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Androgen treatment of male hypogonadism in older males☆

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Abstract

The treatment of primary and secondary hypogonadism with testosterone is well established. Recently, there has been increased awareness that low testosterone levels also occur in chronically ill persons and aging males. Because of sex hormone binding globulin changes, it is more appropriate to make the diagnosis using either free or bioavailable testosterone. A small number of controlled studies have suggested that testosterone replacement in older men improves libido, quality of erections, some aspects of cognition, muscle mass, muscles strength, and bone mineral density. It also decreases fat mass and leptin levels. A number of screening questionnaires for the andropause have been developed. Insufficient numbers of older men have been treated with testosterone to characterize the true incidence of side effects. There is a desperate need for well designed, large controlled trials to establish the value or otherwise of testosterone treatment in older males. Published by Elsevier Ltd.

Keywords: Hypogonadism; Testosterone; Androgen

> "From the beginning of human record, priests, saints, medicine men, farmers and sultans had been demonstrating how clear-cut, sure and simple it was to take the vigour of animals and man away. How? By removing their testicles."

(Paul de Kruif, The Male Hormone, Harcourt, Brace and Company, New York, 1945)

Legend has it that the demigoddess, Semiramus of Assyria was the first to introduce castration as a way to decrease male libido [1–3]. Both the bible and the Talmud recognized that hypogonadism could either be "man made" or "god given." Aretaeus the Capadocian utilized the effects of castration to provide the first clear description of hypogonadism. Both William Hunter of England in the 18th century, and Adolf Berthold of Germany nearly a 100 years later, showed that testicular transplants could transform capons into cocks.

Towards the end of the 19th century Brown-Sequard injected himself with a testicular extract in an attempt to "approximate the strength of the young." While he felt his experiments were successful, these were almost certainly a result of the placebo effect. In 1911, Drs. Levi Hammond and Howard Sutton undertook the first transplant of a human testes into a 19-year-old boy in Philadelphia. This was followed by a series of human testicular transplants by Dr. Victor Lespinasse in Chicago. While he had a number of successes leading to "a strong erection accompanied by marked sexual desire" he did point out that "how much is due to the strong mental stimulus engendered by the operation, and how much to the actual functioning of the (testicular) cells, is impossible to determine." The shortage of a large number of humans willing to donate testicles, lead to Searge Voronoff developing chimpanzee testicular transplants and many of the rich of Europe received these "monkey-gland" transplants. In the United States the shortage of monkeys led to Dr. Brinkley undertaking goat testicular transplants.

The truly scientific approach to testosterone developed with Lemuel Clyde McGee who reported the isolation of the first active extract of the lipid fraction of bull testicles [4]. In 1935 Ernst Laquer working with Organon in Holland isolated a crystalline hormone from bull testicles which he gave "the dreadfull name 'testosterone". Around the same time Adolf Butenandt isolated "androsterone" from 25,000 l of policeman urine. Leopold Ruzicka working with Ciba in Switzerland synthesized androgens from cholesterol. Laquer found that the presence of fatty acids or esterification was necessary to maintain the biological activity of testosterone. This led A.S. Parkes to develop solid pellets of testosterone that could be given intramuscularly or subcutaneously [5].

The concept of testicular disease was first clearly described by Klinefelter et al. in 1941 [6]. Klinefelter's syndrome is characterized by small firm testes, azoospermia, decreased facial and axillary hair, gynecomastia, eunichoid

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Table 1
Systemic diseases commonly associated with low testosterone levels

Renal failure
Cirrhosis
AIDS
Chronic obstructive pulmonary disease
Sleep apnea
Myotonia dystrophia
Hansen's disease
Diabetes mellitus
Sickle cell disease
Hemosiderosis
Protein energy malnutrition

habitus and obesity. It is due to a chromosomal defect, either 47XXY or in the mosaic form 46XY/47XXY. These patients have low testosterone levels and elevated luteinizing and follicle simulating hormone, i.e. primary hypogonadism. This is a relatively common disorder being present in approximately 1 in 500 individuals [7]. In 1944, Kallman [8] described a condition characterized by hypogonadism and anosmia. This disorder is due to a hypothalamic defect in the generation of GnRH. The adverse effects of pituitary tumors on testosterone production have been known since the biblical story of David and Goliath.

