



Testosterone supplementation in the aging male

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World-wide life expectancy at birth for men and women will have increased by about 20 y during 50 y period between 1950 and 2000. As a result, the proportion of the elderly population is expected to increase significantly in the 21st century. Despite this increase in longevity for men and women, men still have significantly shorter life expectancy of approximately 5 y. To further reduce and prevent debilitating disease and disability in elderly men, a question is whether any type of interventions, such as hormone replacement therapy, may play a role in improving the quality of life as proven in post-menopausal women.

Men experience age-related decline of capability physically and mentally. Various symptoms, such as nervousness, depression, impaired memory, inability to concentrate, easy fatigability, insomnia, hot flushes, periodic sweating, reduction of muscle mass and power, bone ache, and sexual dysfunction, are related to this change. The fact that a number of age-related changes resemble features of various hormonal deficiency has led to worldwide interest in the use of various hormonal preparations in an effort to prevent the aging process in elderly men. Even though there have been opinions against hormonal supplementation in the aging male, preliminary studies defining the risk/benefit ratio of androgen supplementation appear to be encouraging.

To understand testosterone supplementation in the aging male, this review will discuss the following important topics: physiology of male hormonal balance, changes in reproductive organs in elderly men, endocrine evaluation of the male, pharmacological effects of testosterone on target organs, available preparations for testosterone, and testosterone supplementation.

Keywords: aging male; hypogonadism; physiology; evaluation; pharmacology; testosterone supplementation

Introduction

The topic of a male menopause has been debated intensely in recent years. Although men do not have an obvious event, such as a discrete change in the menstrual cycle and hormonally-induced hot flushes as seen in later middle-aged women, aging men may experience a decline in sexual, physical and behavioral capacity. Age related decreases in androgen levels, which occur gradually and vary considerably between individuals, have been implicated as the cause of these changes.^{1,2} Symptoms of nervousness, depression, impaired memory, inability to concentrate, easy fatigability, insomnia, hot flushes, periodic seating, and sexual dysfunction have also been observed.

These age related changes linked to declining testosterone levels in men over 50 y of age have

created an intense world-wide interest in the use of various hormonal preparations. Therefore, an understanding of the concepts of hormonal supplementation in the aging male is absolutely necessary to avoid any misunderstanding of possible risks and benefits. The purpose of this review is to provide a current update regarding testosterone supplementation including changes in the elderly, evaluation of these patients, effect of testosterone, and possible risks and benefits related to this kind of treatment.

Physiology of male hormonal balance

The hypothalamus secretes gonadotropin releasing hormone (GnRH) in a pulsatile pattern into the portal system, producing the pulsatile secretion of follicular stimulating hormone (FSH) and luteinizing hormone (LH) into the peripheral blood. These hormone have major effects on the testis. Feedback control is the principal mechanism through which a hormone can regulate the synthesis and action of other hormones.³ For example, a negative feedback mechanism provided by the hypothalamic-

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pituitary–gonadal axis is responsible for the reduced secretion of pituitary LH in the presence of elevated plasma testosterone or estradiol.

The hypothalamic–pituitary–gonadal (HPG) axis

An understanding of the HPG axis is essential for the proper evaluation of the male hormonal milieu and for supplementation of androgen in the elderly male.

Hypothalamus

The hypothalamus is a pulse generator for the cyclic secretion of pituitary and gonadal hormones. The portal vascular system provides a direct communication for delivery of hypothalamic hormone to the pituitary gland, avoiding the systemic circulation. The function of GnRH is to stimulate the secretion of LH and FSH from the anterior pituitary. This function is the result of integrated input from a variety of influence including stress, exercise, gonadotropins and circulating gonadal hormones. The pattern of GnRH secretion is pulsatile or episodic in nature which produces the concomitant cyclical release of the gonadotropins from the pituitary.

