly men has mostly been addressed in small short-term studies, and larger long-term investigations with sufficient statistical power are still needed for a proper evaluation of the benefit-risk-ratio of testosterone treatment. Current data do not support testosterone supplementation in healthy, asymptomatic older men with normal or low-normal testosterone levels. Treatment may be beneficial in older men with clear hypoandrogenic symptoms, especially reduced libido, erectile dysfunction and decreased muscle strength, if testosterone concentration is consistently low, and the patient selection, counselling and follow-up are adequate.

Key words: testosterone, aged, mortality, macrovascular disease, obesity, diabetes mellitus, cognitive function, frailty, fractures, late-onset hypogonadism.

Introduction

Testosterone (T) concentrations decline in older men, and lower T levels have been associated with increased incidence of adverse clinical conditions, including decreased sexual function and cardiovascular, metabolic and central nervous system diseases.[1] Our knowledge on these issues is mainly based on association studies unable to demonstrate cause-and-effect relationships, and only a limited number of prospective studies have been performed. In addition to age, T production is influenced by several lifestyle factors and co-morbidities. Late-onset hypogonadism (LOH), instead of andropause or male menopause, is the currently recommended term for the development of hypogonadism with ageing.[2] In this review, we first summarize briefly the physiology of T production in ageing men, and then discuss the association of T with mortality and common diseases affecting elderly men.

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Basic physiology of testosterone

T, the most important male sex hormone, is synthesized by the interstitial Leydig cells of the testis under regulation of the gonadotrophin luteinizing hormone (LH). T, or its metabolite 5α-dihydrotesterone (5α-DHT), are essential for all masculine functions of the body, including sexual differentiation, development of secondary sex characteristics, spermatogenesis, the masculine features of the muscle–bone apparatus, male-pattern hair distribution and male sexual behaviour.[3] A single regulatory step, the binding of T or 5α-DHT to the androgen receptor, is able to evoke this variety of structural and functional responses.

Testicular androgen synthesis starts from cholesterol, originating from multiple sources: (a) *de novo* synthesis from acetyl coenzyme A, (b) stored cholesteryl esters, (c) exogenous lipoprotein-supplied cholesterol and (d) plasma membrane-derived cholesterol following hormonal stimulation.[4] The next critical and LH-regulated step is the rapid transfer of cholesterol from the outer to the inner mitochondrial membrane, mediated by two carrier proteins, the steroidogenic acute regulatory protein (StAR)[5] and the peripheral-type benzodiazepine receptor (PBR).[6] The first and rate-limiting step of steroid biosynthesis at the mitochondrial inner membrane is the conversion of cholesterol to pregnenolone, catalysed by the cytochrome P450 cholesterol side chain cleavage enzyme (CYP11A1) and auxiliary electron transferring proteins. For the following steps, pregnenolone is translocated to

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the smooth endoplasmic reticulum, to be converted via 17-hydroxypregnenolone, dehydroepiandrosterone (DHEA) and androstenedione to T.

The daily T production is 6–7 mg and about 95% of it originates from the testes, the rest through peripheral conversion of adrenal androgenic precursors to T. The testis also produces small amounts of 5α-DHT, but most of this hormone is formed in peripheral androgen target tissues. Likewise, a small proportion of androstenedione and T are aromatized to oestrogens and they seem to have important physiological functions both within the testis and extragonadally,[7] in particular in bone formation and the hypothalamic feedback regulation of gonadotrophins.

The secretion of steroid hormones is assumed to be a passive process due to their lipid solubility and ease of transit through cell membranes. Accordingly, there is no intratesticular storage of bioactive steroid hormones, except for their sulphate conjugates, and the regulation of circulating steroid hormone concentrations occurs mainly at the level of their biosynthesis. There is diurnal variation in T secretion due to night-time accentuation of LH secretion.[8] Secretion pulses of serum T after the LH secretion peaks (average interval of 2 h) are inconsistent, apparently due to sluggish response of human testicular steroidogenesis to acute gonadotrophin stimulation,[9] and to the buffering effect of steroid hormone binding to plasma transport proteins.[10]

