

UROLOGIC ASPECTS OF ANDROPAUSE

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Life expectancy has increased dramatically during the past century. The population of elderly people is also progressively increasing. Between 2000 and 2050, the proportion of the population older than 60 and 80 years will double and quadruple, respectively.¹ Increasingly, physicians will see elderly people in their everyday practice.

Aging-related health problems, including the gradual decrease in gonadal function in men after middle age ("andropause"), have gained interest in the medical community. The term "andropause" is physiologically incorrect, because, unlike women, men do not experience universal absolute gonadal failure. Some investigators have therefore suggested more appropriate names, such as androgen decline in the aging male² or partial androgen deficiency in the aging male (PADAM).³ Many recent studies have addressed the benefits and risks of androgen-replacement therapy for hypogonadal aging men. However, no conclusive results from long-term large-scale studies have been obtained.⁴ The potential effects on the prostate are a major concern regarding testosterone replacement therapy.

Aging men constitute the majority of urologists' patients. Therefore, urologists should be able to recognize the manifestations of andropause, which are subtle, nonspecific, and frequently not acknowledged. In this study, we performed a PubMed search of English medical reports using the key words andropause, PADAM, hypogonadism, prostate, sexual function, fertility, and testosterone. In addition, conference proceedings were

researched. Data were subsequently organized and summarized.

ANDROPAUSE

Testosterone is the major androgen in the blood. The Leydig cells of the testis produce most of circulating testosterone. Only 1% of plasma testosterone is free. About 11% to 59% is bound to albumin weakly and 40% to 88% is tightly bound to sex hormone-binding globulin.⁵ Bioavailable testosterone refers to albumin-bound plus free testosterone. Both total and free testosterone decline with aging. This was demonstrated in cross-sectional⁶ and longitudinal⁷ studies. The magnitude of the total testosterone decrement averaged 0.11 nmol/L (3.2 ng/dL) per year.⁷ As a result of the age-related increase in sex hormone-binding globulin concentration, the decline in free testosterone is more profound than that of total testosterone.⁴ At the age of 80 years, the mean testosterone concentration is only about 60% of the mean testosterone concentration in the age group of 20 to 50 years.⁸

The etiology of testosterone decline with aging is multifactorial and involves the hypothalamic-pituitary-gonadal axis⁴ among other factors. The most important reason for decreasing testicular androgen production with aging is a decline and alteration in the number of Leydig cells.⁹ Age-related alterations of the hypothalamic-pituitary-gonadal axis also contribute to a decline in testosterone production. There is evidence that elderly men fail to increase their luteinizing hormone in a response to the hypoandrogenic state, resulting in a relative hypogonadotropic hypogonadism.⁹ Multiple other factors also have an impact on serum testosterone levels, including hereditary factors, obesity, diet, stress, depression, chronic diseases such as diabetes mellitus, coronary atherosclerosis, chronic renal failure, chronic liver disease, sleep apnea syndrome, and rheumatoid arthritis, and medications, such as glucocorticoids, smoking, and alcohol intake.^{4,9} Low serum testosterone levels are associated with nonspecific clinical signs and symptoms, such as (a) decreased potency and libido, (b) changes in mood, including depression, irritabil-

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ity, and anxiety, (c) chronic fatigue and sleep disturbances, (d) decreased lean body mass and muscular strength and increased visceral fat distribution, (e) decreased bone mass density, and (f) some regression of secondary sexual characteristics.³ The diagnosis of andropause (or PADAM) requires the existence of some or all of the signs and symptoms mentioned plus a low free or bioavailable testosterone level.

AGING AND FERTILITY

With aging, the testes undergo several histomorphologic changes,¹⁰ including a reduction in the number of Leydig and Sertoli cells, thickening of the basal membrane of the seminiferous tubules, and arteriosclerotic lesions. However, whether these alterations affect semen characteristics has not been clearly defined.

The data on the influence of aging on semen parameters are contradictory. Although some investigators found no decline in semen characteristics in elderly men,¹¹ others either observed significant changes in quality parameters (ie, morphologic characteristics and motility)¹² or found a decline in one parameter only such as semen volume or sperm count.¹³ Aging appears to have no influence on the fertilizing potential of the sperm. More importantly, advanced paternal age did not adversely affect pregnancy outcomes (ie, pregnancy, implantation rate, pregnancy loss, or live birth rate).¹³ On the other hand, male aging is associated with declining fecundity.¹⁴

Regarding the effects of androgen therapy, chronic testosterone administration in physiologic dosages suppresses sperm production by suppressing gonadotropin secretion.¹⁵ After 6 months of weekly intramuscular testosterone enanthate injections, 65% of subjects became azoospermic.¹⁶ In these individuals, the effectiveness of testosterone injections after 1 year was comparable to the effectiveness of an oral contraceptive.¹⁶ These effects were reversible after treatment discontinuation.

