

TOPICAL REVIEW

Testosterone replacement therapy in older adult men

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Summary

Serum testosterone levels decline slowly with normal ageing in men and, although all men are not destined to become hypogonadal as they age, the prevalence of androgen deficiency in the older male is not insignificant. Over the past several decades, there has been an increasing interest in evaluating whether testosterone therapy (male HRT) might be beneficial for certain older men in preventing or reversing some aspects of ageing. The major androgen target organs of interest with regard to beneficial effects of male HRT include bone, muscle, adipose tissue, the cardiovascular system and the central nervous system (libido and aspects of mood). At the same time, potential adverse effects of male HRT on target organs such as the prostate continue to be evaluated. It is the purpose of this review to summarize the information to date with regard to testosterone replacement therapy in the older man and to discuss areas where more research and clinical information need to be forthcoming.

Hormonal replacement therapy (HRT) for post-menopausal women has been studied and discussed for many years. The idea of male HRT, however, is a relatively recent development, with increasing interest in this area occurring only over the past two decades. Reasons for this nascent enthusiasm include burgeoning evidence that testosterone levels decline with normal male ageing (and with age-associated diseases) and an interest in preventing age-related dysfunction and prolonging quality life among an ever increasing population of older adults. The decline in testosterone with age often parallels unfavourable changes in organs upon which androgens act and the goal of male HRT would be to prevent, stabilize or even reverse some of these detrimental target-organ changes.

Keywords: ageing, androgens, andropause, testosterone, therapy

Change in androgen levels with male ageing

Most (about 95%) of plasma testosterone in men is produced by the Leydig cells of the testes and released into the circulation in a pulsatile manner under stimulatory control by luteinizing hormone (LH). The remainder of plasma testosterone comes from conversion from adrenal androgens, largely androstenedione. Nearly all testosterone, which is the most plentiful androgen in the human male,

circulates in blood bound to two proteins, albumin and sex hormone-binding globulin (SHBG); only about 1–2% of testosterone circulates totally freely (Dunn *et al.*, 1981). Testosterone is tightly bound to SHBG, whereas its affinity for albumin is weak (Pardridge & Landaw, 1985). Because of the strong affinity of testosterone for SHBG, the portion of plasma testosterone not bound to SHBG is often called 'bioavailable testosterone' (Manni *et al.*, 1983). Whether non-SHBG bound testosterone is truly the fraction that is available to all androgen target tissues is not clear, however.

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Non-SHBG bound testosterone does appear to be the portion available to the brain (Pardridge & Landaw, 1985) and bone mineral density measurements in older men correlate much better with bioavailable testosterone than they do with total testosterone levels (Khosla *et al.*, 1998). There are data, however, to suggest that testosterone bound to SHBG may be available to the prostate (Sakiyama *et al.*, 1988).

Testosterone can be converted, via a 5 α -reductase, to dihydrotestosterone (DHT), which is the predominant androgen in some organs, such as the prostate. Although DHT is found in plasma, most of the effects of DHT at the target organ level are felt to be due to its local tissue formation from testosterone.

Although conflicting data pertaining to this point are found in the early medical literature, most studies within the past two decades have demonstrated an age-related decline in plasma levels of total testosterone, free testosterone and bioavailable testosterone. (Nankin & Calkins, 1986; Gray *et al.*, 1991; Vermeulen, 1991; Morley *et al.*, 1997). Levels of SHBG increase with age and this age-related increase in SHBG results in a steeper rate of decline in serum levels of 'bioavailable' testosterone than that seen for total testosterone (Stearns *et al.*, 1974; Nankin & Calkins, 1986; Tenover *et al.*, 1987). There are no consistent effects of age on serum levels of DHT.