Anterior pituitary

The anterior pituitary receives about 80% of its blood supply from the hypothalamus through the portal veins. The sensitivity of the pituitary gonadotropins for GnRH varies with an individual's age and hormonal circumstance. The primary pituitary hormones which regulate testis function are LH and FSH which are glycoproteins consisting of two polypeptide chain subunits, alpha and beta.

Testis

Normal male virility and fertility require the collaboration of both exocrine and endocrine functions of the testis. The interstitial compartment of the testis is composed mainly of Leydig cells, which are responsible for steroidogenesis. Although major secretory product of Leydig cell is testosterone, other steroids such as 17OH-hydroxyprogesterone, estradiol, dihydrotestosterone, and growth factor are produced.⁴

Normal testosterone production in male ranges between 4 and 8 mg/d. Testosterone is a strong regular of its own production through negative feedback mechanism of the HPG axis. This effect is generated at the level of the hypothalamus and may have smaller direct pituitary effect on LH secretion.⁵

Testosterone is metabolized into two major active metabolites in the target tissues: (1) the major androgen dihydrotestosterone (DHT) under the action of 5-alpha reductase; and (2) the estrogen estradiol through the action of aromatase. In most peripheral tissues, testosterone conversion to DHT is required as part of the mode of action of androgens; but, in the testis and probably skeletal muscle,⁴ conversion to DHT is not essential for the hormonal effect of testosterone.

Changes in androgen secretion, reproductive capacity, and body composition

Androgen secretion and concentration

From the cross-sectional and longitudinal studies, basal levels of total plasma testosterone are known to have a progressive age-related decrease after age 50. However, these results may be confusing because of the lack of consideration for confounding variables such as environmental factors and medications.

While some studies of perfectly healthy men have reported no age effect on total testosterone levels,⁶ other studies have observed a significant downward trend with age in both total and non-sex hormone binding globulin (SHBG) bound testosterone concentrations.^{1,7,8} Therefore, the concern whether aging along significantly reduces testosterone secretion or total levels is not well defined. However, most investigators agree that circulating bioavailable testosterone decreases with age because of the increase in circulating SHBG. The circulating testosterone which is bound to SHBG is biologically unavailable.

There is also evidence for an effect of aging on the function of hypothalamic–pituitary–gonadal axis from the finding that circadian rhythm in serum testosterone levels was markedly attenuated or absent in healthy elderly men and that there is an attenuation of LH secretory bursts amplitude in normal older men.^{6,9}

Reproductive capacity

Semen analysis in elderly men reveal an alteration in sperm counts with varying degree—decreased, normal, or increased.¹⁰ And a decreased sperm motility and increase in abnormal sperm forms.^{6,10}

An age-related decrease in Leydig cell number and/or reverse secretory capacity has been suggested based on human choriogonadotropin (hCG) stimulation tests which have demonstrated a diminution in the testosterone response in older men.⁶ This finding in older men suggests some degree of

primary testicular failure. Therefore, two factors may contribute to hypogonadism in aging men. One is a slightly decreased production of testosterone and the other is an increase in the circulating fraction of testosterone bound to SHBG.

With regard to sexual function in elderly men, many studies have noted progressive declines in male libido and sexual performance with age and a striking increase in the prevalence of impotence in men over 50. However, after controlling for age, the correlation between serum testosterone levels and sexual activity was not significant,¹¹ suggesting that (1) reduced testosterone levels are not likely to be responsible for sexual dysfunction; and (2) hypogonadism *per se* is an uncommon cause of impotence in elderly men. Based on these findings, the supplementation of testosterone in older men to improve erectile function may be of questionable benefit. Nevertheless, other studies have shown that aging men with high sexual activity levels have greater plasma testosterone concentrations than men with less sexual activity.¹² Although decreases in serum testosterone may have a correlation with the diminished sexual activity in older men, this effect is probably minor compared with the contributions of psychological, social and health factors.⁶