AGING, ANDROGENS, AND SEXUAL FUNCTION

Aging is associated with gradual alterations in sexual response,¹⁷ manifested by a prolonged arousal response and decreased penile sensitivity. Additionally, erection is less rigid and delayed, and orgasm is less intense. Finally, it is associated with rapid detumescence and a prolonged refractory period. However, the differences among individuals vary greatly.¹⁷ Testosterone is thought primarily to stimulate libido at the levels of the central nervous system.¹⁸ Bagatell *et al.*¹⁹ reported on normal men who had a significant decrease in sexual desire, fantasy, spontaneous erections, and masturbation

after a few weeks of androgen suppression by a gonadotropin releasing hormone antagonist. These changes were not found when the subjects received androgen therapy simultaneously with the gonadotropin releasing hormone antagonist.¹⁹

Erectile dysfunction (ED), which is defined as the persistent inability to attain and maintain a penile erection adequate for satisfactory sexual performance,²⁰ is a common condition in the elderly population. The results of the Massachusetts Male Aging Study²¹ indicate that the variable most strongly associated with ED is age. The prevalence of complete ED in that study tripled between men aged 40 and 70 years.

There is a considerable controversy regarding the role of androgens in erectile function. Animal studies from our laboratory using the rat model showed that penile cavernosal and spongiosal cells undergo apoptosis (programmed cell death) in response to castration. In a follow-up work, testosterone activated a *de novo* DNA synthesis in the penis of castrated adult rats, including cavernosal cells.²² In human studies, about 50% of castrated sex offenders could achieve and sustain an erection.²³ Although nocturnal penile tumescence is inhibited by androgen deficiency, erections in response to visual erotic stimuli may be partially androgen independent.²⁴

Korenman *et al.*²⁵ found no difference in serum bioavailable testosterone levels between older men with and without ED. They therefore proposed that ED and secondary hypogonadism are two common independent disorders of aging men.²⁵ Similarly, the Massachusetts Male Aging Study showed no significant correlation between ED and serum testosterone level (whether free, albumin-bound, or total).²¹ The only hormonal decline that correlated with ED in that study was that of dehydroepiandrosterone.²¹ Data from animal and human studies indicate that low-normal range concentrations of testosterone are sufficient to maintain sexual activity, and that there is a threshold level of testosterone, above which no further improvement ensues in response to therapy.^{26,27}

Administration of testosterone to normal eugonadal men enhances penile rigidity, but does not change the circumference or frequency of erections during nocturnal penile tumescence.²⁴ In hypogonadal men, it improves libido and sexual performance.²⁷ Wang *et al.*²⁷ have reported on 227 hypogonadal men between 19 and 68 years old, who were treated by transdermal testosterone for 6 months. Sexual function was assessed by questionnaire. Significant improvements in sexual desire, sexual enjoyment with the partner, and achievement of a full erection were reported after a mean treatment period of 30 days.²⁷ In a study by Morales *et al.*,²⁸ 39% of subjects had a complete re-

sponse (ie, in both libido and erections) and 22% were reported to have a libido response only.

On the other hand, Guay *et al.*²⁹ investigated the impact of raising endogenous testosterone levels in impotent hypogonadal men by administering clomiphene citrate. They found no clear improvement of sexual function as monitored subjectively by questionnaires and objectively by nocturnal penile tumescence and rigidity testing. Sixteen percent of the participants of the initial study group, who had slightly low free testosterone levels, were excluded from the study because of psychogenic ED and normal results on nocturnal penile tumescence studies. In addition, unless testosterone deficiency was severe (free testosterone less than 7 to 8 pg/mL), testosterone replacement therapy did not significantly improve the success rate of sildenafil in patients with ED and hypogonadism.³⁰

It should be kept in mind that androgen deficiency, especially in elderly men, is not the most common cause of ED. Other common vascular, neurologic, and psychological, iatrogenic factors are very likely to coexist with androgen deficiency and prevent the beneficial effects of androgen replacement therapy.

TESTOSTERONE THERAPY AND THE PROSTATE

The development of the prostate and the rest of the male internal accessory sexual structures are androgen dependent.³¹ Full development of the prostate is completed only after puberty, requiring adult male serum testosterone concentrations along with normal type II 5-alpha-reductase enzyme. This enzyme converts testosterone to its active metabolite form dihydrotestosterone.³² Functional androgen receptors are also required for appropriate development. Therefore, in patients with testicular feminization—a congenital defect in androgen receptors—the prostate fails to develop.³³ However, some aspects of neonatal prostate development may be androgen independent. Animal studies showed that castration of neonatal rats did not completely prevent prostate development.³¹