In circulation, the majority of T is bound to sex-hormone-binding globulin (SHBG, 44%), and albumin (54%), and only about 2% appears in unbound free form. Only free T is biologically active, i.e. able to penetrate to androgen target cells. The avid binding of T to SHBG prevents this, but because the binding of T to albumin is loose, this fraction together with free T, that is about 50% of total plasma T, is considered to form the so-called bioavailable fraction of androgens. Plasma SHBG level is under endocrine regulation,[10] increasing clearly by oestrogen and ageing, decreasing somewhat by androgens, and clearly by obesity. If the hypothalamic–pituitary–testicular axis functions normally, changes in SHBG levels do not affect the balance of bioactive androgens, due to fast compensatory changes in the feedback regulation.

Like all steroid hormones, androgens initiate their effects at the cellular level by interacting with high-affinity nuclear receptors.[10,11] The androgen receptor (AR or NR3C4) is a member of the nuclear receptor superfamily of ligand-activated transcription factors, along with those of the other steroid hormones. Unliganded AR occurs predominately in the cytoplasm where it is complexed with several proteins, including various heat shock proteins. AR binds to specific androgen response elements (AREs) in the promoter and enhancer regions of androgen-responsive genes. Highest levels of AR are found in androgen target tissues, such as the accessory male sex organs. The same receptor protein binds both T and 5α-DHT, the latter with up to 10-fold higher affinity. This may function as an amplifying mechanism of androgen action in many target organs, for example the prostate and hair follicle.

The main androgenic functions include the regulation of gonadotrophin secretion, regulation of initiation and maintenance of spermatogenesis, male-type differentiation of the sexual organs during embryogenesis, stimulation of sexual differentiation during puberty and control of male sexual behaviour and potency. An alternative way of grouping the androgen effects is to define them as androgenic, anabolic and psychological. The anabolic androgen actions on muscle are predominantly due to T action, whereas its effects on bone, at least partly, require aromatization of T to oestrogens. LH is the main regulatory hormone of T production, and these two hormones form a classical feedback regulatory loop of the hypothalamic–pituitary–gonadal axis.

Measurement of testosterone production

Testicular androgen production is usually monitored by measuring serum total T levels using immunological techniques (radioimmunoassay, enzyme immunoassay). The levels in men are normally high enough to be reliably measured with these techniques, but if the levels are low, as in children, women and hypogonadal men, the more specific and sensitive mass spectrometric techniques are recommended.[12] The analyses can be supplemented by SHBG measurements, which allow the calculation of free T.[13] Direct free T measurements are not considered reliable, and the reliable method of equilibrium dialysis is too expensive for routine clinical use.[12] Total T measurements are usually sufficient in the assessment of testicular T production in ageing men, but free