Body composition and metabolism

With aging, men witness a decrease in muscle and bone mass, as well as in muscle strength. Declining bone mass predisposes the older men to osteoporosis and hip fracture. Just as with women, the decrease in serum testosterone concentration may be associated with this age related decline in bone density. An increase in body fat, with fat redistribution from peripheral to central stores, also occurs in old age.¹³

Endocrine evaluation of the male

Sex hormone transport in blood

Only 1–3% of testosterone is ‘free’ or unassociated with plasma protein. This fraction is considered the biologically active form. The remainder is bound to albumin or a beta globulin, SHBG, within the blood. About 60% of circulating testosterone is bound to SHBG, while approximately 38% is bound to albumin.⁴ SHBG has a high affinity for testosterone and DHT can also bind estradiol in the peripheral blood, but the binding affinity is lower than that of testosterone. Thyroid hormone and estrogens stimulate SHBG synthesis and the conditions of androgen deficiency, and aging will increase SHBG concen-

trations in the serum. Recent data from studies using liver and brain tissues showed that albumin-bound testosterone can enter tissues as freely as the ‘free’ form, suggesting that albumin-bound fraction of testosterone is biologically available. Therefore, the measurement of free plus albumin-bound testosterone provides an accurate estimate of bioactive fraction of androgen.^{4,14}

Evaluation

The aging male who presents with climacteric symptoms such as flushing, inability to concentrate, fatigue, and impaired sexual function should undergo an endocrine workup. The endocrine tests generally obtained include testosterone, LH, and FSH. It can be argued that an endocrine evaluation should begin with the measurement of serum testosterone, and that further evaluation is needed only if the concentration of testosterone is low. Unfortunately, many compensated states of testis failure in which serum testosterone level is usually normal may be missed with this approach especially in the aging male.⁸ The routine use of prolactin is less defined since isolated hyperprolactinemia is a rare abnormality and since most patients with hyperprolactinemia have abnormally low testosterone levels. Patients who present the symptoms of hyperprolactinemia such as decreased libido and headache with depressed testosterone levels, are suggestive of prolactin abnormality.

While hormonal status is usually evaluated by measurements of serum hormonal levels, the concentration may not be an accurate marker for the levels which exert their action on target organs. Androgen deficiency can be better demonstrated by measuring a bioavailable testosterone, free and albumin-bound fractions of circulating testosterone. Measuring total testosterone in aging men may not be adequate to determine whether they have testosterone deficiency because an increase in circulating SHBG occurs with age. Measurement of bioavailable or free fractions of testosterone should be needed to correctly make diagnose the hypogonadism in men after age 50.

As it is well known that normal men demonstrate a clear circadian rhythm in serum testosterone levels,¹⁶ blood samples for testosterone assay should be taken in the morning when testosterone levels are highest to account for circadian variation.

Pharmacological effect of testosterone on target tissues

The effects of testosterone on male reproductive tract organs and vital organs are very complex, and

the biochemical details have not been fully elucidated. However, testosterone may affect numerous bodily systems and functions including; hematopoiesis, calcium homeostasis, bone mineralization, lipid metabolism, carbohydrate metabolism, and prostate growth.

Effect on lipids metabolism and heart

Because abnormalities of lipid metabolism are the principal risk factors for the development of atherosclerosis and cardiovascular disease, the main causes of mortality in older men, an understanding of the effects of testosterone on the lipid profile is critical prior to supplementation. Researchers have suspected for years that testosterone has an unfavorable impact on lipoprotein profiles, resulting in a greater susceptibility to coronary artery disease.¹⁷ A placebo controlled, double blind, crossover study demonstrated a depression of high density lipoprotein cholesterol (HDL-C) levels after testosterone treatment. The net effect was an elevation of the total cholesterol/HDL-C ratios.¹⁸ Other report has shown similar results for HDL-C, reporting that the depression of HDL-C were associated with increase in hepatic triglyceride lipase and HDL apoprotein AI and AII turn over and catabolism.¹⁹