The maintenance of morphology and functional activity of the adult prostate is also androgen dependent. In mature rats, castration caused a reduction of 45% in prostatic relative blood flow at 24 hours after castration.³⁴ It has also been reported that castration caused an 85% and 81% decrease in total epithelial weight and total ventral prostate lobe weight, respectively.³⁵ Hypogonadal men have repeatedly been found to have a reduced total prostate volume compared with eugonadal men.^{36–38}

Considerable uncertainty exists regarding the long-term effects of androgen replacement therapy on the prostate. Several questions need to be answered, including the role of androgens in the pathogenesis of benign prostatic hyperplasia (BPH) and prostate cancer; whether testosterone therapy initiates BPH or prostate cancer; the effects of testosterone therapy on an existing cancer; and how serum prostate-specific antigen (PSA) levels are affected by androgen deficiency and androgen replacement.

ROLE OF ANDROGENS IN PATHOGENESIS OF BPH AND PROSTATE CANCER

BPH is clearly associated with aging. Its prevalence increases from 8% in the fourth decade to more than 70% in the seventh decade.³⁹ There is evidence that BPH is initiated probably before age 30 years.³⁹ Genetic and environmental factors seem to be involved in the pathogenesis of BPH. The role of androgens in that process is not completely clarified. BPH originates from the transition zone of the prostate, the same area that has greater hormonal sensitivity in primates.⁴⁰ In a study of anabolic androgen abusers, the total prostate volume was normal compared with age-matched healthy eugonadal men.⁴¹ The central prostate volume was, however, increased by 20%, and the central prostate volume/peripheral prostate volume ratio was increased by 77%.⁴¹ No differences in hormone concentrations could be established between patients with BPH and controls.⁴² The estrogen/androgen ratio increases with aging because of the gradual decline in androgen levels. Therefore, the relative decrease of androgens compared with estrogens seems to be an initiating factor for BPH.⁴²

The etiology of prostate cancer is multifactorial and includes aging and hormonal, genetic, and environmental factors. Despite extensive study, the exact role of androgens in this context is unclear. Several investigators have examined the correlation between serum androgen levels and the occurrence of prostate cancer. Carter *et al.*⁴³ did not find any significant differences in age-adjusted luteinizing hormone, sex hormone-binding globulin, or calculated free testosterone among men who developed prostate cancer and those who did not. In another longitudinal study, Gann *et al.*⁴⁴ reported a strong correlation between prostate cancer risk and high normal testosterone levels. A racial variation in the incidence of prostate cancer can also be observed, which may be explained by differences in testosterone biosynthesis and metabolism. Other factors should also be considered, including androgen tissue concentrations, rate of testosterone reduction to dihydrotestosterone, and sensitivity of androgen receptors.³

TABLE I. Effects of testosterone therapy on PSA levels and prostate volumes in hypogonadal men

Reference	n	Duration (mo)	Administration	Effects on	
				PSA	Prostate Volume
Behre <i>et al.</i> , ³⁷ 1994	78	41.5 ± 36.2	Oral, TTS, IM	NS	NS
Jin <i>et al.</i> , ⁴¹ 1996	15	18	Anabolic steroid abusers	NS	TPV: NS, CPV: 20% ↑
Meikle <i>et al.</i> , ³⁶ 1997	29	Up to 12	IM, TTS	NS	NS
Snyder <i>et al.</i> , ⁴⁵ 2000	18	12–36	TTS	NS	NS
Jin <i>et al.</i> , ³⁸ 2001	54	32	Implants, IM	NS	TPV: NS, CPV: NS

KEY: PSA = prostate-specific antigen; NS = no statistical difference between testosterone-treated hypogonadal men and normal men; IM = intramuscularly; TTS = transdermal therapeutic system; TPV = total prostate volume; CPV = central prostate volume; ↑ = increase in the treatment group (statistically significant).

DOES TESTOSTERONE THERAPY INITIATE BPH OR PROSTATE CANCER?

Both cross-sectional and longitudinal studies have shown that the administration of testosterone in hypogonadal men increases the prostate volume from subnormal to normal values compared with age-matched normal men, especially in the central zone.^{36–38,45} The increase in prostate volume with testosterone replacement therapy, however, was not clinically significant.²⁷ Therefore, most investigators agree that nonobstructive BPH is not a contraindication to testosterone therapy.⁴ The effects of testosterone therapy on PSA levels and prostate volumes in hypogonadal men are summarized in Table I.

It could not be demonstrated that testosterone administration to hypogonadal men increases the risk of prostate cancer.² However, considering the long natural history of prostate cancer and the limited observation time with testosterone therapy, the long-term safety of exogenous testosterone is still unknown.