The decline in testosterone with age is due to a decrease in testosterone production; testosterone clearance actually slows with age (Vermeulen *et al.*, 1972). Young adult men exhibit a circadian rhythm in their plasma levels of testosterone, with peak levels occurring in the morning then falling slowly by about 35% during the day. This daily fluctuation in serum testosterone is attenuated in older men (Bremner *et al.*, 1983). The physiological causes for a decline in testosterone production with age are multifactorial. The predominant change appears to be at the level of the testes, where there is a decline in Leydig cell number and in the activity of the enzymes in the metabolic pathway governing testosterone production (Neaves *et al.*, 1984; Takahashi *et al.*, 1983). The ability of the testes to increase testosterone production in response to increased gonadotrophin stimulation also is attenuated in older men (Tenover, 1992). There is additional evidence that age-related alterations in hypothalamic-pituitary function also contribute to the decline in testosterone. An overview of available data supports the view that older men fail to demonstrate an appropriate increase in LH secretion in response to a hypo-androgenic state. Most older men with low testosterone levels have gonadotrophin levels (especially LH levels) that are within the normal young male adult range, resulting in a relative hypogonadotropic hypogonadism.

The decline in serum testosterone with age is not universal. Most cross-sectional or longitudinal studies evaluating testosterone levels with age have been undertaken in a population of predominantly Caucasian men; little data are available as regards other ethnic groups. In addition, the rate

Table 1. Examples of prevalence of testosterone deficiency in older men

Ref	Age range (years)	Number of men evaluated	Serum total testosterone (ng/mL)	Percent of population
A	20–100	300	< 32	22% (60–80 years) 36% (80–100 years)
B	50–87	817	< 30	11.4%
C	75–101	77	< 25	33%
D	65–83	360	< 35	19% (> 65 years) 37% (> 70 years)
			< 30	11% (> 65 years) 22% (> 70 years)
E	40–69	1017	< 25	4.7% (40–49 years) 5.7% (50–59 years) 8.3% (60–69 years)

Ref: A, Vermeulen & Kaufman (1996); B, Lunglmayr (1997); C, Morley *et al.*, 1997; D, Tenover, unpublished data; E, McKinlay, J.B., from the Massachusetts Male Aging Study, unpublished data.

of testosterone decline among individual men can vary greatly, is impacted by disease and medications and does not inevitably result in hypogonadism. The prevalence of true hypogonadism in the older male population is uncertain, largely because there is no agreement on how to define it in this age group. There is no target-organ change, physiological finding or symptom that readily assists with this definition. It also may be that there will be no single plasma level of testosterone to define all older men as hypogonadal; the desired level of testosterone that maximizes target-organ effects may vary according to the androgen target organ of interest, as well as being different among individuals.

Currently, rather than defining what level of testosterone makes the average older man testosterone deficient, replacement studies have recruited older men with baseline testosterone levels at or below the lower limit of the normal range for young adult men and then evaluated androgen target-organ responses to testosterone therapy. This strategy allows testosterone to be raised to levels that are 100–200% above baseline, yet maintained within the normal physiological young adult range. Table 1 gives some examples of the prevalence in older men of various levels of testosterone deficiency, as defined by some of these studies.

Androgen target organ changes with age

Accompanying the male ageing process are a number of clinically detrimental physiological changes in organs and functions that, at least in the younger adult hypogonadal male, can be positively influenced by testosterone replacement (Table 2). Among these changes seen with age are: (1) a decrease in muscle tissue mass and a decline in muscle strength; (2) an increase in adipose mass, particularly in

Table 2. Androgen target organs: change with age and with testosterone replacement in hypogonadal young adult men

Target organ or function	Change with	
	Age	Testosterone replacement
Muscle mass	-	+
Muscle strength	-	+
Adipose mass	+	-
Bone mass	-	+
Libido	-	+
Erectile dysfunction	+	-
Mood; sense of well-being	NC/-	+

+ = increase; - = decrease; NC = no change.

intra-abdominal fat; (3) a decline in bone mass and an increased incidence of osteoporosis and minimal trauma fractures; (4) a decline in the quality and quantity of sexual thoughts and enjoyment; (5) an increase in erectile dysfunction; and (6) a decreased sense of well-being.