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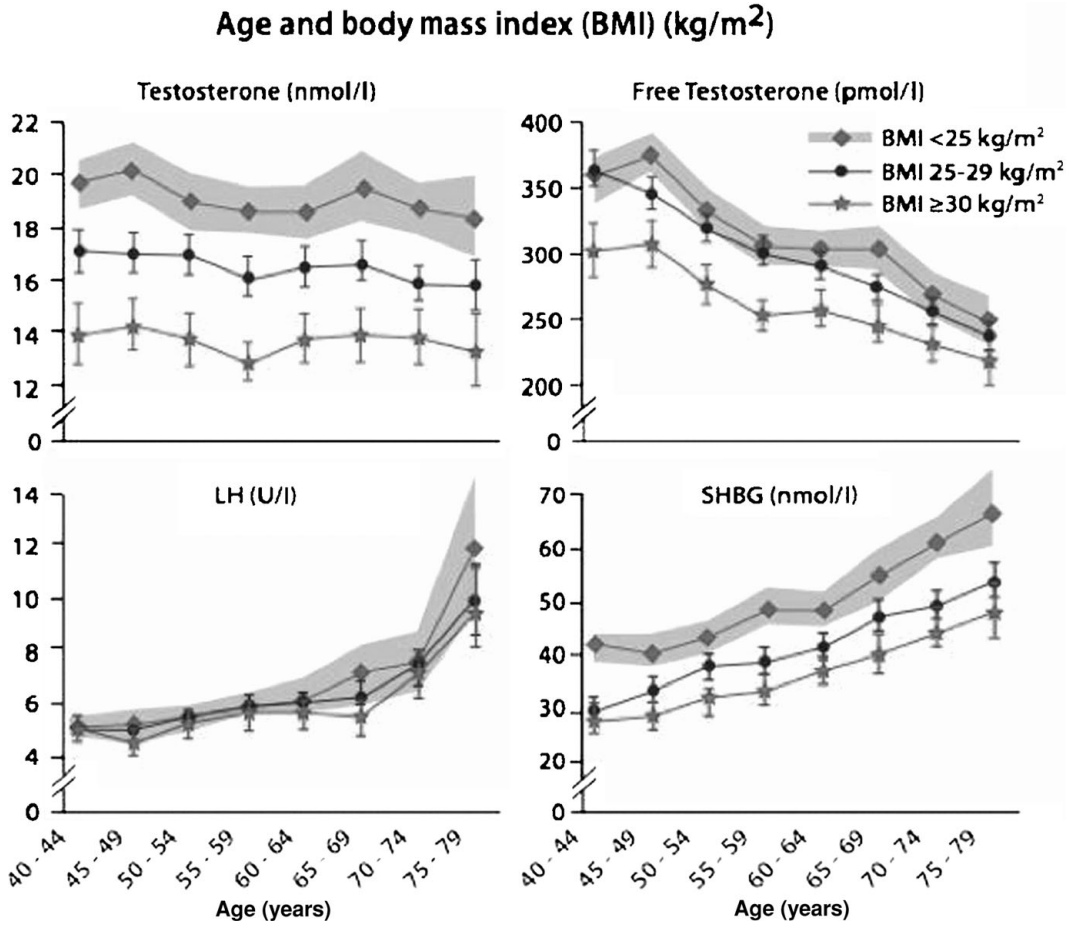


Figure 1. Relationship between age, body mass index (BMI) and hormones in middle-aged to ageing men. The data are from the European Male Ageing Study ($n = 3220$). The cohort was stratified according to BMI into three groups: normal weight (BMI < 25 kg/m^2), overweight (BMI 25–29 kg/m^2), and obese (BMI ≥ 30 kg/m^2). Mean (95% CI in *shaded area* and *vertical lines*) total T, free T and SHBG were significantly lower at all ages in the overweight and obese compared with non-obese men. The total T and SHBG age trends in the three BMI categories were similar (indicating no interaction between BMI and age); the free T age trend in the obese group was less steep than in the other two groups (indicating an interaction between BMI and age). From ref. 14, with permission.

T may provide additional information in cases suggestive of borderline hypogonadism.[14]

Changes in testosterone production and action during ageing

T production decreases with ageing.[15,16] According to a large recent study (European Male Ageing Study (EMAS), $n = 3220$)[14] serum level of total T decreased between 40–49 and 70–79 years of age on average from the level of 17.6 to 15.9 nmol/l (0.5% per year) and that of free T from 350 to 230 pmol/l (1.1% per year, Figure 1). The higher magnitude of the latter change is explained by simultaneous increase in the level of SHBG, whereby the proportion of free T declines. A concomitant increase of circulating LH levels with age reveals that the decrease of testicular function is primary, as the feedback regulatory link attempts to compensate it by increase of LH. Longitudinal studies detect an additional secular decline in T levels, which may be as high as the per year cross-sectional decline.[17] Selection

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bias of cross-sectional studies, increasing adiposity, smoking cessation and accumulation of endocrine disrupting compounds in the environment have been suggested as causes of this trend. Age-related decreases of similar magnitude have been reported in total T (0.8% per year) and in free and albumin-bound T (2% per year) also in other studies.[15,18] If we consider as the criterion of low T a level below the lower limit of the reference range, i.e. <10 nmol/l, then the frequency of biochemical hypogonadism increases from 8.5% in 40- to 49-year-old men to 13.5% in 70- to 79-year-old men.[14] If calculated free T is used as the criterion, the frequency of hypogonadism increases in the oldest age group threefold. However, these figures do not equate with genuine LOH, because the majority of ageing men with low T remain asymptomatic.

