

COMMENTARY

Androgen Replacement Therapy in the Aging Male—A Critical Evaluation

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Recent years have seen an increasing interest in the study of the aging male, with a particular interest in the problem of whether so-called rejuvenating hormones and, more specifically, androgens can improve quality of life, counteract progressive skeletal muscle loss and strength, prevent falls and fractures, prolong independent living, and reduce the dependence on medical care.

Almost a decade has elapsed since the first studies on androgen supplementation in elderly men were published (1, 2) and, in the view of the persisting controversies concerning this problem as well as the increasing public interest for rejuvenating hormones, it may be indicated to evaluate critically the clinical relevance of the relative androgen deficiency in elderly males, the diagnostic criteria of androgen deficiency, as well as the risks and benefits of androgen supplementation in elderly men.

Male hormone replacement therapy implies, of course, that elderly men have a significant deficit in male hormone. Therefore, the first question to be answered is whether the common occurrence of the age-associated decline of testosterone levels is inherent to the aging process and occurs also in healthy men or whether the observed decline is the consequence of intercurrent disease, obesity, stress, relative physical inactivity, medications, etc.

After years of controversy, due to differences in the characteristics of the population studied and variation in the timing of blood sampling (morning or afternoon) or the frequently small number of elderly subjects studied, authors now agree that in healthy men also there is a clear, slow but continuous, age-dependent decline of testosterone (T) levels, which is more pronounced for free T (FT) than for total T, a consequence of the age-associated increase of the levels of sex hormone binding globulin (SHBG); at 75 yr of age mean total T level in the morning is about two thirds of the mean level at 20–30 yr of age, whereas the mean FT and bioactive T (FT plus albumin bound T) level are only 40% of the mean levels in younger males. Moreover, the circadian rhythm of plasma T levels, with higher levels in the morning than in the evening, is generally lost in elderly men (3). However, wide

interindividual variations exist due to genetic factors, body mass index, diet, social habits (alcohol, tobacco), and stress, and about 20% of males over 70 yr old have T levels in the upper third of males 20–40 yr of age (4). This is in clear distinction to the situation in postmenopausal women who all have clearly decreased estradiol levels. It is important to mention that this decrease, observed in cross-sectional studies, has now been confirmed by longitudinal studies (5–9). However, the androgen deficiency in elderly men is generally moderate; therefore, some authors have suggested the term partial androgen deficiency in the aging male (PADAM). Others, in analogy with the term menopause in women, use the term andropause, although distinct from women in menopause, elderly men retain their reproductive capacity.

Although the decrease in (F)T levels occurs in healthy elderly men, it is evident that sequelae of intercurrent disease (10), medication, environmental, psychosocial, and socioeconomic factors accelerate this age-associated decrease. Recently, the important role of abdominal obesity in the age-associated decrease of T levels has been stressed (10–12).

Clinical significance of the age-associated decline in androgen levels in elderly men

Androgens have many physiologic actions, but does the age-associated decrease in (F)T levels have clinical significance, and does it indicate hypogonadism? Evidence for the clinical significance could be provided by the eventual similarity between signs and symptoms of aging and androgen deficiency, respectively, in young men, the existence of a significant correlation between symptoms and (F)T levels, and the eventual beneficial effect of androgen supplementation in elderly men with low T levels.

Similarity of signs and symptoms of aging and androgen deficiency, respectively, in young men. The age-associated decrease in muscle mass and strength, energy and work capacity, body hair, and hematopoiesis; the decrease in sexual drive and activity, bone mass, and cognitive function; the decline of memory and of the sense of general well being; the difficulties in concentration; and the increase in abdominal fat mass are reminiscent of the symptomatology of androgen deficiency. However, these symptoms are multifactorial in origin; aging is accompanied by a decrease of almost all physiological functions and, as far as the endocrine system

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is concerned, by a decrease not only of gonadal and adrenal androgen secretion but also of GH secretion. Moreover, the age-associated decrease in physical activity is partly responsible for the decrease in muscle mass and bone mineral density (BMD) (13). Hence, it is not surprising that the correlation between aging symptoms and T levels is often rather poor.