In contrast, other studies have not demonstrated any consistent pattern regarding the effects of testosterone on HDL-C and other lipoproteins. For instance, a beneficial effect of testosterone was reported on lipoprotein(a) (Lp(a)), which was recently regarded as an independent risk factor for aggravating atherosclerosis. Another recent study carried out to evaluate the effect of testosterone on plasma Lp(a) concentration showed a significant decrease in Lp(a) concentration after administration of exogenous testosterone,^{20,21} perhaps indicating a beneficial effect on heart and vascular disease. Another study demonstrated both the adverse and beneficial effect of testosterone on lipid metabolism in hypogonadism. The authors reported that the increase in total cholesterol and LDL-C concentration after testosterone treatment were adverse effects, whereas the increase in HDL and LpA-I concentrations and the lack of changes in Lp(a) concentration were the beneficial effects.²²

Considering all the data reported, major lipid subfractions do not seem to be adversely affected by the administration of testosterone in men. Larger, more detailed studies with long-term follow-up are needed to define whether exogenous testosterone supplementation has an adverse effect on lipid metabolism.

With regard to the effect of testosterone on the heart, it has been claimed that testosterone might be one of the gender related risk factors for coronary heart disease in men.^{19,23} Men have lower levels of

HDL-Cholesterol, increasing the risk of coronary heart disease compared to women. This phenomena may be due to the effects of testosterone on insulin resistance and modulation of vasoconstrictor neurotransmitters rather than on lipid profile.^{24,25} Therefore, it might be assumed that lower level of serum testosterone would have a beneficial effect on atherosclerotic risk. However, in one recent study,²⁶ testosterone and free testosterone which may be the biologically active form of testosterone, correlated negatively with the degree of coronary artery disease and also negatively correlated with the risk factors fibrinogen, plasminogen activator inhibitor1, and insulin. Therefore, hypotestosteronemia in men may be a risk factor for coronary atherosclerosis. The declining testosterone level and increasing atherosclerosis with age in men is consistent with this concept.

Apart from lipid metabolism, factors such as blood volume, cardiac and vascular smooth muscle, and alterations in the coagulation system could adversely or positively influence the effect of testosterone on heart disease.¹⁹ Therefore, the net effects of testosterone administration on the heart and coronary vessels still need to be determined from large scale, long term studies.

Effect on the haematopoietic system and fibrinolysis

It has been clearly documented that androgens promote erythropoiesis by stimulating the multipotent stem cells and erythroid progenitors, resulting hemoconcentration in men.^{19,27} The patient with chronic obstructive pulmonary disease, sleep apnea and elevated body mass index (BMI), should be followed carefully during testosterone treatment as the risk of development of a high hemoglobin and haematocrit level is increased in these populations. An investigation in which injectable testosterone was administered for 1 y showed a fall in plasma fibrinogen concentration after 16 weeks of treatment. The authors noted that testosterone treatment did not appear to be prothrombotic from the phenomena that the raised activation marker, like antithrombin III had returned to pretreatment levels, indicating the creation of a new equilibrium.²⁸

Effect on the body composition

Muscle is an important target for testosterone, and in this tissue 5-alpha reductase is very low.⁴ Testosterone replacement for adult men with hypogonadism leads to an increase in lean body mass and muscle strength, decrease in body fat, and an increase in body density.^{23,29} The increases in lean body mass were reported to be mainly in the legs.³⁰ In another

study, it was shown that increasing testosterone concentrations in the older men increased skeletal muscle protein synthesis and strength, which were mediated by stimulation of the intramuscular insulin like growth factor (IGF) I system.³¹ The findings that androgen therapy may produce a beneficial impact on body composition are consistent in many studies.