In the 1940s a number of publications appeared describing a "male climateric." Heller and Myers [9] demonstrated that climateric (from the Greek for "rung of a ladder") symptoms could be reversed by testosterone. They utilized a quazi-controlled placebo trial to demonstrate this effect. Werner [10] was the first to describe the symptoms of the climateric, which included nervousness, decreased potency, decreased libido, irritability, fatigue, depression, memory problems, sleep disturbances, numbness, tingling and hot flushes. Ernest Hemmingway took testosterone for the last decade of his life, providing us with one of the longest safety trials for testosterone administration. Gooren [11] has reported in detail the safety of testosterone administered for 10 years in a small group of men.

Fig. 1 demonstrates the regulation of the hypothalamic–pituitary–testicular axis and the importance of sex hormone binding globulin in limiting the availability of testosterone to tissues. It is important to realize that numerous systemic diseases have been demonstrated to interfere with testosterone production, either directly at the testicular level or indirectly by modulating hypothalamic–pituitary function (Table 1).

1. Effects of aging on the hypothalamic–pituitary–testicular axis

Baker et al. [12] were the first to clearly show a decline in testosterone with aging. Their study, however, included a number of persons with systemic illness. Four longitudinal studies have shown a decline in testosterone with aging [13–16]. These studies also demonstrated an increase in SHBG with aging, resulting in an even more marked decline in free or bioavailable testosterone with aging. Total testosterone levels decline at approximately the rate of 1% per annum and bioavailable at a rate of 2% per annum. While FSH levels tend to increase monotonically with aging, luteinizing hormone levels while increasing remain in the normal range until extreme old age when they often increase to very high levels [13,17]. The true prevalence of hypogonadism in older males is unknown with no ideal epidemiological study existing. Table 2 provides estimates of the prevalence of hypogonadism based on the available studies.

Table 2
Prevalence of hypogonadism in older males

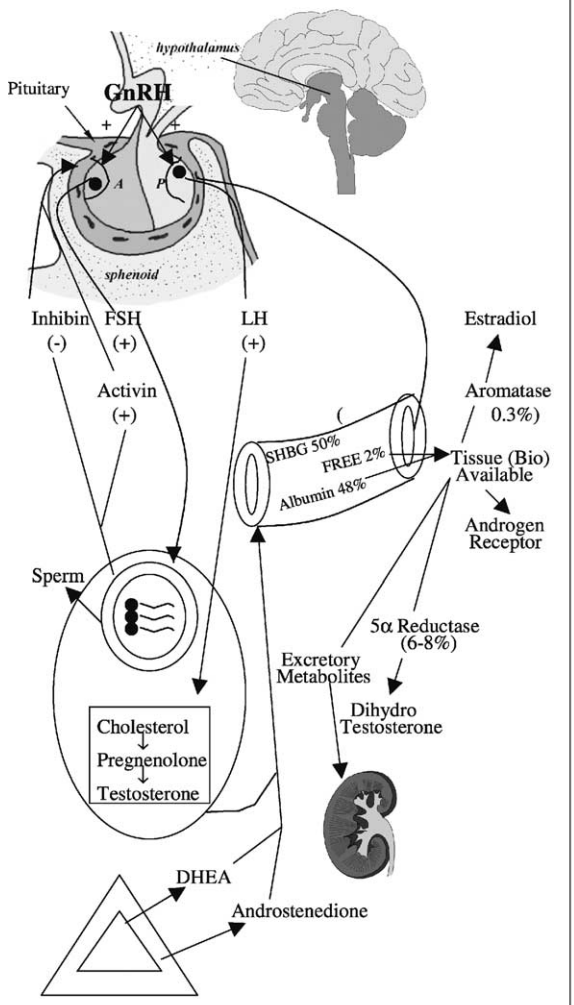
Age (years)	Percent hypogonadal		
	Baltimore longitudinal study	Mayo clinic	Canadian physicians
40–59	2–9	2–6	5–30
60–69	34	20	45
70–79	68	34	70
>80	91	–	–

The development of age-related hypogonadism appears to involve deficits at multiple levels of the hypothalamic–pituitary–testicular axis. These changes have been reviewed in detail elsewhere [18–20]. In brief, there is evidence for a decreased responsiveness of the testes to human chorionic gonadotrophin, increased testosterone feedback at the hypothalamic–pituitary level, decreased responsiveness of the pituitary to GnRH and perhaps most importantly asynchronous (chaotic) release of GnRH from the hypothalamus (Fig. 1). There appears to be increased endogenous opioid tone in middle age, decreasing LH release and a loss of opioid tone in persons beyond 70 years of age, allowing LH to increase more prominently at this age [21,22]. With aging there is a loss of the circadian rhythm secretion of testosterone [23]. The combination of all these factors is responsible for producing a pattern of secondary hypogonadism in the aging male.