Correlation between aging symptoms and (F)T levels. Whereas the age-associated decrease of BMD with an exponential increase in bone fracture rate with age (14, 15) is well established, the role of the partial androgen deficiency in aging males in this decrease remains to be established (16). Indeed, available data are equivocal, some studies showing a significant, albeit weak, association between FT levels and BMD at some but not all bone sites (13, 17, 18), whereas others did not find any correlation (19–21). Recently, several large-scale studies, involving several hundreds of elderly men (22–24), found bio-T to be significantly associated with bone density at radius, spine and hip; however, the correlation with bioestradiol, the levels of which decline in elderly males, was even stronger, suggesting that part of the androgen effects on bone are at least partially indirect, mediated via their aromatization (25). Nevertheless bio-T also was correlated with all regions of proximal femur BMD and total body BMD after adjustment for age (24). Barrett-Connor *et al.* (26) observed a significant negative graded association between levels of total and bioavailable estradiol but not bio-T and fracture prevalence in males (median age 67 yr, range 56–87 yr) independently of age, body mass index, or exercise.

On the basis of these recent large-scale studies it seems reasonable to accept a role of the decreased T levels in the age-associated osteopenia.

Aging is also accompanied by an increase in abdominal fat mass and a decrease of muscle mass. We (27) as well as Seidell *et al.* (28) and Tchernof *et al.* (29) observed abdominal fat mass to be inversely correlated with FT, independently of age. Visceral fat accumulation is highly significantly associated with increased risk of cardiovascular disease, impaired glucose tolerance, and non-insulin-dependent diabetes mellitus (syndrome X) (30, 31). Whether the abdominal obesity is the consequence of the low T levels or vice versa is not clear. Indeed, obesity induces a decrease of T levels via a decrease in SHBG levels, and morbid obesity (BMI >35) also induces a decrease of FT (11).

The age-associated decline in muscle mass (12 kg between 20 and 70 yr of age), which is most pronounced for the fast twitch type II fibers (32), is a major contributor to the age-associated decline in muscle strength and early onset of fatigue (33) and a strong predictor of falls, fractures, and loss of independent living. In fact, maximal muscle strength correlates with muscle mass independently of age (34)

Whereas van den Beld *et al.* (24) observed that in men 73–97 yr of age, serum T levels were, independently of age, positively related to isometric grip strength and leg extension strength, and Abassi *et al.* (35) observed a correlation between T levels and severity of loss of muscle function in institutionalized men who have lower T concentrations than healthy elderly men, Baumgartner *et al.* (36) observed in elderly men (65–97 yr old) a significant correlation between FT and muscle mass, but not grip strength. Verhaar *et al.* (37),

similarly, did not find any association between T levels and muscle strength.

It should be stressed that although a correlation exists between the lower T concentration and reduced muscle function in older men, T is not the only factor responsible for the age-associated muscle loss.

The prevalence of atherosclerosis in men increases spectacularly with aging. In the view of the higher prevalence in men than in women, the decrease of high density lipoprotein cholesterol (HDL-C) levels at puberty in boys (38), the atherogenic lipid profile in hirsute women, and the sporadic reports of premature cardiovascular disease in athletes abusing anabolic/androgenic steroids, this difference is generally considered to be related to the higher androgen levels in men. Nevertheless, the vast majority of cross-sectional studies show a positive correlation between FT levels and HDL-C (39–41) and a negative correlation with fibrinogen, plasminogen activator inhibitor-1 (42), and insulin levels as well as with coronary heart disease (43, 44), but not with cardiovascular mortality (45–47). However, the correlation between T levels and HDL-C and insulin sensitivity is only observed within the physiological male concentration range of T (48, 49). Androgen blockade by GnRH leads to an increase of HDL-C and, to a lesser extent, of total cholesterol, the effect of which is neutralized when T enanthate was injected in parallel, to maintain physiological T concentrations (48), whereas supraphysiological T levels induce an increase in low density lipoprotein cholesterol (LDL-C) and a decrease of HDL-C (40). Moreover, it should be realized that, beside the effects on lipids, T has direct effects on several vasoactive factors such as endothelin (50), prostacyclin, and thromboxane A₂ (51).