The most important factor in the decline of T in adult men is overweight (in particular increased waist/hip ratio), and thereafter various co-morbidities.[14] In the EMAS study, when the body mass index (BMI) increased from <25 kg/m^2 to >30 kg/m^2, total T decreased by 4 nmol/l (about 25%). Being mildly overweight (BMI >25 kg/m^2) decreases serum T more than the increase of age from 40 to 80 years; the trend is similar with free T (Figure 1). Low T is a risk factor of imminent metabolic syndrome and type 2 diabetes.[19] Age-related decline of T is primary testicular (associated with increased LH levels), whereas the overweight-associated decline is secondary hypothalamic (no compensatory increase in LH).[15] This is important because lowering of circulating cholesterol may reduce the substrate for androgen production. Some,[20] but not all,[21,22] studies have shown mild decrease in T levels during cholesterol-lowering treatment with statins.

Androgens and mortality

An independent inverse association between serum T concentration and mortality has been demonstrated in several longitudinal studies.[23–28] In cause-specific analysis, increased rate of mortality existed in cardiovascular[24,25] and respiratory[24] diseases, and in some,[25] but not in all,[24] studies also in cancer deaths. However, in the population-based Caerphilly study no association between total T and all-cause mortality was found.[29] Similarly, based on the Massachusetts Male Aging Study, Araujo *et al.*[30] concluded that endogenous sex hormone levels have only relatively weak associations with mortality. They found that, in multivariate-adjusted models, higher free T was associated with mortality from ischaemic heart disease and inversely with mortality from diseases of the respiratory system, whereas total T was unrelated to mortality. Total T may not be the only anabolic marker of poor prognosis, because concomitant low baseline concentrations of bioavailable T, IGF-1 and DHEA sulphate increased the hazard ratios for mortality compared with low value in only one of them.[26]

Androgens and atherosclerosis

Male gender is one of the risk factors for coronary artery disease (CAD). Androgens, or the lack of oestrogens, have been regarded as the proximate cause of this risk factor.[31,32] There is substantial evidence that levels of the sex hormones T, oestradiol (E2) and DHEA are associated with cardiovascular disease (CVD) risk.[31–35] Androgens have important influence on cardiovascular function, and androgen receptors are expressed in vascular tissues, including the endothelium, smooth muscle and myocardium.[32]

Among 39 studies on the relationship between circulating T and CAD, sixteen demonstrated lower levels of T in CAD patients compared with healthy controls, 16 showed no difference in T, but none suggested association of high levels of T with CAD.[32] The largest study including 2512 men[36] showed no difference in basal T between men with and without ischaemic heart disease during a 5-year follow-up. Similarly, in two large long-term prospective cohort studies, no correlation between baseline T levels and subsequent development of CAD was found in middle-aged and elderly men.[37,38]

Low serum T levels have been associated with faster progression of subclinical atherosclerosis,[39,40] and an independent inverse association between T and occurrence of aortic atherosclerosis,[39] and T and carotid intima-media thickness[41] have been demonstrated. Low levels of total and free T were detected in male subjects with angiographically measured coronary atherosclerosis[42] but no association between peripheral arterial disease and T was found in another study.[43] This discrepancy may be attributable to the fact that peripheral arterial disease encompasses subjects with less severe atherosclerosis than those with severe aortic atherosclerosis.[39] Likewise, no association between endogenous T

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and CAD or cardiovascular disease events was found in the Honolulu Heart Program,[44] and in some other studies.[36,37,44–47] Recently, low T levels have been associated with the occurrence of stroke or transient ischaemic attacks[48] and with arterial stiffness.[49] Interestingly, E2 has been associated in an inverse manner with cardiovascular disease risk, especially in older men.[47]

In summary, the cross-sectional data suggest an association between low T and CAD, but a significant and independent association has not been confirmed in large prospective studies. Extreme androgen deficiency may be associated with increased cardiovascular morbidity but physiological levels may be cardioprotective.