2. How to measure testosterone

Classically, testosterone levels have been measured by radioimmunoassay. The validity of this method is dependent on the quality of the available antibodies. Over recent years variability in the quality of antibodies has become fairly common. In addition, when new antibodies are introduced, normal ranges with healthy young persons need to be established. Validity of these assays should be confirmed by mass spectroscopy, the true gold standard.

However, a greater problem is whether the true tissue available hormone levels can be gauged from measuring total testosterone. Because of the changes in SHBG levels with aging and in systemic diseases, it is felt that some measure of non-SHBG bound testosterone may be a better



Age-Related Changes

Loss of circadian rhythm

Alterations in opioid tone

Asynchronous production of GnRH

(?) increased inhibitory effect of testosterone at pituitary

Decreased bioavailable estradiol

Increased SHBG

Decreased bioavailable testosterone

(?) decreased receptor/postreceptor function

Decreased testosterone production

Maintained dihydrotestosterone levels

Decreased dehydroepiandrosterone from the adrenal

Fig. 1. Regulation of testosterone in men and age related changes; SHBG: sex hormone binding globulin; ?: uncertainty concerning binding; DHEA: dehydroepiandrosterone; GnRH: gonadotrophin releasing hormone.

measurement. In young persons, 50–60% of testosterone is SHBG bound, 1–2% is free and 35–48% is loosely bound to albumin. Free testosterone can be measured by dialysis or ultracentrifuge techniques. Both free and albumin bound, the so-called bioavailable testosterone can be measured by ammonium sulfate precipitation of tritiated testosterone bound to SHBG. It should be noted that the most common free testosterone measurement available in the United States is an analog assay method which has been clearly demonstrated to not measure free testosterone [24–27].

The two free testosterone measurements (dialysis and ultracentrifuge) and bioavailable testosterone levels are highly statistically correlated with one another in healthy young persons. When either diagnosis free testosterone levels or bioavailable testosterone are used as a “gold standard,” total testosterone misclassifies in between 35 and 45% of hypogonadal males [27].

Studies by Pardridge and co-workers [28,29] have shown that tissue availability correlates most closely with bioavailable testosterone, not as well with free testosterone by dialysis, and poorly with total or SHBG-bound testosterone. While some tissues may bind and actively internalize SHBG-bound testosterone, this is uncommon and involves small amounts. Thus, it is generally believed that bioavailable testosterone is the best in vitro measure of in vivo tissue availability of testosterone.

A number of calculated free and bioavailable testosterone measures utilizing total testosterone, SHBG, albumin and the

K_D of testosterone to SHBG have been developed. Recently, we have found variability of the K_D with aging (unpublished results). This reduces the value of calculated free or bioavailable testosterone. In addition antibodies to SHBG give different normal values depending on the antibody used ([30] and unpublished results). Differences in values by different antibodies may reflect that while SHBG exists of two polypeptide chains covalently bound, multiple dimeric forms circulate as variants of the two subunits exist because of differing amounts and types of carbohydrate side chains [31]. Both of the above mentioned factors can result in calculated values failing to correspond to measured free or bioavailable values.

Salivary testosterone represents an ultrafiltrate of testosterone from the circulation. While some metabolism of testosterone occurs in the salivary glands, it appears that salivary testosterone may correlate better with bioavailable testosterone than does total testosterone ([32] and unpublished observations). Our preliminary studies suggest that salivary testosterone has better sensitivity but poorer specificity than total testosterone in diagnosing hypogonadism. As such it may make an excellent screening test for hypogonadism.