The inverse correlation between T levels and the severity of coronary artery disease as reported by Phillips *et al.* (43), may be related to the fact that low androgen levels are accompanied by an accumulation of abdominal visceral fat (28, 29), which is known to be associated with increased cardiovascular risk factors (52), and Tchernof *et al.* (29) observed that upon multivariate analysis, adjusting for visceral obesity, the correlation between androgen levels and lipid parameters lost its significance.

As to the role of the age-associated decline in T levels in the highly negative correlation between sexual desire, arousal, activity, and age, Schiavi (53) reported that men desiring intercourse with a greater frequency than once a week, had higher T levels than men with lower frequency. Moreover they observed (54) that men with the primary diagnosis of hypoactive sexual desire had significantly lower T levels than controls. Similarly, Pfeilschifter *et al.* (55) reported that men with greater sexual activity had higher bio-T levels than men with a lower frequency and they conclude that androgen deficiency may contribute to the age-related decline in male sexuality. Nilsson *et al.* (56) finally, in an epidemiological study of 500 51-yr-old men, observed that low levels of bio T were associated with low sexual activity.

However, other authors (57, 58) did not observe any correlation between plasma T levels within the normal range and sexual activity. Moreover, it is known that healthy males have much higher T levels than required to maintain sexual function, although Schiavi (53) as well as Bancroft (59) suggested that circulating androgen levels in elderly men might

be insufficient to sustain nocturnal penile tumescence and adequate sexual function.

As to erectile dysfunction, which increases dramatically with age, whereas androgens, acting both centrally and peripherally (60) are essential for normal penile erection and T-stimulating nitric oxide synthesis in the corpora cavernosa (60, 61), androgen deficiency is rarely the major cause of impotence in elderly males, although it may play a subsidiary role. There is good evidence that, whereas nocturnal penile tumescence is androgen dependent, erection in response to visual erotic stimuli is androgen independent (62). Davidson *et al.* (63) suggested that the effects of T may be mediated via changes in genital sensitivity.

Finally there is good evidence for a strong correlation between T levels and cognitive performance such as spatial abilities or mathematical reasoning (64, 65), findings which were confirmed in Western and non-Western groups of healthy males (64). Studies addressing correlations between T levels and cognitive functions specifically in elderly men are not available.

As to the role of T in the depressed mood frequently observed in elderly men, whereas data in the literature are rather divergent [for review see Christiansen (66)], a recent large study by Barrett-Connor *et al.* (67) involving 856 men age 50–89 yr showed a significant inverse correlation between bioavailable T and a depression score, independent of age and weight.

In summary, many aging symptoms in men are suggestive of androgen deficiency and, in fact, there frequently exists a weak correlation of these signs with plasma T levels; many, but not all, studies show the persistence of these correlations after correction for age.

Nevertheless, it should be kept in mind that most of the aging symptoms are multifactorial in origin and that the age-associated decrease in GH levels might play an important role in the symptomatology (68), because symptoms of GH deficiency in young men and the symptoms of aging again show a striking similarity; decrease in muscle mass, increase in abdominal fat, thinning of the skin, asthenia, and adynamia.

Aging and adrenal androgens

Aside from a decrease in the secretion and plasma levels of T, aging is accompanied by a decrease of the plasma levels of the major adrenal androgen, dehydroepiandrosterone sulfate (DHEAS). The age-associated decrease is the most important decrease of all hormones; at 75 yr of age, mean DHEAS levels are only 20% of levels in young adults and, whereas rather important interindividual variations exist, all men and women show an important age-dependent decrease (69–71).