Effect on bone metabolism

A group of androgen metabolites, 5β -androgens (β -DHT and β -androstenediol), act specifically on bone marrow tissue, suggesting that marrow stem cells have a unique receptor for these hormones.⁴ A progressive loss of trabecular bone density with time occurred in the patients who had bilateral orchiectomies. The data from the studies evaluating the effect of testosterone on bone mineral density (BMD) in hypogonadism showed that androgen supplementation led to increases in BMD.³⁰

Supplementation of testosterone may have a beneficial effect on bone metabolism in aging men.²³ However, the effect of androgen administration on the bone mass of normal men has not been elucidated.

Effect on respiration, body fluid and glucose metabolism

Testosterone administration in men with hypogonadism could exacerbate sleep-related breathing disorders. In patients who are predisposed to sleep apnea such as obese men, elderly men, and patients with chronic obstructive pulmonary disease, the risk for sleep-related breathing disorders will be increased.¹⁹

The administration of androgens is reported to cause fluid retention, aggravating hypertension, peripheral edema, and congestive heart failure.²³ Low testosterone and SHBG concentrations in elderly men were associated with increased development of diabetes³² and men treated with testosterone had decreased insulin resistance.³³ Testosterone administration also produced a decrease in fasting glucose in blood.⁶

Effect on behavior and mood

In the studies assessing the effect of supra-physiological doses of testosterone on aggressiveness, treatment with testosterone resulted in a higher degree of aggressiveness in comparison to placebo.³⁴ In hypogonadal men, testosterone replacement

therapy was reported not only to improve mood parameters, such as energy and sense of well-being, but also to decrease negative mood parameters like nervousness and irritability.³⁵ These results suggest that testosterone exerts some effect on mood and behavior in men. However, data has also indicated that testosterone produces no significant effects on the central nervous system. One study employing a double-blind, placebo controlled design concluded that supra-physiological doses of testosterone, when administered to normal men, does not result in an increase in angry behavior.²⁶ Another study showing that neither mood nor behavior was altered in both testosterone treatment and placebo group is consistent with this conclusion.³⁷ The effect of testosterone on central nervous system can not be fully clarified as human behavior is influenced by confounding effect of social learning.

Effect on sexual function

Androgens have been known to be necessary for erectile function, sexual desire and ejaculation in men. The relationship between androgen levels and age-related decline in sexual function in the aging men is very complex because sexual function in the elderly men is affected by many factors including physiological decline of hormonal levels, psychological, and organic diseases, which are very common in this age group.

While the relationship between serum testosterone level and sexual function in men has been reported to vary from little evidence^{38,39} to androgen-dependent of sexual function,^{11,40} recent data support the theory that androgens have a beneficial effect on sexual function. The addition of exogenous testosterone was reported to significantly increase frequency of masturbation, sexual activity and early morning erection in eugonadal men,¹¹ and enhance the rigidity of nocturnal penile erections (NPE) in normal subjects.⁴¹ In the study of hypogonadal men,⁴² three months of androgen supplementation increased the number of NPE responses, but responses to audiovisual sexual stimulation (AVSS) were not improved. Therefore it was suggested that NPE may be androgen dependent, while erectile response to AVSS is androgen independent. Based on the finding that hypogonadal men produced a normal response to AVSS, sexual dysfunction occurring in hypogonadal patients may be due to loss of sexual desire and not a direct result of androgen deficiency.

Recent evidence suggests that androgens have a direct effect on erectile tissues. Testosterone may exert its role in erections by modulating the expression of nitric oxide synthase (NOS) in the corpus cavernosum, thus increasing production of nitric oxide.^{43,44} However, exact action mechanisms

of androgens on neurotransmitters in penile tissue will be further investigated.⁴⁴ Whether the effects of androgen on sexual function are dependent on serum level of androgens of individuals, what level of serum testosterone is necessary to maintain enhanced sexual function in men, and how long testosterone supplementation should be given to improve sexual activity are all questions that remain to be answered.

