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Androgen deficiency in the aging male: benefits and risks of androgen supplementation☆

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Abstract

There is now convincing evidence that in a subset of aging men, increasing with age, plasma testosterone levels fall below a critical level resulting in hypogonadism. This state of testosterone deficiency has an impact on bone, muscle and brain function and is maybe a factor in the accumulation of visceral fat which again has a significant impact on the cardiovascular risk profile. From the above it follows that androgen replacement to selected men with proven androgen deficiency will have beneficial effects. There is, however a concern that androgen administration to aging men may be harmful in view of effects on prostate disease. Benign prostate hyperplasia (BPH) and prostate cancer are typically diseases of the aging male, steeply increasing with age. But epidemiological studies provide no clues that the levels of circulating androgen are correlated with or predict prostate disease. Similarly, androgen replacement studies in men do not suggest that these men suffer in a higher degree from prostate disease than control subjects. It seems a defensible practice to treat aging men with androgens if and when they are testosterone-deficient, but long-term studies including sufficient numbers of men are needed.

Keywords: Testosterone; Aging; Bone; Muscle; Psyche; Prostate disease

1. Introduction

Aging is characterized by a progressive decline of virtually all physiological functions. Among them is the secretory capacity of the endocrine glands. Hormones do play an important part in homeostasis. While most elements in the aging process are not, or only to a certain point, amenable to intervention, hormonal dysfunctions, compared with other age-related events, are relatively easy to diagnose, and they lend themselves to corrections more readily than other age-related ailments. Laboratory methods in the assessment of endocrine (dys)functions are rather precise, and are mostly non-invasive and affordable. For this reason, it is worthwhile discussing the hormonal factors involved in aging.

The hormonal system undergoes profound changes with aging. The hormones affected are the gonadal hormones, the adrenal hormones—dehydroepiandrosterone (sulphate) and androstenedione—and growth hormone. They have received a great deal of attention over the years since their decline is rather universal in the human. There are publications of clinical results of replacement therapy with these hormones but a definitive benefit/risk balance is awaiting further study. Such studies should include large numbers of subjects and should be of sufficient duration to allow conclusions as to long-term benefits and the potential side effects. In fact, such studies should, ideally, include several thousands subjects and should last several years. The feasibility of such studies is seriously hampered by the latter two facts. The logistics and the costs of such large-scale studies are prohibitive.

This contribution will focus on androgen deficiency of the aging male. Androgen deficiency is by no means universal in the aging male, and its diagnosis is not as simple as it would look like. In this issue of this journal Dr. John Morley addresses the thorny issue of establishing, with reasonable certainty, androgen deficiency in the aging male. This contribution will focus on potential benefits and potential risks. There is a relatively large experience with androgen substitution to men. As a result, there is a reasonable amount of insight into benefits and risks, be it that this experience has been gained in younger men.

2. Age-related decline of androgen levels

It has long been controversial as to whether men show a decline in testosterone levels with aging. The first studies were done in clinical populations whose impaired

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health situation might have been the explanation of the lower-than-normal testosterone levels. However, several methodologically sound studies in healthy men show that testosterone, particularly free, bioactive levels of testosterone, do decline with aging, though there is considerable inter-individual variation.

Androgens have a large number of non-reproductive effects; they are important anabolic factors in the maintenance of muscle mass and bone mass and in non-sexual psychological functioning. A small portion of secreted androgens in the male is aromatized to estrogenic hormones. There are recent insights that these estrogens fulfill a significant role in the male.

Not only androgen production declines with aging, but also the secretion of growth hormone and adrenal androgens diminishes. The biological actions of androgens and growth hormone are largely intertwined. Some anabolic effects of androgens have growth hormone-related factors as intermediaries.