Does this decrease have clinical significance? Although it has been reported that in animals that do not secrete DHEAS, administration of DHEAS generally in pharmacological doses, has antiatherogenic, immunostimulatory, and anticarcinogenic effects, the effects of DHEAS in man remain questionable. Functional parameters of daily living in the oldest males were reported to be lowest in men with the lowest DHEAS levels (72), whereas data of Abassi *et al.* (73)

show that men with higher DHEAS levels appear to be more fit and leaner than men with lower DHEAS levels. This, of course, does not indicate a causal role of DHEAS in physical fitness or general well-being. Moreover, it has been reported that men with low DHEAS levels would be at higher risk of cardiovascular mortality within the next 2 yr (74, 75), but this has not been confirmed (76, 77). Finally, the increase in physical well-being after DHEAS administration reported by some authors (78) was not confirmed by others (79), but there is some evidence that DHEAS administration to men with Addison's disease improves general well-being (80, 81).

Hormone replacement therapy

Diagnosis of androgen deficiency in elderly males. As the clinical symptoms of hormone deficiency in elderly males are rather vague and aspecific and as a substantial number of elderly men have (F)T levels within the normal range for young adults, we can state that hormone replacement therapy (HRT) is only warranted in the presence both of clinical symptoms suggestive of hormone deficiency and of decreased hormone levels. Moreover, eventually present primary causes of the decreased androgen levels should be adequately treated before starting HRT.

How do we define hypogonadism in elderly males? Clinical signs of relative androgen deficiency in elderly men most easy to objectify are a decrease of muscle mass and strength, a decrease of bone mass and osteoporosis, and an increase in central body fat. Other signs such as a decrease in libido and sexual desire, forgetfulness, loss of memory, difficulty in concentration, insomnia, as well as a decreased sense of well-being are rather subjective impressions that are more difficult to measure and differentiate from hormone-independent aging.

As to subnormal (F)T levels, it should be realized that it is still unknown whether the requirements of elderly males are identical with the requirements of younger men. There is some evidence for increased sensitivity to androgens in elderly males, for example, at the level of the feedback system (82–85), whereas several (86–91), but not all (92, 93), studies show a decrease of the androgen receptor (AR) concentration in tissues of elderly animals and men, suggesting a saturation of the receptor sites at a lower T concentration and a decrease of the maximal genomic effect of T. Also, changes in the CAG repeat length of the AR gene may be involved in the age-related decline of plasma T levels. The latter appear to decline more rapidly in subjects with a lower number of CAG repeats (7). This is possibly the consequence of a higher androgen sensitivity; a large number of CAG repeats as in the Kennedy syndrome are accompanied by androgen resistance and increased T levels.

Moreover, even in the young men, it is not clear whether T concentrations in the normal range are required for full androgenic effects in the different androgen-responsive organs. It has been reported repeatedly that T levels at half the concentration found in young males, are appropriate for sustaining normal libido and sexual activity (94).

In fact, there is no clinically useful biological parameter reflecting androgen activity. It has been suggested that SHBG capacity might be such a parameter (95) but, whereas the

decrease of SHBG after T treatment indicates androgen activity, a single basal SHBG level is difficult to interpret; the level is determined by several hormonal and nonhormonal factors, such as GH, insulin, thyroid hormones, obesity, and medications.

It should be realized, finally, that normal hormone levels do not imply *per se* normal physiological effects; indeed, the interaction of the ligand with the hormone receptor as well as the presence of coactivators and coinhibitors will determine the biological effects.