Effects on the prostate

It has been assumed that administration of testosterone may enhance prostatic growth in benign prostatic hyperplasia (BPH) and accelerate the progression of prostate cancer. However, there is no evidence to support the hypothesis that administration of testosterone in hypogonadal or normal men leads to the development of BPH, or that androgen administration will enhance the progression of prostate cancer from the preclinical to clinical state.¹

In a study of hypogonadal men, prostate size and prostate specific antigen (PSA) concentration were shown to increase. But the prostate still remained within a normal size range for eugonadal men of the same age and within normal levels of PSA for a controlled population.⁴⁵ In another longer-term study using the oral androgen testosterone undecanoate in hypogonadal men, no increase in prostate

size and no evidence of prostate cancer was observed.⁴⁶

Most of the recent studies evaluating the prostate serially by the methods of transrectal ultrasonography (TRUS), PSA, uroflowmetry (UFR) showed no, if any, significant changes in these parameters with androgen supplementations.^{15,47} The suggestion is that androgen supplementation will not have any major, obvious adverse effects for the risk of developing prostate cancer and BPH in healthy individuals. Again, longer term studies are absolutely needed to confirm whether administration of testosterone has a deleterious effect on prostate disease.

Available preparations for testosterone

The main routes for testosterone administration are oral, injectable, and transdermal (Table 1). Oral preparations have the advantage of easy administration, easy dose adjustment, and immediate treatment discontinuation in case of a complication. Disadvantages are fluctuating serum levels of testosterone and a low peripheral testosterone level. Another potent disadvantage of oral preparations such as fluoxymesterone and methyltestosterone is hepatotoxicity. But the oral androgen testosterone undecanoate (Andriol[®]) has a unique mode of action. It is absorbed from the digestive tract with lipids into the thoracic duct and to the general

Table 1 Available preparations for testosterone

Route	Generic name	Brand name	Advantage	Disadvantage
Oral	Testosterone undecanoate	Andriol	Easy administration and dosage adjustment	Fluctuating serum level
	Fluoxymesterone	Halotestin		Lower peripheral level
	Methyl testosterone	Metandren Virilon		Hepatotoxicity
Injection	Testosterone cypionate	Depo testosterone	Low cost	Non-physiological testosterone level in serum
	Testosterone enanthate	Delatestryl		
	Combination of four testosterone esters	Sustanon 250		
Transdermal	Scrotal	Testoderm	Normalized serum testosterone level good clinical response	Shaving scrotal area, skin irritation and detaching patch
	Non-scrotal	Androderm Testoderm		More skin irritation than nonscrotal

circulation. Therefore, it can avoid immediate breakdown in the liver and the serious side of effect of hepatotoxicity, which is possible with other oral preparations.⁴⁶

Testosterone injections are inexpensive in comparison to the other preparations. However, injections tend to produce a non-physiological serum testosterone level, which reaches a rapid peak after injection and then gradually declines over two weeks. Transdermal delivery systems have two forms: a scrotal and non-scrotal.^{40,48} Both induce good clinical responses. When wearing patches for 24 h, serum testosterone levels maintain normal levels consistently. Circadian variation appears, mimicking a normal physiological cycle. However, patches have the disadvantage of high cost and resultant skin irritation, which is more severe with the non-scrotal patch. As compared to non-scrotal patches, scrotal patches have the advantage of easy concealment and the disadvantage of high serum DHT levels are resorption due to the effect of 5 α -reductase in the scrotal skin.⁴⁸ The scrotal area needs to be shaved to keep the patch in place.