In conclusion, while much controversy exists, it would appear that bioavailable testosterone, utilizing the ammonium sulfate precipitation technique, is the best available in vitro technique for diagnosing hypogonadism. However, it needs to be recognized that circulating factors such as saturated fatty acids increase SHBG binding and unsaturated fatty acids inhibit binding [33]. Further, in addition to the circadian rhythm of testosterone in younger men, marked week to week variations in total and bioavailable testosterone exist and there is some evidence supporting a circannual rhythm.

3. The androgen receptor, androgen action and aging

A single 99K_D androgen receptor binds both testosterone and dihydrotestosterone. The best characterized abnormality of the androgen receptor is Kennedy's syndrome, a condition associated with spinal and bulbar muscular dystrophy [34]. This condition has an increase in trinucleotide CAG repeats leading to androgen insensitivity. These CAG repeats encode variable length glutamine repeats in the N-terminal of the androgen receptor. The normal CAG repeat lengths range from 6 to 39, with a mean of 22. Overall, an increase in CAG repeats is associated with a decline in androgen action. A decrease in CAG repeat length is associated with increase in risk and severity of benign prostatic hypertrophy and prostate cancer [35,36]. One study found that in older men the lower the serum testosterone, free testosterone or calculated bioavailable testosterone levels, the less CAG repeats [37]. This could explain the increased testosterone inhibitory feedback on luteinizing hormone reported in some older men. The same study suggested that low testosterone levels associated with shorter CAG repeat lengths was predictive of dysphoria being present in older men [38].

There is a small amount of evidence that there is a decline in androgen receptor gene activation in the hippocampus and genital skin of older, compared to younger men, with no change being present in the prostate unless benign prostatic hyperthropy is present [39–41]. There are at present no studies on androgen mRNA activation in aging humans.

4. Positive effects of testosterone therapy in older persons

Overall, there are limited studies on the effects of testosterone replacement therapy in older persons. Table 3 provides a summary of the findings to date, based on a recent review by us [32]. The majority of studies have found that testosterone increases libido and improves the quality of erections. Morley and Tariq [42] have reported that testosterone will restore erections in persons who originally failed sildenafil. This would appear to be due to the ability of testosterone to enhance the synthesis of nitric oxide.

Testosterone has been shown to improve spatial memory in two studies [43,44] and, in one study [45], working memory in older males. It improved verbal memory in one study but not in two others [43,44,46]. In another study it had a minor effect on trailmaking B [47]. As far as effects on mood are considered, it increases positive and decreases negative mood parameters [48], but has no effect on dysphoria or depression [43,46,47,49].

Testosterone either prevents the loss of bone or increases bone mineral density [32,48,50,51]. This is most clearly demonstrable in men who have low testosterone levels at baseline, receive higher levels of testosterone replacement and do not receive concomitant calcium and vitamin D. Testosterone decreases fat mass including abdominal subcutaneous fat [32,52]. Leptin levels are increased in older men with declining testosterone levels and testosterone administration decreased leptin levels in older males [46].

Testosterone decreases LDL cholesterol in older men. Depending on the route of administration it has no effect on HDL cholesterol or produces a small decrease. This is counterbalanced by the effects of oral testosterone on hepatic lipase, which results in increased cholesterol clearance. Recent studies suggest that testosterone causes coronary artery vasodilation [53,54] and may improve quality of life in men

Table 3
Studies that examine the effect of testosterone in older men

Condition	Subjects (*n*)	Studies (*n*)	Positive studies (*n*, %)
Libido	253	8	7 (87)
Muscle mass	234	10	7 (70)
Muscle strength	201	11	7 (64)
Fat mass	209	10	8 (80)
Bone mineral density	170	7	6 (86)
Cognition	101	5	3 (60)

Based on studies reviewed in reference [32].

with angina. In one study it failed to increase endothelial mediated vasodilation [54]. The effects of testosterone on major cardiovascular events is unknown, though one small retrospective study suggested that it was not harmful [55].

5. Frailty, sarcopenia and testosterone

Loss of muscle mass with aging is associated with sarcopenia and frailty [56–60]. Loss of muscle mass with aging and declining muscle strength is associated with a reduction in free or bioavailable testosterone levels [61–63]. This decline in testosterone has also been associated with a reduction in function [63]. Testosterone appears to increase lean mass, but the effects on muscle strength are less clearcut [32]. In a small group of frail men receiving rehabilitation, testosterone improved physical function [64]. In another study, supraphysiological amounts of testosterone increased postoperative strength and physical function but did not reduce hospitalization and rehabilitation duration [65]. A single small study showed no improvement in quality of life (measured by the SF-36) in men receiving testosterone [66].