Strategies have to be devised to let the aging male benefit from new medical insights into the aging process. The track record of hormonal intervention to combat the signs and symptoms of the aging male has not been glorious. Up to the present day there is a considerable misuse of hormonal preparations in the medical care of aging men. The following contribution will address a number of pertinent issues. Only on the basis of sound scientific data a consensus will be reached in this controversial issue. Part of the controversy surrounding this subject is the terminology to describe the age-related changes in the secretion of androgens. Terms like male menopause or andropause more or less suggest that, similarly to women, all men go through a profound decline of their androgen production from middle age on, but it should be stressed that the age-related decline of androgens in men follows a totally different pattern in comparison to the menopause. Several studies now document that androgen levels decline with aging (for review see [1]). Initially, cross-sectional studies [1–3] but later also longitudinal studies [4,5] have documented a statistical decline of plasma testosterone by approximately 30% in healthy men between the ages of 25–75 years. While it now has been shown that plasma testosterone, and in particular free testosterone decline with aging, it remains uncertain what percentage of men becomes actually testosterone-deficient with aging. Stringent criteria for testosterone deficiency have not been formulated. In a study of 300 healthy men between the ages of 20–100 years, Vermeulen et al. [3], defining their reference range of testosterone between 11 and 40 nmol/l, found one man with subnormal testosterone in the age group between 20 and 40 years, but more than 20% above the age of 60 years while 15% of men above the age of 80 years still had testosterone values above 20 nmol/l. The implication is that the fall of testosterone levels below normal is not universal in men but affects only a certain proportion of men. The term ‘partial androgen deficiency of the aging male’ (PADAM) has been proposed to describe this phenomenon. The androgen deficiency is partial in two ways: (1) the decline in androgen levels is not as profound as the decline of estrogens in menopause and (2) it affects only a proportion of aging men, increasing with age. This term is certainly to be preferred over the above terms but it may miss the point that the decline of androgen levels in some aging men qualifies for the diagnosis of hypogonadism, a state of testosterone deficiency characterized by signs and symptoms of androgen deficiency. It is increasingly realized that androgens have a large number of non-reproductive effects; they are important anabolic factors in the maintenance of muscle mass and bone mass and in non-sexual psychological functioning. The latter are important constituents of well-being in old age. So, the state of androgen deficiency if it occurs in aging men has clinical relevance. The latter condition cannot be dismissed as irrelevant or only a fashionable form of medical care for affluent aging men.

The following will address the relevance of lower-than-normal testosterone levels in aging men and the potential side effects of androgen administration to aging men.

3. Clinical relevance of declining androgen levels with aging

3.1. Bone mass

Similar to the situation in women men show a progressive loss of bone with an exponential increase in the incidence of bone fractures with aging [6,7], be it that the exponential increase in men starts at a later age (6–8 years later) than in women. Both androgen levels and bone mass decline with age. The actions of androgens on bone might be indirect. A recent paper found evidence that bioavailable testosterone levels are positively associated with insulin-like growth factors; the latter correlated again with bone mineral density of the femur and the calcaneus [8]. The available studies in hypogonadal men receiving androgen replacement treatment show that their bone mass increases but does not become normal [9]. Some studies have found a beneficial effect of androgen supplementation in old age on bone density [10–12] or on biochemical indices of bone turnover. A recent well-designed study demonstrated that elevation of testosterone values in men over 65 years to mid-normal levels for young men did not increase lumbar spine density overall but did increase it in those men with low pretreatment serum testosterone levels [13]. The latter validates the assumption that lower-than-normal androgen levels in aging men are a factor in the development of osteoporosis. A role for estrogens, aromatization products of androgens, on the health of male bones is becoming clear. Two cases of men with an impairment of the biological effects of estrogens, presenting with delayed epiphyseal closure and osteopenia have stirred up attention for the role of estrogens in acquiring and maintaining BMD in men. It could

be shown in another man with aromatase deficiency that estrogen administration had a significant beneficial effect on skeletal growth and bone maturation (for a review see [14]). Androgen receptors are present at low densities in osteoblasts, which express 5α-reductase activity. So, there is evidence that androgens exert effects on (peak) bone mass in men in their own right but part of the effects may be ascribed to aromatization to estrogens which may occur locally in bone and may therefore not be fully evident from plasma levels of estrogens. The presently available evidence supports a role of estrogens in the bone loss of aging men [7,15]. So, with the present state of knowledge it would therefore seem desirable that for induction and maintenance of bone mass the type of androgens administered should be aromatizable.