T therapy and coronary heart disease

In hypogonadal men, replacement therapy with T may have beneficial effects on bone density,[50] muscle mass,[51,52] body composition[51–53] and cognition,[54,55] but considerable controversy still remains regarding the indications for T supplementation in ageing men.[56]

T replacement therapy may improve exercise tolerance in chronic stable angina,[57] and infusion of T into coronary arteries seems to improve coronary artery blood flow in CAD patients.[58–60] The sum of ECG ST-segment depressions immediately after the exercise test decreases after T therapy.[61] Studies on T replacement therapy have not revealed increased incidence of cardiovascular disease or events such as myocardial infarction, stroke or angina[62] or other major adverse effects.[63] Thus therapeutic doses of exogenous T may have beneficial effects on cardiovascular risk factors, but the data do not justify uncontrolled use of T in the prevention of cardiovascular disease,[32] and definitive assessment of the long-term effects of T replacement therapy on cardiovascular health requires more prospective, placebo-controlled studies.[56]

Metabolic effects of androgens

Metabolic syndrome, initially named as syndrome X,[64] is a cluster of central obesity (measured as increased waist circumference), raised triglycerides, reduced HDL-cholesterol, raised blood pressure and increased fasting plasma glucose.[65] The syndrome helps to identify subjects at high risk of CVD and type 2 diabetes mellitus.

The prevalence of both metabolic syndrome and hypoandrogenaemia increases with advanced age. Therefore, it is not surprising that they may occur simultaneously, and the existence of a hypoandrogenic-metabolic syndrome in men has been suggested.[66] The prevalence of obesity is high among men with isolated hypogonadotropic hypogonadism referred to hospital for treatment of obesity,[67] and over a wide age range men with type 2 diabetes mellitus have a lower free T concentration than non-diabetic men.[68]

The relationship between T and insulin sensitivity has been demonstrated both in cross-sectional and longitudinal studies. In elderly men, there is positive correlation between T and insulin sensitivity, and hypogonadal men are twice as insulin resistant as eugonadal men.[69] Withdrawal of T treatment increases insulin resistance in middle-aged men with idiopathic hypogonadotropic hypogonadism without any changes in body composition,[70] suggesting that insulin sensitivity can be modulated by T also in an adipose-tissue-independent manner.

In the prospective Massachusetts Male Aging Study, lower levels of total T and SHBG and the existence of clinical androgen deficiency at baseline each predicted later development of metabolic syndrome, especially in initially non-obese men.[71] Similarly, during an 11-year follow-up, men with total T, free T and SHBG concentrations at the lower fourth had a clearly increased risk of developing metabolic syndrome and diabetes.[19] On the other hand, metabolic syndrome itself is a risk factor for later development of hypogonadism.[72]

Studies on effects of exogenous androgens or androgen deprivation on metabolism are scarce, and have usually been small, short and often performed in prostate carcinoma patients. Studies on androgen deprivation in patients with prostate cancer indicate increased risk of developing dyslipidaemia, insulin resistance, hyperglycaemia and metabolic syndrome.[73] In androgen deficiency, T treatment reduces the accumulation of visceral fat, prevents the loss of muscle and fat-free body mass but does not affect total body and abdominal subcutaneous fat masses.[74] In type 2 diabetic hypogonadal men, T treatment improves insulin sensitivity and reduces total cholesterol and visceral adiposity.[75]

The intimate connections between T and metabolic syndrome suggest a common underlying cause. One possibility is the hypogonadal-obesity[76] or hypogonadal-cytokine-obesity[77] cycle where, at low T, an increased triglyceride uptake to visceral adipocytes takes place, resulting in increased

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adipose mass. This favours catabolism of T to E2, and the increase in visceral adiposity further worsens hypoandrogenaemia and the metabolic syndrome.

Low serum T concentration is associated in skeletal muscle with markers of impaired mitochondrial oxidation, also known to be associated with metabolic syndrome, suggesting a mechanism by which T could influence metabolic syndrome.[69] Insulin sensitivity seems to correlate with testicular capacity to produce T, rather than with the pituitary gonadotrophin reserve.[78]

In summary, obesity is a central component of metabolic syndrome and an important factor contributing to hypoandrogenaemia. In these situations, weight reduction remains the cornerstone of treatment.