A recent study by Wittert et al. [67] suggested that testosterone increased lean mass but not muscle strength in men who were borderline but not frankly hypogonadal (78). The mechanism by which testosterone enhances muscle mass and strength is not clear. It may have a direct effect on muscle fibers or an indirect effect by increasing muscle insulin growth factor I. Alternatively, it may act on satellite cells or increase the recruitment of precursor cells.

Overall testosterone, either alone or in combination with exercise, has tremendous potential to prevent sarcopenia and frailty in older males. However, well-designed large clinical trials in sarcopenia and/or frail men are essential to determine whether this potential is a reality or merely a modern urban myth.

6. Adverse effects of testosterone

A major side effect of testosterone replacement therapy in older men is the ability of testosterone to stimulate erythropoeisis to produce polycythemia. This occurs in between 6 and 25% of older men [19]. The associated increase in blood viscosity can result in a significant risk of thrombotic events.

In most older men testosterone produces a small increase in prostate specific antigen [19]. No clear relationship between testosterone therapy and the development of benign prostatic hypertrophy or prostate cancer have been shown. However, the number of men treated is very small compared to the numbers needed to demonstrate the long term risks of testosterone on the prostate. Clearly, testosterone should not be given to men with diagnosed prostate cancer. The mechanisms by which androgens modulate prostatic cells leading to cell diversion are unclear [68]. The androgen receptor stimulates cyclin dependent kinases and regulate prostate cellular differentiation. The effects of the androgen receptor, after being activated by testosterone or dihydrotestosterone, involve complex interactions with a series of other hormones and growth factors.

Testosterone appears to worsen central sleep apnea, but may improve or at least not worsen obstructive sleep apnea [19]. Testosterone can also produce gynecomastia and increase water retention occasionally leading to hypertension or worsening congestive cardiac failure.

Table 4
The Saint Louis University androgen deficiency in aging males (ADAM) questionnaire

Questionnaire (circle one)			
Yes	No	(1)	Do you have a decrease in libido (sex drive)?
Yes	No	(2)	Do you have a lack of energy?
Yes	No	(3)	Do you have a decrease in strength and/or endurance?
Yes	No	(4)	Have you lost height?
Yes	No	(5)	Have you noticed a decreased enjoyment of life?
Yes	No	(6)	Are you sad and/or grumpy?
Yes	No	(7)	Are your erections less strong?
Yes	No	(8)	Have you noticed a recent deterioration in your ability to play sports?
Yes	No	(9)	Are you falling asleep after dinner?
Yes	No	(10)	Has there been a recent deterioration in your work performance?

A positive answer represent yes to (1) or (7) or any three other questions.

7. Symptom screening tests for hypogonadism in older males

Three screening tests for hypogonadism in older males have been developed viz the ADAM [69], the Massachusetts Male Aging Survey (MMAS) Questionnaire [70] and the Aging Male Survey (AMS) [71]. The ADAM has been translated into multiple different languages and is widely utilized throughout the world (Table 4). It was revalidated in French and Belgium [72]. It has excellent sensitivity but in general populations it has a sensitivity around 30%. This can be improved by excluding persons with depression and erectile dysfunction. The AMS seems to be equivalent to the ADAM in our preliminary studies. The MMAS questionnaire is based more on epidemiological than symptom characteristics of men with low testosterone. It has a worse sensitivity but better specificity than the other two questionnaires. The ADAM has been used to follow response to treatment.

8. Conclusion

Low bioavailable testosterone levels associated with a variety of symptoms are fairly common in middle aged and older men. It is suggested that the appropriate diagnostic approach to the andropause is to utilize one of the symptom

screening questionnaires and if it is positive, this should be followed up by the measurement of at least two bioavailable testosterone measurements a week apart. The combination of symptoms and a low bioavailable testosterone level makes the diagnosis of the andropause. At present, treatment of the andropause is to improve quality of life and thus, should not be continued if there is no symptomatic improvement. All men who have low bioavailable testosterone levels should have a bone mineral density test and, if osteopenia or osteoporotic, should receive treatment for those conditions.

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