

ANDROGEN DEFICIENCY IN THE AGEING MALE: POTENTIAL CLINICAL IMPORTANCE AND THERAPEUTIC CONSIDERATIONS

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INTRODUCTION

Expectation of life is increasing all over the world [1]. A considerable shift in the demographic structure of the population in Central Europe is forecast for the next 30 years. By the year 2015 every fourth man and by the year 2030 every third man will have reached or exceeded the age of 60. This development will have a serious impact on the health system. More and more men will suffer from the typical diseases of old age. From the perspective of urology/andrology, lower urinary tract symptoms (LUTS), cancer of the prostate and sexual dysfunctions will be to the fore.

Whether men actually do have a climacterium and – like in women – treatment with sexual hormones is indicated has been the subject of controversial debate for many decades. As early as 1939, Werner drew attention to the potential associations between hot flushes, sleep disorders, depressive moods, lack of drive and high urine gonadotropin levels in older men [2, 3]. Several studies confirmed that the androgen levels decrease constantly in old age [4–6], but that only about 20–30% of all men develop a partial testosterone deficiency. Therefore, the terms “andropause” or “climacterium virile” are not really appropriate [7].

They have been replaced by the expression “partial androgen deficiency of the ageing man” (PADAM). Today, PADAM is the subject of intensive research aimed at identifying the possible negative effects on the endocrine target organs, and finding a rational basis of hormone replacement therapy.

SEXUAL STEROIDS IN THE AGEING MAN

The causes of age-related hormone changes (Table 1) are to be found in primary testicular and pituitary-hypothalamic disorders, and in the negative effects of chronic disease, obesity and regular alcohol consumption [8, 9].

Changes in testicular microcirculation lead to degeneration of the Leydig cells and to a decrease in Leydig cell

Table 1. Androgen deficiency in the ageing man: Multifactorial causes

Hypothalamus, pituitary gland	Altered pulse and amplitudes of LH
Testes	Decrease in Leydig cell mass, micro-circulation disorders, chronic disease
Periphery	Increased plasma binding, loss of circadian rhythm, clearance rates?
Target organs	Molecular biologic mechanisms?

mass [10]. At the same time, changes in the pulsatility and pulse amplitudes of luteinizing hormone (LH) occur [11].

The data on the prevalence of PADAM in various age groups differs quite considerably depending on the testosterone discrimination value that is selected [12]. The total testosterone level is found to be below a lower threshold of 11 nmol/l in about 3% of men aged 50–59, 9.6% of men aged 60–69, 23.5% of men aged 70–79, and 34.3% of men aged over 80 [13–15].

In plasma, testosterone is bound to albumin and SHBG (sexual hormone binding globulin). The SHBG levels increase with age. As a result, the bioavailable and free testosterone fractions decrease more rapidly than the total testosterone [16]. Therefore, measurement of the bioavailable testosterone instead of the total testosterone is recommended in ageing men [17]. Whether and to what extent potential age-related changes in metabolism, receptor concentration and receptor affinity in the target tissues can influence their sensitivity for the sexual hormones is still under investigation [7].

Dehydroepiandrosterone (DHEA) is a biologically weak androgen that is produced primarily in the adrenal cortex. The adrenal gland also reduces androgen production with increasing age. The biosynthesis of DHEA can drop to only 30% of the baseline value.

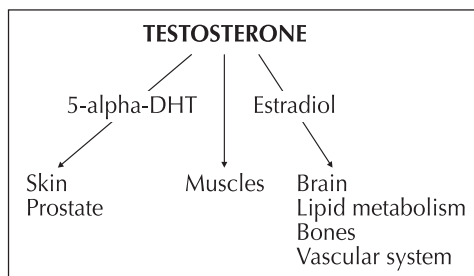


Figure 1. Effect of androgens and estrogens on the hormonal target organs

In men, estrogens are produced mainly by aromatization of testosterone and androstendione in the fatty tissue, where the aromatase activity is very high. About 50 to 150 µg estradiol and 50 to 130 µg estrone are produced daily [18]. DHEA can also be converted into estrogens. The postulate that the estrogens decrease with age as well as the androgens was not confirmed by all studies [13, 15].

Testosterone acts on the peripheral target organs both directly – e.g. in the muscles – and via its metabolites (Fig. 1). In the prostate and the skin, 5-alpha-dihydrotestosterone (DHT) has a strong intracellular effect. Next to the androgens, estrogens also play a role in the brain, skeleton, vascular endothelium and in lipid metabolism.

POTENTIAL CLINICAL IMPACTS OF PADAM

Androgen deficiency symptoms

Hot flushes, depressive moods, sleep disorders, loss of cognitive function, nervousness, lack of drive, poor performance, fatigue, loss of libido, dry skin and muscle weakness are the typical symptoms that may be associated with PADAM (Table 2). However, low testosterone values were not always found in men with the typical symptoms.