Because there is no generally accepted cut off value of plasma T for defining androgen deficiency, and in the absence of convincing evidence for an altered androgen requirement in elderly men, we consider the normal range of (F)T levels in young males also valid for elderly men. In our healthy male nonobese population 20–40 yr of age ($n = 150$), the mean of log-transformed early morning T levels was 21.8 nmol/L (627 ng/dL), the mean $- 2$ SD was 12.5 nmol/L (365 ng/dL), and the mean $- 2.5$ SD was 11 nmol/L (319 ng/dL). For FT, measured by equilibrium dialysis or calculated from T and SHBG levels (96), the mean was 0.5 nmol/L (14 ng/dL), the mean $- 2$ SD was 0.26 nMol/L (7.4 ng/dL), and the mean $- 2.5$ SD was 0.225 nmol/L (6.5 ng/dL). If we take as the lower normal limit and threshold of partial androgen deficiency, a conservative value of 11 nmol/L for T and 0.225 nmol/L for FT, which represent the lower 1% value of healthy young males, then it appears that more than 30% of men over 75 yr old have subnormal (F)T levels. Most authors use rather similar values (1, 2, 9, 13, 97, 98). It should be mentioned that direct FT assays using a T analog, do not yield a reliable estimate of FT (96). The age-associated decline in (F)T levels has both a testicular (decreased Leydig cell number) and central origin, the latter being characterized by a decrease in the amplitude of LH pulses in elderly men. Hence, many elderly men have normal LH levels and we do not consider an increase in LH levels to be required for the diagnosis of hypogonadism in elderly men (84). As already mentioned, in the absence of a reliable, clinically useful biological parameter of androgen action, these criteria of hypogonadism of the aging men are somewhat arbitrary.

The treatment aims at restoring hormone levels in the normal range of young adults and, more importantly, at alleviating the symptoms suggestive of the hormone deficiency. However, the ultimate goals are to maintain or regain the highest quality of life, to reduce disability, to compress major illnesses into a narrow age range, and to add life to years.

What are the effects of androgen supplementation in elderly man with subnormal (F)T levels? Before discussing the beneficial effects of androgen supplementation in elderly males, it should be stressed that the number of well controlled studies is still small; the number of patients having been involved in such studies is limited to a few hundred. Hence the experience is limited and the clinical results should be interpreted critically.

There is no doubt that in young androgen-deficient men T supplementation increases fat free mass and muscle strength and decreases body fat, with improvement of insulin sensitivity (98, 99–104). Androgens induce their spe-

cific response via the AR, which regulates the androgen-responsive target genes. Following androgen treatment, Sheffield-Moore *et al.* (105) observed an increase in AR messenger RNA in healthy young men, and in older men long-term androgen administration increased AR transcription at 1 month with a return to base line levels after 6 months (105, 106). Androgen administration to healthy older men increased insulin-like growth factor 1 messenger RNA; decreased the concentration of the inhibitory insulin-like growth factor binding protein 4 (107); and, increasing protein synthesis (99, 105–107), induced myotrophic effects in skeletal muscle (104, 105).

After androgen supplementation to elderly men, generally at a biweekly dose of 200 mg T enanthate, several authors (1, 2, 106, 108) reported a significant, albeit often relatively modest, increase in muscle mass (± 2 kg) (1) and/or arm circumference and generally of grip strength, whereas fat mass generally is decreased modestly (106, 109). Also Urban *et al.* (106) reported that T administration to elderly men increases skeletal muscle strength. A recent study of Snyder *et al.* (97), on the other hand, reported an increase in lean body mass (LBM) but without increase in strength of knee extension or flexion, whereas Clague *et al.* (110) after a 12-week administration of T, found neither an increase of LBM nor muscle strength.

Bhasin *et al.* (111) stresses that although muscle strength is an important aspect of muscle function, it is not the most important. Muscle power, defined as the rate of power development is strongly correlated to performance of functional activities such as rising from a chair, stair climbing, *etc.*; such an increase, more specifically of the lower limb muscles, would be important, improving mobility and stability and preventing falls and, hence, fractures (110).