EFFECTS OF TESTOSTERONE THERAPY ON EXISTING CANCER

Obviously, documented prostate cancer is an absolute contraindication to testosterone therapy. Moreover, it appears that testosterone administration may promote the growth of subclinical prostate cancer, which is very frequent in elderly men. Therefore, it is crucial to rule out prostate cancer before the initiation of testosterone therapy and to monitor the prostate throughout the treatment period. The second Annual Andropause Consensus 2001 Meeting recommended performing digital rectal examination (DRE) and serum PSA measurement before treatment, at 3 and 6 months, and yearly thereafter (personal communication, R. Shabsigh, 2002). In addition to that recommendation, the PSA level should be determined 1 month after initiation of therapy to find the patient with previously undiagnosed prostate cancer that may behave in a very aggressive fashion after testosterone replacement therapy. Finally, from a cancer

perspective, intramuscular testosterone depot preparations can be problematic, because the peaks of serum testosterone could result in cancer progression similar to the early luteinizing hormone-releasing hormone analog “flare” tumor progressions. Testosterone replacement should therefore be administered using a gel or a patch to achieve a physiologic pattern.

HOW ARE SERUM PSA LEVELS AFFECTED BY ANDROGEN DEFICIENCY AND ANDROGEN REPLACEMENT?

Serum PSA levels can be affected by aging, prostate volume, and prostate cancer.⁴⁶ Especially in younger men, age-adjusted PSA cutoffs should be taken under consideration when testosterone replacement therapy is administered. Untreated hypogonadal men, however, can have significantly lower serum PSA concentrations than controls.³⁷ Testosterone replacement therapy can result in an increase in serum PSA levels to the high normal range.^{35,36} On the other hand, testosterone does not significantly change serum PSA levels in eugonadal men.⁴¹ PSA has been routinely used along with DRE to detect or exclude cancer before the initiation of testosterone treatment.

However, in a study of 77 untreated hypogonadal men with normal DRE findings and serum PSA levels of 0.4 ng/mL or less, prostate cancer was detected by biopsy in 14% and 29% in the entire group and in men aged 60 years old or older, respectively.⁴⁷ Furthermore, Schatzl *et al.*⁴⁸ reported that patients with prostate cancer and low serum testosterone concentrations have lower serum PSA levels than those with normal serum testosterone levels. Interestingly, in the same study, the Gleason scores were significantly higher in the androgen-deficient group. Thus, it was recommended by one investigator to perform prostate biopsies before initiation of testosterone therapy, especially in elderly men.⁴⁷ Other investigators did not agree with that² and suggested performing a prostate biopsy only if abnormalities were detected by DRE or if PSA levels were increasing rapidly during testosterone therapy (an increase of 1.5 ng/mL or greater

in two determinations at 3 to 6-month intervals or an average annual increase of 0.75 ng/mL or greater; personal communication, R. Shabsigh, 2002). Finally, a promising advancement in this area is the development of specific androgen receptor modulators.⁴⁹ These are a new family of synthetic nonsteroidal molecules that display selective preferential activities for androgen receptors in certain tissues such as muscle, bone, and central nervous system. Specific androgen receptor modulators are not substrates of the 5- α -reductase enzyme and are therefore not converted to dihydrotestosterone. Consequently, they do not have a proliferating activity in the prostate.

OTHER POTENTIAL SIDE EFFECTS OF ANDROGEN REPLACEMENT

Androgen substitution can have potentially adverse events on many other organs and organ systems that should be mentioned. Testosterone stimulates renal erythropoietin production, and may therefore lead to polycythemia.⁵⁰ Exacerbation of a pre-existing sleep apnea has also been reported after testosterone administration.⁵⁰ Regarding body composition, testosterone leads to a decrease in body fat, increase in lean body mass, and changes in muscle strength.⁵⁰ Bone density may be increased in elderly men undergoing testosterone therapy, although additional longer term data are needed to confirm that androgen replacement can sustain a stabilization or reversal of bone loss in this age group.⁹

CONCLUSIONS

Aging in men is associated with a progressive decline in serum androgen levels. The diagnosis of andropause or PADAM should be based on both clinical and laboratory criteria. A gradual decrease of sexual function in aging men is a commonly observed phenomenon. It seems that testosterone levels in the low-normal range might be sufficient for maintaining normal sexual function. No conclusive data are available about the influence of aging on semen parameters. However, the fertilizing capacity of spermatozoa is not affected by male age, at least in vitro.

Several studies have suggested a benefit of testosterone replacement on psychological, sexual, and physical functioning in aging men with low serum testosterone levels. The administration of testosterone results in a significant increase in serum PSA levels and prostate volumes, especially the volume of the central zone, without exceeding the normal limits for age-matched normal men. Testosterone therapy is absolutely contraindicated in a patient with prostate cancer. Prostate cancer should therefore be ruled out before testosterone

treatment. Large-scale, long-term clinical studies are needed to resolve the issues related to andropause and assess the long-term risk versus benefit profile of androgen replacement therapy in aging men.

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