3.2. Lean body mass and muscle strength

Androgens have an anabolic effect on muscles, specially the muscles of the upper body. With aging there is a decrease in muscle mass, most of the times associated with an increase in adipose tissue, predominantly in the abdominal and also upper body regions [16]. The interesting question whether the synchronism of the decline of muscle mass and of androgen levels with aging is causally interrelated has not been resolved [17]. In a cross-sectional study in aging men, 65–97 years of age, muscle mass was significantly associated with serum free testosterone, physical activity, cardiovascular disease and IGF-1. But grip strength, probably more relevant, was associated with age independent of muscle mass [18]. Three studies that investigated the effect of testosterone supplementation to small groups of aging men found an increase of lean body mass and an improvement in handgrip strength [18] or on lower limb muscle function, though the magnitude of the improvement was not reported [19]. Tenover [12] did find an improvement in lean body mass but no clear increase in muscle strength. A recent study established that administration of testosterone to men over 65 years of age, achieving serum levels in the mid-normal range, decreased fat mass, increased lean body mass but did not increase the strength of knee extension and flexion [20]. Another recent study of parenteral testosterone administration over 12 weeks found neither an increase in lean body mass nor in muscle strength. This study focused on lower extremity muscles being probably more relevant for stair climbing, chair rising and walking [13]. Strength of the quadriceps and triceps surae are much more significant in old age since they determine gait speed, balance, rising from a seated position and stair climbing and they are most impaired in old age. A very positive effect of resistance training has been observed in aging subjects (for a review see [21]). In conclusion: the causal role of declining androgen levels with aging in loss of muscle mass/strength awaits further corroboration. Androgen therapy may have an effect on lean body mass but the effects on muscle strength are much less certain. Declining growth hormone levels might be significant as well.

3.3. Androgens and sexual/psychological functions

Reliable studies on the relationships between androgens and psychological functions are of rather recent date. There is now solid evidence that androgens stimulate sexual appetite. With regard to erectile function the situation is somewhat less clear. It has become clear that in males between 20 and 50 years approximately 60–80% of the normal physiological levels suffice to maintain sexual functions and that increasing testosterone levels above that threshold adds little to sexual functioning. Whether this holds true for aging men remains to be established. Most aging men complain of erectile failure rather than of loss of libido; therefore it is not certain that their sexual functioning will improve much upon androgen supplementation.

There is some evidence to suggest that testosterone may influence performance on cognitive tasks [22,23], which is supported by the finding that testosterone administration to older men enhances performance on measures of spatial cognition. Testosterone has also been associated with general mood elevating effects, and some studies have found associations between lowered testosterone levels and depressive symptoms [23,24]. Depression is not rare in aging men and impairs their quality of life [25]. So the effects that declining levels of androgens may have on mood and on specific aspects of cognitive functioning in aging are well worth to be researched.

4. Androgens and gynecomastia

Gynecomastia develops in cases of an increased estrogen/androgen ratio, or more precisely an estrogen/androgen ratio that effectively acts at the breast tissue (for review see Gooren [26]). The aging process itself is associated with a loss of androgen production, a rise of sex hormone binding globulin, and an increase of adipose tissue, the site of aromatase activity enabling the conversion of androgens to estrogens. Plasma estradiol levels do not decline with aging. The combination of these factors leads already to a prevalence of spontaneous gynecomastia in old age. Administration of aromatizable androgens may lead to gynecomastia in both puberty and old age, in all likelihood when the subsequent increases of estrogens and androgens tip the balance in favor of a higher estrogen/androgen ratio. This side effect is medically innocent and may subside over time. Patients with liver or renal disease or hyperthyroidism may be particularly predisposed to the development of gynecomastia.