Testosterone replacement therapy in older men

Although there have been a number of studies involving male HRT over the past decade, large, well-designed evaluations are limited and the data available with regard to male HRT is at least 20 years behind that for HRT in the post-menopausal female. Nonetheless, by evaluating studies that are available and grouping results on the basis of target organ responses, some sense can be gained of where knowledge in the field currently stands.

Beneficial effects

The potential benefits of male HRT are listed in Table 3.

Table 3. Potential benefits and risks of testosterone therapy in older men

Benefits	Risks
Preserve or improve bone mass and prevent fractures	Fluid retention
Increase muscle mass	Precipitate or worsen sleep apnoea
Increase strength and stamina	Develop gynaecomastia
Improve physical function	Produce polycythemia
Improve libido	Hasten development of benign or malignant prostate disease
Improve well-being and mood	Increase cardiovascular disease risk
Decrease cardiovascular risk	

Bone

There have been at least six published studies to date that have reported on the effects of testosterone therapy in older men with regard to either biochemical parameters of bone turnover or bone mineral density (Jackson *et al.*, 1987; Greenspan *et al.*, 1989; Tenover, 1992; Morley *et al.*, 1993; Katznelson *et al.*, 1996; Reid *et al.* 1996). These studies have lasted from 3 to 18 months, with the shorter-term studies evaluating only bone turnover parameters. Some, but not all, of the studies enrolled older men who were osteoporotic at baseline and one evaluated testosterone therapy in men undergoing chronic treatment with glucocorticoids. In general, the rate of bone degradation was shown to be slowed by testosterone therapy, whereas bone mineral density seemed to increase (Table 4). Whether positive effects on bone density can be maintained over longer periods of time than have been studied, what might be the optimal level of testosterone replacement to achieve maximal benefit for bone and whether testosterone therapy would ultimately lower the rate of osteoporotic fractures in older men are all unknown at this time.

Body composition and strength

There have been at least five published trials of testosterone therapy in older men that have evaluated body composition changes; three of these trials, along with one additional trial, have evaluated some aspect of strength (Tenover, 1992; Morley *et al.*, 1993; Marin *et al.*, 1993; Urban *et al.*, 1995; Katznelson *et al.*, 1996; Sih *et al.*, 1997). Table 5 is a summary of the body composition and strength changes that have occurred in these trials. Consistently there have been changes in body composition with testosterone therapy, either a decline in body fat, an increase in lean body mass, or both. The magnitude of the fat mass changes in older men, when they occur, appears similar to that seen with testosterone replacement in young hypogonadal men, whereas the lean body mass changes produced are usually less dramatic. Whether this implies that the muscles of older men are less responsive to the anabolic effects of testosterone than are the muscles of young men is not yet known. A small number of studies have suggested that insulin sensitivity may increase with testosterone therapy in the older man, but whether this is due to the therapy-related decline in fat mass is uncertain.

In terms of strength changes seen with testosterone HRT in older men, most, but not all studies have demonstrated a statistically significant increase in strength with therapy (Table 5). Most of these studies have been blinded and placebo controlled, but most have also used only grip strength as the primary strength measure. Only one of these studies has evaluated the effects of testosterone on lower extremity (LE) strength.

While the principal aim of improving muscle mass in the older man would be to maintain or improve muscle strength so that mobility and function are maximized and

Table 4. Testosterone therapy effects on bone in older men

Ref	Treatment (months)	Study N	Parameters of bone turnover		Bone density	
			Formation	Degradation	Spine	Other
A	7-14	6	-	-		
B	12	4			+	+
C	3	13	NC	-		
D	3	8	+			
E	18	29	-	-	+	
F	12	15		-	+	NC

- = decrease; + = increase; NC = no change.

Ref: A, Jackson *et al.*, 1987; B, Greenspan *et al.*, 1989; C, Tenover, 1992; D, Morley *et al.*, 1993; E, Katznelson *et al.*, 1996; F, Reid *et al.*, 1996.