Androgens and physical function, frailty and falls

Muscle strength is a key factor in maintaining independence in older people, while decreased muscle strength is a risk factor for falls, frailty and disability.[79,80] Muscle strength and skeletal muscle mass decrease with ageing but are only weakly associated with circulating T concentrations.[81,82] Walking speed and the ability to rise from a chair and to climb stairs both correlate, although moderately, with muscle strength.[83] Low T correlates with poorer performance of activities of daily living,[84] and severe illness and low body mass index, components of frailty in older men, are associated with low T.[85] In institutionalized men, low T levels are associated with greater mortality[28,86] and decreased physical function.[28] Observational epidemiological studies have shown an association not only between T and muscle mass and strength, but also between T and physical performance and fall risk.[87,88]

Of frailty components, grip strength and physical activity, but not exhaustion, slow walking or weight loss, are associated with total T, whereas SHBG correlates with weight loss, exhaustion and physical activity.[89] In clinical trials in healthy older men and in men with chronic illnesses, T supplementation improves muscle strength[90–92] and self-reported physical function.[93]

Lean and fat mass of the body are strongly associated with grip strength and physical function, indicating the possibility that T influences physical function via an indirect association with body composition.[94] In a recent study, handgrip strength in ageing men correlated with serum bioavailable, but not with total, T.[95]

Some androgen trials in older men have reported improvements in muscle strength[92,96,97] and performance-based measures of physical function,[98,99] but other trials have failed to confirm these improvements.[93,100] T administration is associated with dose-dependent increases in skeletal muscle mass, leg strength and power, but may not improve muscle fatiguability, walking speed and stair climbing power.[101] A recent meta-analysis of major randomized, controlled trials of androgen treatment concluded that T replacement therapy has beneficial effects on muscle strength.[102]

Androgens and bone

In men trabecular bone loss starts early, but cortical loss later in life, together with decreasing bioavailable oestrogen and T levels.[103] In older men the skeletal effects of T may mainly be mediated by oestrogens produced by aromatization from T.[104,105] When the association of sex steroids with bone mineral density (BMD) was studied in 20- to 90-year-old men, subjects with low free E2 or T levels were more likely to have low BMD, whereas low SHBG level was protective for osteopenia.[106] The association of BMD and free E2 was strongest among men over 70 years of age, whereas free T and BMD showed no association in this age group. Similarly, in adult males both total and free E2 were associated with proximal femur strength, whereas total or free T were not.[107]

Decreased BMD strongly predicts later occurrence of fractures. Two large prospective studies have suggested the importance of oestrogens rather than T in the prevention of fractures in older men. Subjects with lowest bioavailable E2 or highest SHBG levels had a greater risk for non-vertebral fractures, whereas bioavailable T was not independently associated with the risk.[108] It was highest in men who were at the same time in the lowest quartiles of bioavailable T and E2 and in the highest quartile of SHBG. In another study, total and free E2 and T were all inversely, and SHBG directly, associated with fracture risk, but in the multivariate analysis only free E2 and SHBG had an independent association with the risk.[109]

The effect of androgen supplementation on fracture prevention has not been investigated in elderly males, but some small-scale studies using BMD as a surrogate end-point have been published. In older men and women, increases in

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hip and spine BMD after DHEA sulphate therapy were associated with increased E2 levels but not with total or free T concentrations, suggesting that the beneficial effects were not caused directly by DHEA sulphate.[110] In another study, a 2-year treatment with DHEA, vitamin D and calcium increased spine BMD in elderly women but not in elderly men.[111] Administering intramuscular T enanthate treatment for 12 months to men with decreased T levels increased lumbar but not femoral neck BMD.[112] Similarly, a meta-analysis of trials including 365 men concluded that intramuscular (but not transdermal) T therapy moderately increases lumbar BMD, whereas the results in femoral neck were inconclusive.[113]

Thus in some body areas, T therapy may beneficially affect BMD, possibly through a secondary oestrogen action. In elderly men, lifestyle changes, prevention of falls, supplementation of calcium and vitamin D and in some situations bisphosphonates remain the key components in fracture prevention.