5. Androgens and cardiovascular effects

Traditionally it is thought that the relationship between sex steroids and cardiovascular disease is predominantly determined by the relatively detrimental effects of androgens on lipid profiles. It is then paradoxical that in cross-sectional

studies of men low levels of testosterone [27–29] appear to be associated with coronary disease and myocardial infarction. Recent research shows indeed that the effects of androgens are much wider than on lipids alone and that there are effects on other biological systems, such as fat distribution, endocrine/paracrine factors produced by the vascular wall (such as endothelins, nitric oxide), blood platelets and coagulation. These studies suggest the intriguing possibility that, in spite of the overall negative effects on androgens on lipid profiles, a lower-than-normal androgen level in aging men is associated with an increase of atherosclerotic disease. It is now commonly accepted that a preferential accumulation of fat in the abdominal region is associated with an increased risk of non insulin dependent diabetes mellitus (NIDDM) and cardiovascular disease, not only in obese subjects but even in non-obese subjects [30]. A large number of cross-sectional studies have established a relationship between abdominal obesity and cardiovascular risk factors such as hypertension, dyslipidemia (elevated levels of cholesterol, of triglycerides, of low-density lipoproteins and low levels of high density lipoproteins), impaired glucose tolerance with hyperinsulinemia, a cluster known as the 'insulin resistance syndrome' or 'metabolic syndrome' [31,32]. A number of studies have documented that visceral obesity is associated with low plasma total testosterone levels [33–36]. It remains to be determined whether testosterone administration to men with visceral obesity and low testosterone levels will improve their cardiovascular risk profile.

The above information is also relevant to the subject of prostate disease since obesity and hyperinsulinism and high leptin levels (an index hormone of obesity) seem associated with prostate disease in old age (see below).

6. Androgens and hematopoeiesis and sleep apnea

Young hypogonadal men have lower red blood cell counts and hematocrits than age-matched controls. These values increase upon administration of androgens to hypogonadal men [37]. Healthy older men tend to have similar or slightly lower hematocrit values than young adult men [38]. Two studies of elder men receiving androgen administration have shown increases of hematocrit of up to 7% [11,12]. Androgen replacement therapy may result in polycythemia [19,39]. In some cases of polycythemia phlebotomy or withholding androgen administration is required. There is very likely a relationship with peak levels of testosterone associated with the treatment modality. Parenteral testosterone injections with high peak levels of testosterone produced higher hematocrit values compared to oral and transdermal testosterone treatment modalities [40].

Sleep apnea is relatively uncommon but debilitating disorder occurring almost exclusively in men, particularly when they age. In men suffering from sleep apnea, low total and free testosterone levels have been found [41,42] which may be secondary to their abdominal (visceral) obesity. Several androgen replacement studies provide evidence that androgen administration to hypogonadal men may induce [42] or exacerbate sleep apnea in elderly men [43,44]. Also in a study of Matsumoto et al. [37] it was shown that androgen levels may play a role in the pathogenesis of obstructive sleep apnea and that this may be a complication of testosterone therapy, though the relevance of androgens for obstructive sleep apnea could not be shown in a study wherein the pure antiandrogen flutamide was used and no improvement of sleep apnea was observed [45]. Since these apnoeic events and the ensuing oxygen desaturation may lead to cardiovascular complications it is pertinent to enquire elder men about this symptom and to measure and follow up haematocrit values before and during androgen administration. Care must be exercised in men who are overweight, heavy smokers, or who have chronic obstructive airway disease.