Testosterone supplementation

The proportion of the elderly population is expected to increase significantly in the 21st century. Despite this increase in longevity for men and women, men still have significantly shorter life expectancy than women by approximately 5 y.⁴⁹

The aging man may experience a decline in sexual, physical, and behavioral capacity, and may experience various symptoms related to this change, such as nervousness, depression, impaired memory, inability to concentrate, easy fatigability, insomnia, hot flashes, periodic sweating, reduction of muscle mass and power, aching bones, and sexual dysfunction. The fact that a number of age-related changes resemble features of various hormone deficiencies has led to worldwide interest in the use of hormonal preparations to alleviate the symptoms of aging in elderly men. Even though some commentators have warned against the use of hormonal supplementation in the aging male, preliminary studies defining the risk/benefit ratio of androgen supplementation appear to be encouraging.¹

To understand the debate surrounding testosterone supplementation in the aging male, the author will review the following important topics:

- (1) Rationale for the opinions against hormonal supplementation in the aging male;
- (2) Situations in which hormonal supplementation may benefit the aging male;
- (3) The use of testosterone supplementation in the aging male;
- (4) Risks of testosterone supplementation.

Rationale for the opinions against hormonal supplementation in the aging male

The data outlined below provide the arguments against the use of androgen supplementation in elderly men:

- Although the Massachusetts Male Aging Study reported a significant decrease in testosterone level with aging, a substantial number of elderly men continue to have serum testosterone concentrations within the normal range found in younger men;^{1,13}
- In a meta-analysis, serum levels of testosterone were found to be inversely correlated with age. However, this relationship disappeared when men with ill health were excluded from the analysis.⁶ This suggests that low testosterone levels in elderly men are related to ill health in this age group;
- The symptoms of fatigue, irritability, loss of energy, depression, and decreased sexual activity, which are representative of androgen deficiency in the aging male, may be caused by any number of factors, including stress;^{50,51}
- Studies of testosterone supplementation in elderly men have shown no improvements in some parameters, such as frailty. Moreover the possibility that testosterone supplementation may increase the risk of subclinical carcinoma of prostate and cardiovascular disease cannot be excluded;²
- Because the long-term studies of testosterone therapy for elderly men with low serum testosterone level have not yet been completed, testosterone supplementation for older men is not indicated.²

Situations in which hormonal supplementation may benefit the aging male

Age-related decreased in androgen level vary widely between the individuals. The favorable effects of hormonal replacement therapy can be expected in men with clearly decreased serum level of testosterone.⁵¹ The reported proportion of the population who are considered hypogonadal differs between several studies and depends on how the term hypogonadism is defined. If hypogonadism is defined as having a testosterone level in the lowest quintile and gonadotropin levels in highest quintile, about 4% of men in aged 40–70 y are considered hypogonadal. When the definition of hypogonadism is a testosterone level below the lower range of normal healthy young men, about 20% of men 55 y and older would be diagnosed as having hypogonadism. Furthermore, it has been suggested that if

hypogonadism is defined as testicular failure and diagnosis is made on the basis of the level of bioavailable testosterone, the prevalence in old men might be as high as 50%.²³ Vermuelen and Kaufman⁵ reported study of 300 healthy men using a definition of hypogonadism as a morning level of testosterone below the lower limit of normal (12 nmol/L). Using this definition, none of the men aged 20–40 y had testosterone levels within the hypogonadal range, but 7% of those aged 40–60 y, 21% of those aged 60–80 y and 35% of those over the age had hypogonadism. The elderly men who meet these criteria might be good candidates for testosterone supplementation, and expect improvement of age-related symptoms.

The use of testosterone supplementation in the aging male

About 20–30% of men over the age 60 y who are considered to have a subnormal testosterone level^{5,23} may be appropriate for androgen supplementation. Recent studies in older men^{8,23} have shown that testosterone supplementation has beneficial effects on:

- bone density and bone turnover;
- muscle mass and strength;
- body composition;
- possibly their sense of well-being and energy level;
- sexual function and libido.