Cognitive functions

Clinical studies of the associations between androgen hormones and cognitive functions investigate primarily testosterone and DHEA [19]. DHEA is supposed to have a positive influence on well-being and on the memory [20]. The results from open analyses with

sometimes very small samples for DHEA are still mostly very divergent, but there are relevant indications for a connection between testosterone and cognitive abilities. A prospective, placebo-controlled, double-blind study showed that the transdermal administration of testosterone improved the spatial perception of older men [21], whilst other cognitive functions such as verbal and optical memory remained unaffected. During the therapy, a significant increase in circulating estradiol was observed. The authors postulate that the metabolization of testosterone into estradiol is of importance.

Sexual disorders

Androgens stimulate the sexual interest, the libido, and the spontaneously and visually stimulated erections directly [22]. They also play a role in ejaculation. In ageing men with disorders of the libido and sexual excitability, lower plasma testosterone levels are frequently observed [23].

Bagatell et al [24] suppressed the endogenous testosterone production in younger men with a Gn-RH agonist, and at the same time replaced testosterone at different doses. A reduction in circulating testosterone to about 50 % of the baseline value had no negative

effects on sexual behavior. From this, it can be deduced that a partial androgen deficiency does not have to result in a sexual dysfunction. Anderson et al [25] observed that an increase in testosterone to the supra-physiological range affected the interest in sexuality, but not the sexual behaviour.

Erectile dysfunction increases with age. The causes are multi-factorial, whereby the androgen deficiency plays a subordinate role. The mainly responsible factors are cardiovascular diseases, diabetes, depressions and neurological changes [26–29]. Hargraeve and Gosh [30] found that low testosterone levels were rare in men aged between 50 and 70 with impaired potency, and even in hypandrogenic patients they were unable to achieve any relevant therapeutic effect with testosterone.

Although a relevant effect on impotence cannot be expected of the exogenous androgens compared with Viagra, intracavernous injections and mechanical aids, they can be used specifically for disorders of libido and sexual excitability in men with an androgen deficiency.

Muscular weakness and osteopenia

It has been shown that there are connections between sexual steroids, muscles and the skeleton. Testosterone has an anabolic effect on the muscles [31, 32]. Testosterone deficiencies reduce the muscle mass and decrease the muscle power.

Both androgens and estrogens play a role in the male bone metabolism. Men also develop osteoporosis in old age, but generally it occurs later than in women [33]. Hypogonadism is an important risk factor [34–41].

The extent to which a partial testosterone deficiency is responsible for the

Table 2. Partial androgen deficiency in the ageing man: Potential clinical effects

- Sexuality (interest and libido)
- Cognitive functions
- Bone density
- Muscle power
- Vigilance
- Concentration
- Atherogenic lipid profile (LDL, HDL cholesterol)
- Insulin resistance
- Visceral fat
- Haematocrit
- Hot flushes
- Sleep disorders

development of osteoporosis in ageing men is currently under discussion. Analyses of the correlation between bone density and men with PADAM showed controversial results [42]. It has however been confirmed that exogenous testosterone given to ageing men with partial testosterone deficiency will improve bone density [43].

A central role in the physiology of male bone metabolism is attributed to estrogens [37, 44]. For example, bone destruction due to orchidectomy in men with prostate cancer can be prevented by concurrent treatment with estradiol.

UROLOGICAL-ANDROLOGICAL DIAGNOSTICS IN AGEING MEN (ANDROCHECK)

The main focus of urological-andrological diagnostics in ageing men is on the lower urinary tract complaints, the early diagnosis of prostate cancer and sexual dysfunctions. Hormonal deficiencies and the associated functional disorders of the hormonal target organs are becoming more and more topical. The term "androcheck" has been introduced for the regular medical examination of ageing men for early detection of the relevant changes.

The prostate volume increases by about 5% every year. As of the age of 70, lower urinary tract symptoms increase with a high significance [45]. Moderate or severe prostate symptoms must be expected in almost every man over the age of 80. About 25% of men have to be treated for BPH, whereby a further increase in this incidence must be expected in view of the increasing life expectancy. The development of

modern, efficient pharmacological therapies (1-alpha blockers, 5-alpha reductase inhibitors) allows us to treat mild and moderate obstructive disorders of the urinary tract efficiently. Early identification of lower urinary tract symptoms is important if we want to improve the quality of life of ageing men.