7. Prostate disease and androgen supplementation in old age

An immediate concern of androgen supplementation in old age is the development and/or progression of prostate diseases such as benign prostate hyperplasia (BPH) and prostate carcinoma. It is widely accepted that both conditions do not develop without testosterone exposure early in life, up to early adulthood. The present position of experts in the field is that androgens do not truly cause BPH or prostate carcinoma but that they have a 'permissive' role, evidenced by the beneficial effects of treatment aiming to reduce the biological effects of androgens on both conditions [46]. Several studies have found that the prevalence of microscopic prostate cancer and its precursor lesions increases strongly with aging, with a prevalence of 33–50% found in men between 60 and 70 years of age [47]. However, only a small subset of these men (4–5%) will actually go on to develop clinically detectable carcinomas [46].

It is highly remarkable that androgen related prostate diseases such as benign prostate hyperplasia and prostate carcinoma develop in a period of life of men when serum androgen levels are declining in most men, so androgens alone are unlikely to serve as the only causative factor. It is, however, of note that finasteride, a 5α-reductase inhibitor, reducing DHT levels, is capable of reducing prostate volume in patients with BPH [48] evidencing a role of DHT in BPH. Similarly, LHRH-agonists and flutamide reducing respectively androgen production and androgen biological action, are capable of reducing prostate volume in men with BPH. Plasma DHT levels in elderly men are either unchanged or slightly decreased [2] but a slightly elevated DHT level has been found in men with BPH [49]. There is evidence that the development of BPH is correlated to serum estradiol levels [50]. Since benign prostatic hyperplasia (BPH) occurs typically in the aging male, the resultant increase in the estradiol/testosterone ratio has been implicated in its pathogenesis, mainly on the basis of observation

in dogs. Histologically, BPH is more of a stromal disease than an epithelial disease. For example, one study found that concentrations of estradiol and estrone increased in the stroma but not in the epithelium, as a function of age [51]. In the normal situation, as opposed to BPH, the concentration of estradiol and estrone are higher in the epithelium of the prostate than in the stroma. The stromal dihydrotestosterone (DHT) level shows no correlation with age [51]. One hypothesized mechanism for the effects of estrogens on the prostate is that estrogens can induce transcriptional activity of the androgen receptor [52]. From this, it would seem that the inhibition of the biological effects of estradiol might have a beneficial effect on stromal hyperplasia, but studies using the aromatase inhibitor atamestane show that the reduction of estrogen level, has no consistently beneficial effect on clinically already established BPH [53,54]. The relationship between estrogens and prostate cancer has received less attention. A recent study indicates that estradiol levels were lower while cortisol levels were higher in men with prostate cancer compared to age-matched men with lower urinary tract symptoms [55]. While the studies in laboratory animals and in vitro show increasingly a convincing role for estrogens in prostate pathology of old age, reduction of estrogen action has as yet not resulted in successful therapeutic interventions in established prostate disease. If the increasing estradiol/androgen ratio, commonly encountered in aging men, is significant for the development of prostate disease, administration of androgens to aging men might restore their estradiol/androgen ratio to more youthful values, even though part of the administered androgens will be aromatized to estrogens but androgen administration might still tip the balance in favor of a stronger androgenic component.

The results of the Massachussets Male Aging Study showed convincingly that, with our current understanding of prostate cancer risks, sex steroids only account for 11% of the risk factors; 30% is related to nutrition and 40% by other factors, largely not subject to change, such as height, weight and family history [56]. There is presently no evidence that those who do go on to develop carcinomas have higher androgen levels [57]. While the prevalence of microscopic prostate cancer is similar in different parts of the world, the progression to clinical cancer varies strongly, with the highest prevalence in those parts with a Western lifestyle. Thus it is probable that lifestyle factors, such as nutrition, might play a role. With regard to BPH, there is no evidence that androgen administration to hypogonadal [58,59] or to eugonadal men [60] increases the incidence of BPH over that observed in control eugonadal men. A number of studies of androgen supplementation in elderly men who were not hypogonadal, have shown that, in the short term there is only a modest increase in size and in levels of prostate specific antigen (PSA), not exceeding values found in control subjects [58,60,61].

So, it would seem that non-obstructive BPH is no contra-indication against androgen administration but obstructive BPH is.