Older men with subnormal level of testosterone would be suitable candidates for testosterone supplementation.^{6,15}

Testosterone impacts on sexual function in a number of ways, not simply affecting erectile function. Men with low testosterone levels may be able to achieve an erection, but their sexual desire, mood, and general behavior are very underactive; these would be expected to improve during testosterone supplementation. Furthermore, intensity of orgasm and ejaculation may also improve with this kind of intervention.⁵² Although patients may be advanced in age, testosterone supplementation (when indicated) can enhance their quality of life. When hypogonadism is secondary to hypothalamic or pituitary dysfunction, the underlying disease should be addressed first before hormonal supplementation is considered.¹⁵

The goal of testosterone supplementation in the aging male is less well defined, but may be summarized as the following:

- Elderly men receiving hormonal supplementation should benefit from the disappearance of symptoms related to partial androgen deficiency in the aging male (PADAM);

- Serum levels of testosterone and its metabolites, such as DHT and estradiol, should reach a certain level with exogenous testosterone supplementation, although the exact level is still under debate. Weksler⁵³ advocates a serum level of between 240 and 460 ng/dl as a reasonable target, whereas others⁵⁴ recommend a level of 400 and 900 ng/dl.

It should be noted that periodic follow-up is mandatory during supplementation to detect as early as possible any adverse reactions related to treatment. Before initiating testosterone therapy, a full assessment should be undertaken, including measuring body weight, pulse rate, blood pressure, complete blood cell count, and identifying sleep-related apnea. The prostate should also be examined. The most effective method for early detection of prostate cancer is the combined use of PSA and Digital Rectal Examination (DRE).⁵⁵ However, Morgentaler *et al*⁵⁶ performed sextant prostate needle biopsy in 77 patients with low total testosterone or free testosterone levels, with normal results of DRE and PSA levels of 4.0 ng/ml or less. They identified prostate cancer in 14% of the entire group and in 29% of the patients who were older than 60 y. They therefore concluded that a high prevalence of prostate cancer was identified by the transrectal ultrasound-guided biopsies in men with low testosterone level despite normal PSA levels and no abnormal findings on DRE. Because we still do not have sufficient information on these issues, further study is needed to validate this view.

Risks of testosterone supplementation

Several on-going, long-term studies examining the efficacy and safety of testosterone supplementation for healthy older men with low serum testosterone levels have not yet been completed. However, preliminary studies defining the risk/benefit ratio of androgen supplementation appear to be encouraging.

Major concerns of testosterone supplementation in older men are the risks of (1) exacerbating cardiovascular disease; and (2) the possibility of predisposing or accelerating malignant prostatic disease. Other concerns include accelerating benign prostatic hyperplasia, water retention, increased blood volume, exacerbation of sleep apnea, and possibly even causing gynecomastia.^{1,23}

It is well known that androgen administration promotes the growth of clinical adenocarcinoma of the prostate. Testosterone should not be prescribed to men with evidence of prostate cancer. Because of the potential of developing a prostatic neoplasm during testosterone treatment, it can be speculated for the patients to be followed closely with a serum PSA level and DRE. The second International

Androgen Workshop recommended that androgen administration is contraindicated if serum PSA level is above normal, and should be stopped if increase of 2.0 ng/ml at any time or an increase of 0.75 ng/ml/y occurs over 2 y period.¹

Patients with polycythemia vera should not be given testosterone and patients with a modestly increased haematocrit should be followed carefully during treatment. Furthermore, periodic blood counts are needed in patients with chronic obstructive airway disease, sleep apnea and elevated BMI during testosterone treatment because of the risk of development of high hemoglobin and haematocrit levels in these patients.⁵⁷ The risk for sleep-related breathing disorders should be carefully assessed when testosterone treatment is considered for patients who are predisposed to sleep apnea such as obese men, elderly men, and patients with chronic obstructive pulmonary disease. Moreover, physicians should have a high index of suspicion during the administration of androgens for developing congestive heart failure, fluid retention, peripheral edema, and hypertension.

Conclusion

Although hypogonadism is not inevitable with aging, evidence suggests a progressive age-related decrease in androgen secretion and reproductive capacity in a significant number of older men. The clinical significance of this change requires further study to define the risk/benefit ratio of androgen supplementation, and well-designed, long-term clinical studies are needed to determine their possible risks and benefits.

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