Androgens and cognitive function

The brain possesses receptors for all steroid hormones, and androgen receptors are expressed in multiple brain areas.[114] The primary androgen is T, which can be metabolized to the more potent androgen 5α-DHT. It is also converted to E2 by aromatase, an enzyme found in brain and other non-reproductive tissues. Because of the decrease of serum concentrations of T with age, it has been hypothesized that the age-related decline in sex hormone levels in men may be associated with the decline in cognitive function.[115] Conspicuously, T levels in older healthy men are lower among those who possess the E4 allele of apolipoprotein E, a potent contributor to Alzheimer's disease (AD) risk.[116]

Several population-based studies dealing with the relationship of endogenous sex hormones and cognitive function, such as memory, executive functions and processing speed in elderly men have been published.[55,117–120] Men with higher levels of bioavailable T had better scores on the Blessed Information-Memory-Concentration (BIMC) test, although the associations were relatively weak. In these elderly men, high T predicted better performance on several tests of cognitive function. Linear and non-linear associations were found, suggesting that an optimal level of sex hormones may exist for some cognitive functions.[117]

In ageing men, the subsequent development of AD was inversely associated with free T index (FTI), and calculated free T concentrations were lower in men who developed AD.[119] The suppression of T for the management of prostate cancer resulted in a twofold increase in plasma β-amyloid concentrations in elderly men,[121] and T was found to be protective for human primary neurons in culture independent of oestrogen action.[122] These data, combined with previous studies in men without dementia, suggest the possibility that T may inhibit cognitive decline and reduce the incidence, or delay the age of onset, of AD in men.[54,55,117,123] A linear association of T with cognitive function seems to be true especially in the oldest age category, and it could be hypothesized that, due to the increasing vulnerability of ageing men, decreased T levels in them lead to an imbalance of cognitive functioning, while in younger men the balance is preserved by other factors.[120]

T supplementation has not been found to affect cognition[52,54,124–126] even in studies where an increase in lean body mass or other metabolic effects were recorded.[124] Studies with T supplementation in men with cognitive impairment of AD disease have yielded mixed findings.[127–129]

In summary, the association of T and certain cognitive functions in men is curvilinear, which suggests the presence of an optimal sex hormone level. T supplementation has not been shown to affect cognitive function.

T and sexual dysfunction

Low T results in decreased libido.[130,131] Erectile dysfunction (ED) and lower urinary tract symptoms affect quality of life of older men.[132] The prevalence of ED rapidly increases with age, especially after 60 years.[133,134] As demonstrated recently in the European Male Ageing Study, subjects with lowest levels of total, free and bioavailable T also receive lowest scores in the overall sexual functioning questionnaire.[135] The studies evaluating the effect of T treatment on ED and libido have been small and of short duration. A meta-analysis based on 656 evaluable subjects receiving either T or placebo for 1–36 months concluded that T moderately improves erectile function, the number of successful intercourses, sexual thoughts and motivation, and overall sexual satisfaction.[136] The effects were seen in subjects with a low baseline T concentration but were much weaker or absent in eugonadal men. The

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recent international guidelines on the treatment of LOH list men with ED and/or diminished libido and T deficiency as candidates for T therapy.[137] In borderline cases, a short therapeutic trial may be justified, but in any case, the absence of therapeutic effect calls for reassessment of the causal mechanisms behind the symptoms and cessation of T therapy. Sexual dysfunction is often associated with chronic conditions, such as cardiovascular disease, obesity and diabetes.[130] T and phosphoesterase-5 inhibitors may have synergistic effects in LOH.[137] Amongst others, prostate and breast cancer are contraindications for T therapy, and all men above 45 years of age should be screened for them and polycythaemia before, and at regular intervals during, T therapy.[2,137]

Conclusions and future directions

Decreasing T production is associated with male ageing, but it leads in only a minority of men to symptomatic hypogonadism, i.e. LOH, when the commonest complaints are related to sexual function. Rather than ageing *per se*, associated overweight, and other co-morbidities, are the major causes for the decline in T. Prevention of ageing-associated weight gain is apparently the most effective way to avoid LOH. T replacement therapy can be used in selected patients, but it should be limited to those with a clearly defined LOH diagnosis. Follow-up of prostatic, haematological and cardiovascular risk factors is important during the treatment. Long-term risks of androgen therapy are not yet known. An interesting future concept is whether T, in addition to replacement therapy, could also be used as anabolic pharmacotherapy of frailty in elderly people.

Conflicts of interest

The authors declared no conflicts of interest.

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