The prevalence of prostate cancer increases very significantly with ageing. 30–40% of all men aged 60 have preclinical prostate cancer. The progression to clinical carcinoma varies from region to region and is depending on alimentary factors, whereby animal fat plays a significant role [46]. Androgens stimulate the biological activity of clinical prostate cancer. It is uncertain whether and to what extent androgens might also play a relevant role in the promotion from preclinical to clinical prostate cancer. In a prospective longitudinal observation study, Heikkiä et al [47] were unable to find a correlation between the testosterone level and the development of prostate cancer. So far, it has not been finally established whether testosterone treatment in ageing men has an influence on the natural course of BPH and the incidence of prostate cancer [48, 49]. There is also speculation as to whether higher androgen levels might even be able to delay the development of prostate cancer [50].

Cancer of the prostate must be excluded before and during the treatment with androgens [51, 52]. Since the introduction of PSA in prostate diagnostics, an efficient early detection has become possible [53]. About 20% of all prostate carcinomas do not result in an increased PSA and can only be detected by rectal palpation. Morgenthaler et al [54] found that prostate cancer occurs more frequently than assumed hitherto in men with low tes-

tosterone levels, despite normal PSA and rectal palpation. This observation gives rise to speculations that the positive predictive value of PSA might be limited in hypandrogenic men.

Whilst the methods for the diagnosis of urinary tract complaints, prostate cancer and sexual function disorders have generally been standardized, there are no generally valid guidelines for the diagnosis of PADAM. The development of both structured and validated questionnaires for objectivating the symptoms and methods for the detection of androgen deficiency are necessary. Preliminary experience is available with the ADAM Questionnaire in St. Louis [55]. In Germany, a questionnaire for the relevant symptoms, the social environment and appropriate indications for age-related morbidity is currently being validated [56].

In order to diagnose a partial androgen deficiency, several testosterone measurements are required. Due to the physiological fluctuations, individual values have a limited power of expression, since they may deviate considerably from the actual mean value. It is also possible to pool proportional parts of several plasma samples taken at intervals of 20 to 30 minutes for the measurement.

Testosterone must be measured in the first half of the day, since the diurnal

rhythm of testosterone levels disappears with age [57] and a partial testosterone deficiency may therefore be overlooked if the measurements are carried out in the second half of the day (Fig. 2).

EFFICIENCY AND RISKS OF HORMONE SUPPLEMENTATION

Hormone supplementation for ageing men has not become a routine therapy yet. It still raises a number of issues with regard to the long-term effects and potential risks.

Currently, the use of DHEA and estrogens in addition to testosterone is being considered. The administration of estrogens is based on the idea of exploiting the positive effects of estrogens on the brain, skeleton and vascular system without the potential negative side effects of androgens.

Testosterone

Testosterone supplementation should be considered,

- if the testosterone level is lower than 11 nmol/l,
- if there are clinical signs of a testosterone deficiency,
- if the PSA level is within the normal range, and
- if the prostate is unsuspicious in palpation.

An ideal method of testosterone administration must

- allow aromatization into estrogens,
- have a low metabolism into 5- α -DHT, the highly effective androgen in the prostate,

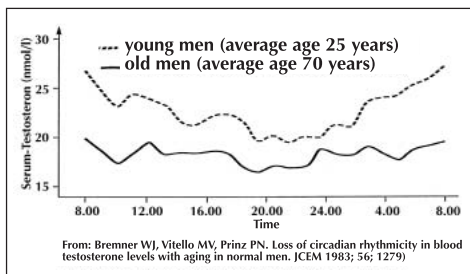


Figure 2. Circadian testosterone rhythm in young and old men

- maintain physiological testosterone levels in the plasma for longer periods and avoid supra-physiological levels,
- cause as little stress as possible, and
- the costs must not be high [58].

Currently, intramuscular, oral, transdermal and implant systems are available (Table 3). The most commonly used forms are testosterone esters, e.g. testosterone enanthate. They are administered by intramuscular injections (250 mg) at intervals of several weeks, and the levels are supra-physiological immediately after the injection (Fig. 3). Before the injection, the levels quite frequently drop to the subnormal range again. The patient often perceives this roller-coaster effect subjectively.

Of the oral forms of administration available to date, the 17-alpha-alkylated androgens have proved hepatotoxic. Therefore, they are no longer used. Testosterone undecanoate, which is absorbed via the lymphatic vessels, can be administered orally. Because of the short half-life, several administrations per day are required. The short-

term fluctuations in plasma level are a disadvantage (Fig. 4).

Fairly constant plasma levels can be maintained and the biorhythm of testosterone imitated (Fig. 5) with the transdermal administration systems [59]. Testoderm must be applied to the scrotal skin daily in order to absorb the amount of testosterone required for supplementation. The disadvantages are shaving of the scrotum, compliance problems, and the high degree of metabolization into 5-alpha DHT.

Testosterone bucyclate has an excellent kinetic profile and maintains a fairly constant level of testosterone for 3 months at a dose of 600 mg. Another very promising preparation for long-term supplementation is testosterone cipionate.