Table 5. Testosterone replacement and body composition and strength in older men

Ref	Treatment (months)	Study N	Body fat*	Lean body mass*	Strength
A	3	13	NC	+ (3.2%)	NC (grip)
B	3	8	NC		+ (grip)
C	9	31	- (6.4%)	NC	-
D	1	6			+ (LE)
E	18	29	- (14%)	+ (5%)	
F	12	17	NC		+ (grip)

*Numbers in parenthesis are percentage change from baseline.

+ = increase; - = decrease; NC = no change.

Ref: A, Tenover, 1992; B, Morley *et al.*, 1993; C, Marin *et al.*, 1993; D, Urban *et al.*, 1995; E, Katznelson *et al.*, 1996; F, Sih *et al.*, 1997.

preserved, no testosterone replacement studies to date have evaluated the effects on functional performance. In addition, all studies to date have been in generally healthy older men. Whether male HRT would be beneficial for muscle mass, strength and function in more frail men has not yet been addressed.

Sexual function and mood

There are no clinical trials that have evaluated the effect of testosterone therapy on aspects of sexual function in healthy older men with low or low-normal testosterone levels. There are, however, some studies that have evaluated the effects of raising plasma testosterone levels in older men with various types of sexual dysfunction. In general, men with low libido have shown improvement, whereas erectile dysfunction is only occasionally improved by such therapy (O'Carroll & Bancroft, 1984; Carani *et al.*, 1990; Guay *et al.*, 1995). Several blinded, placebo-controlled testosterone replacement studies in older men have evaluated effects on 'sense of well-being' or other aspects of mood. Although these studies are small, they

have shown that older men on testosterone report an improved or higher sense of well-being when compared with a similar group receiving placebo (Tenover, 1992; Marin *et al.*, 1993).

Cardiovascular system

Compared with pre-menopausal women, men have a higher incidence of cardiovascular disease and cardiovascular mortality. Whether this is due largely to the beneficial effect of oestrogens or lifestyle patterns for women, or whether there is also the possibility that androgens in men play a deleterious role in this sexual dichotomy, is unknown. Most epidemiological studies have shown that higher serum testosterone levels correlate with lower, rather than higher, cardiovascular disease risk in men (Bagatell & Bremner, 1995).

Cardiovascular disease risk factors that might be affected by sex steroids include serum lipoprotein profiles, vascular tone, platelet and red blood cell clotting parameters, and the direct process of atherogenesis. There are no data as yet on the effects of testosterone therapy in older men on most of these parameters. Several preliminary studies have suggested that testosterone therapy may decrease platelet aggregation or decrease vascular tone, but these data need to be expanded. Effects on serum lipoprotein levels in older men are the one area where testosterone therapy has been more extensively evaluated. In general, parenteral testosterone therapy (by intramuscular injections or scrotal or transdermal patch) in older men has led to a decrease in total or low density lipoprotein-cholesterol levels, with no change or a small decrease in high-density lipoprotein-cholesterol levels (Bagatell & Bremner, 1995). These lipoprotein changes with testosterone therapy are modest and the ultimate impact on cardiovascular disease is unknown.

Adverse effects

The only absolute contra-indications to male HRT at this current time are the concomitant diagnosis of prostate or

breast carcinoma. Other potential risks of male HRT have either been reported in studies of replacement in older men or inferred from studies involving either physiological replacement therapy in young hypogonadal men or from pharmacological (supraphysiological) therapy in young eugonadal men.

Potential risks of male HRT in older men are listed in Table 3. Many of these adverse effects can be predicted by pretreatment medical history, examination, or laboratory testing and others are easily manageable if they arise during therapy. Several of the potential adverse effects, however, such as long-term effects on the prostate, are virtually unknown. Because of the uncertainty regarding the effect of male HRT on cardiovascular disease, this category is also mentioned in the potential risk list.

Modest, usually transient, fluid retention (up to several kilograms in weight gain) is possible, especially within the first few months of HRT, but is not as dramatic with testosterone as it is with the use of oral anabolic steroids such as oxandrolone. No studies of male HRT with testosterone have yet reported problems with peripheral oedema or exacerbation of hypertension or congestive heart failure, but studies to date have only involved relatively healthy older men. In the chronically ill or more frail older man, fluid retention might pose a concern.