Tissue concentrations of testosterone and dihydrotestosterone in the prostate are substantially higher than serum concentrations; it could be that a modest increase in androgens in the peripheral circulation, as would be the aim of androgen supplementation in old age, has no large effect on intraprostatic androgen levels. As to how far an androgen, that can be aromatized to estradiol but cannot be reduced to DHT by 5α-reductase, signifies progress with regard to safety for the prostate, remains to be determined [62]. It might theoretically be detrimental since the testosterone/estradiol balance might tip to the estrogen component. Thus, even if there are no reasons for immediate concern, testosterone administration should be administered to aging men with caution. The following recommendations were formulated with regard to safety of androgen administration to aging men by Snyder [63], and later updated by Morales [64]. Before testosterone treatment men should be screened for prostate cancer because existing prostate cancer is, to some extent, testosterone dependent. Screening of the aging male should include a digital examination of the prostate and most men will expect to have their PSA value measured. It is beyond the scope of this review to discuss the specificity and sensitivity of PSA and of the ratio of free to total PSA in the diagnosis of prostate cancer. It is also a well-known fact that PSA levels are age dependent as well as related to the size of the prostate.

There is evidence that in the normal range of PSA levels the rate of change of PSA levels over time provides useful information. An annualized rate of change of >0.75 ng/ml per year (or the so-called PSA velocity) for 2 years should lead to urologic evaluation and prostate biopsy. If the first value of PSA was >4.0 ng/ml then an annualized rate of 0.4 ng/ml should be taken as a guideline [63]. Such guidelines allow to administer androgens to individual hypogonadal aging men with due concern for adverse effects on the prostate [64].

7.1. Conclusions

There is now convincing evidence that in a subset of aging men, increasing with age, plasma testosterone levels fall below a critical level resulting in hypogonadism. This state of testosterone deficiency has an impact on bone, muscle and brain function and is maybe a factor in the accumulation of visceral fat which again has a significant impact on the cardiovascular risk profile. From the above it follows that androgen replacement to selected men with proven androgen deficiency will have beneficial effects. The almost immediate reflex it to question androgen administration to aging men in view of its potentially harmful effects on prostate disease. BPH and prostate cancer are typically diseases of the aging male steeply increasing with age. This reflex response needs rethinking. Epidemiological studies provide no clues that the levels of circulating androgen are correlated with or predict prostate disease. Similarly, androgen replacement studies in men do not suggest that these men suffer in a higher degree from prostate disease than control subjects. This in spite of the fact that treatment with parenteral

testosterone is part of the time associated with strongly supraphysiological testosterone levels. Studies providing a definitive answer whether testosterone replacement to aging men is safe with regard to the initiation or progression of prostate disease would require inclusion of several thousands of men and the finances and logistics for such studies are lacking.

The fact that prostate diseases occur in men when most men show an age-related decline of androgens has prompted research into factors other than androgens to explain the age-related increase in prostate disease. On the basis of animal models of BPH the role estrogens has received serious attention, though this has not resulted in substantial therapeutically successful interventions aiming at reducing estrogen effects on the prostate. Such interventions would conflict with the recent evidence that estrogens are significant for men for the health of their bones, brain and cardiovascular function. In epidemiological studies elements of the so-called metabolic syndrome have been found to correlate with prostate disease (obesity, hyperinsulinism, hyperleptinemia). It is remarkable that the metabolic syndrome is associated with lowered testosterone levels and might theoretically be improved with androgen administration!

On the basis of the above information it seems a defensible practice to treat aging men with androgens if and when they are testosterone-deficient. A follow up with regard to side effects is needed. Before androgens are prescribed a digital rectal examination of the prostate, a prostate symptom score and determination of PSA level should be undertaken. A re-evaluation after 3 months should take place where after the patients can be checked after larger intervals. Naturally, the patients should be forewarned that prostate symptoms may occur during androgen administration which may or may not be related to the administration of androgens.

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