The subcutaneous implantation of testosterone pellets is no longer common but it is becoming increasingly interesting, since constant testosterone levels for up to 6 months must be guaranteed.

The objective endpoints of testosterone supplementation are anabolic effects on the muscles and effects on the

Table 3. Methods of testosterone administration

Oral	
17-alpha methyl testosterone	not indicated
Testosterone undecanoate	levels fluctuate, 5-alpha-DHT increased
Injection	
Testosterone enanthate	roller-coaster effect
Testosterone cipionate	
Transdermal	
Scrotal	fairly constant testosterone levels, shaving of the scrotum, compliance enhancer dermatitis
Non-scrotal	
Implant	
Crystalline implants	irreversible in the event of complications
In the clinical test phase	
19-nortestosterone	
Testosterone cyclodextrin sublingual	
Testosterone undecanoate intramuscular	
Testosterone bucyclate	

bone density, cognitive dysfunctions, libido and sexual excitability. Several studies have shown positive effects on the muscles and bone density [12, 31, 60–62] and on the spatial cognitive functions [21]. So far, the prostate risk of long-term supplementation with testosterone has not been fully established yet. Obligatory monitoring procedures for patients on exogenous testosterone include erythropoiesis, liver function, body weight, PSA, rectal-digital palpation, prostate volume and uroflowmetry, among others.

Dehydroepiandrosterone (DHEA)

The DHEA levels decrease with age; the clinical relevance is not fully established [63]. A number of effects are attributed to DHEA (Table 4), which partly result from experimental studies and the clinical implications of which

are purely speculative. Since the production and metabolism of DHEA differs quite considerably in humans and in animals, the results of animal studies are only transferable to humans to a limited degree.

There are virtually no prospective controlled studies that have been able to demonstrate the positive effects and risks, as a workshop of the International Health Foundation showed in December 1997. One prospective study indicated an improvement of erectile dysfunction in comparison with the placebo [64].

Estrogens

Estrogens play a role in bone metabolism, the brain, lipid metabolism and vascular endothelium. Alpha-estradiol does not have any proliferating and feminizing side effects. Various protec-

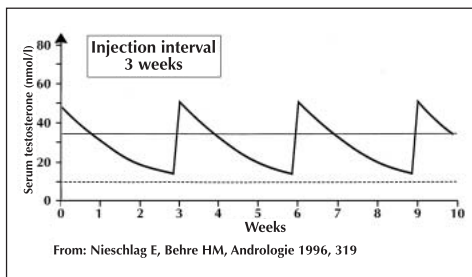


Figure 3. Testosterone levels after intramuscular injection of testosterone enanthate

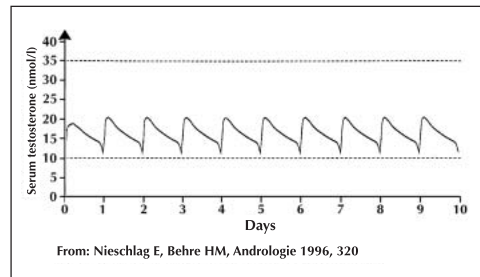


Figure 5. Testosterone levels after scrotal transdermal application (Testoderm)

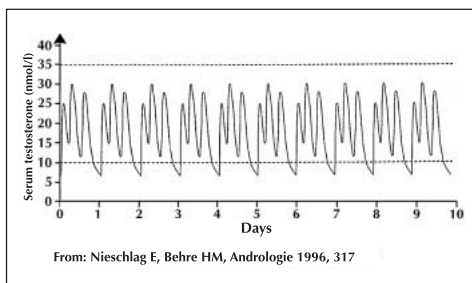


Figure 4. Testosterone levels after oral testosterone undecanoate

Table 4. Speculative effects of dehydroepiandrosterone

- Cognitive functions
- Immune competence
- Neuroprotective effect
- Protective effect in arteriosclerosis
- Anti-ageing
- General health (well-being)
- Improvement of libido
- Anabolic effects
- Fat reduction (men)
- Increase in bone density

tive effects are attributed to the estrogens. The development of estrogens for men is still at an experimental stage [65]. Prospective controlled clinical studies with ageing men have not been completed yet, and therefore the risk-benefit profile is still largely unknown. Currently, estrogen therapy for ageing men still has a purely speculative nature.

OUTLOOK

The constantly increasing life expectation of the male population is making the diagnosis and therapy of lower urinary tract symptoms, cancer of the prostate, sexual dysfunctions and age-related functional disorders of the testes more and more topical. Early detection in regular check-ups (androchecks) could help to detect and treat the relevant diseases as early as possible and thus to improve the health status of older men. Partial androgen deficiency and its potential effects on the hormonal target organs has become an intensive area of research in andrology and thus for the urologist. Impulses are coming from modern methods of androgen administration and the development of non-feminizing estrogens. The ageing man is a very topical issue for urology.

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