Sleep apnoea has been reported to contribute to low serum testosterone levels and testosterone therapy has been reported to exacerbate sleep apnoea (Sandblom *et al.*, 1983; Santamaria *et al.*, 1988). Although the reports are limited, because sleep apnoea is prevalent in the middle-aged and older man, evaluation for this condition by history prior to initiation of male HRT and throughout treatment is recommended.

Development of breast tenderness occurs in a small number of older men on HRT, and frank gynaecomastia also can develop, although this is even more uncommon. Since many older men, when given testosterone replacement, demonstrate a relatively greater percentage increase in serum oestradiol levels, when compared to serum testosterone levels, this may contribute to the breast changes reported. Often times this side-effect can be overcome with a downward adjustment in HRT replacement dose.

Testosterone replacement therapy in older men often can result in a significant increase in red blood cell mass and haemoglobin levels. The increases reported are much larger than those usually seen when young hypogonadal men are given testosterone replacement. In some cases, in which polycythemia has developed with male HRT, it has been necessary to either terminate therapy or decrease the dose of testosterone used for replacement (Tenover, 1996; Sih *et al.*, 1997). While the coexistence of sleep apnoea and elevated body mass index may contribute to the development of polycythemia in certain cases, this has not been true for many men studied (Krauss *et al.*, 1991; Drinka *et al.*, 1995). The method of testosterone replacement may affect the magni-

tude of the change in red blood cell mass, with those methods that give a more uniform level of testosterone within the physiological range throughout the dosing period showing less of an effect on red blood cell mass.

Both benign prostatic hyperplasia (BPH) and prostate cancer are diseases common to older men and both are promoted by androgens; androgen deprivation therapy has been used for the treatment of both of these processes. What is unknown is whether male HRT places an older man at increased risk of developing clinically significant prostate disease from pre-existing, but subclinical, disease. A number of testosterone replacement studies in men aged 40–89 years have evaluated serum levels of prostate specific antigen (PSA), prostate size or functional parameters such as urine flow rates or urinary bladder residual volumes (for review, see Tenover, 1996). The vast majority of these studies have reported no significant change in PSA, prostate size, or urinary functions with testosterone therapy, nor has there been a reported increase in the incidence of detectable prostate cancer. However, since both prostate cancer and BPH are diseases with long natural histories, and the observation time to date with testosterone therapy in older men is limited to less than 800 man-years, the long-term effects of male HRT on the prostate of older men is still of concern.

Given the possible adverse effects of testosterone therapy in the older adult man, screening for parameters related to potential risks of androgen therapy should be performed prior to the initiation of treatment. Such evaluation should include a history for potential sleep apnoea, significant symptoms of BPH, or personal or family history of prostate carcinoma; a physical examination, including a digital rectal examination of the prostate; and screening laboratory tests, including haemoglobin and PSA levels. To decrease the likelihood of pre-existing prostate cancer in an older man, if the digital rectal examination is abnormal or if an elevated PSA level is found, the man should be referred for ultrasound and biopsy of the prostate prior to initiation of androgen therapy.

Concluding remarks

Within the past two decades, knowledge of the potential benefits and risks of male HRT has increased significantly, although the data are perhaps 20 years behind what is available for female HRT. While larger and longer term studies of male HRT are needed, a composite of currently published trials suggest that male HRT may have benefit in terms of improving bone mineral density, increasing muscle mass and strength, and, in some men, improving libido and mood. Whether these effects translate, however, into decreased long-term fracture risk, functional improvements or stabilization, and improvement in overall quality of life are uncertain. In the short term (up to three years), the adverse effects of male HRT seem predictable and manageable, but the longer term effects on target organs such as the

cardiovascular system and the prostate are yet to be determined. Thus, although there may be a strong push by the lay media and/or the pharmaceutical industry to initiate

male HRT, men interested in such therapy should be counselled that the risk/benefit ratio for the therapy is yet to be determined.

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