As to osteoporosis, all studies show that in hypogonadal men androgen supplementation increases bone mass (100, 102, 103, 112), although normal adult bone mass is not reached (113). Also in eugonadal men with osteoporosis, T esters (250 mg/2 weeks) increased BMD (114). Again, the effects in elderly men are less convincing. Morley *et al.* (2) observed an increase in osteocalcin levels, an index of osteoblast activity, whereas Tenover (1) reported a decrease of hydroxyproline excretion, an index of bone resorption, and more recently (Tenover J. S., personal communication) in a 3-yr study involving 70 elderly men, an increase in BMD at all measured sites. However, neither Orwoll and Klein (14) nor Sih *et al.* (108) could observe any effect of T supplementation on biochemical parameters of bone turnover. Snyder *et al.* (115), in a study involving 108 elderly subjects, observed that HRT increased BMD of the lumbar spine, but not of the hip, in patients with clearly subnormal T levels, but not in the whole elderly population studied, which included, all subjects with a T level below 16.5 nmol/L (475 ng/dL), a value which certainly is not in the hypogonadal range. On the other hand, it is evident that morbidity of osteoporosis relates essentially to hip fractures! It may be of interest to mention that in orchidectomized aged rats, the threshold concentration of T, necessary for prevention of loss of both bone and LBM is clearly lower than for prostate and seminal vesicles (116). Whether this applies also to the aged man requires further research, but would explain that the effects of T on

BMD of elderly men, are limited to men with clearly decreased (F)T levels.

Finally, HRT only makes sense when other causes of osteoporosis, such as insufficient calcium or vitamin D intake have been excluded (117).

As to the effects of T replacement on sexual activity, the effects in young hypogonadal men are spectacular (98, 101, 103), but supraphysiological doses of T administered to young healthy men for contraceptive purposes did apparently not affect frequency of intercourse, kissing, or fondling (118). Anderson *et al.* (119), injected 200 mg T enanthate weekly for 8 weeks to normal men and observed a significant increase in sexual interest, awareness, and arousal, which was, however, not reflected in modification of overt sexual behavior, which they suggest may be more determined by social factors. Morley *et al.* (2) as well as Hajjar *et al.* (120) observed that also in elderly men T replacement improves libido substantially. Wang *et al.* (98, 121) also reported improvement of sexual function; however, their data suggests that there is a threshold level of T above which there is no further enhancement of response. Interestingly, Carani *et al.* (122), in a patient with aromatase deficiency, reported evidence that estrogen might have a role in male sexual activity, but not in sex orientation.

Most authors (98, 106, 123) observed that androgen substitution in hypogonadal males improved mood, energy, sense of well being, and friendliness, whereas T levels were negatively correlated with nervousness and irritability. These significant correlations with T levels were only observed when T levels were below the normal range, which suggests that once a minimally adequate T/dihydrotestosterone (DHT) level was achieved, further increase did not further contribute to improvement of mood (98, 123).

Similarly in elderly males, androgen replacement therapy has been reported to increase the sense of well being (2, 124, 125).

Androgen supplementation in elderly hypogonadal men improves also spatial cognition (1, 126) and verbal fluency (127, 128), but no effect was seen on memory (108).

As to the influence on plasma lipids, atherosclerosis, and cardiovascular disease, it is well known that administration of T to surgically or chemically castrated males, or female to male transsexuals (129), as well as supraphysiological T levels in men (40, 129–131) induce a decrease of HDL-C and an increase of triglyceride levels. But administration of 250 mg T im once per week for 6 months to young healthy men resulted in a decrease of total and LDL-C, as well as in a slight, nonsignificant decrease of HDL-C and in a decrease of lipoprotein(a) levels (132).

Most (1, 2, 125, 133), but not all (134), studies on androgen replacement in elderly men report a fall in total and LDL-C, with no significant effect on HDL-C and an improvement of insulin sensitivity (127, 135–137). Moreover, a tendency to a fall of arterial blood pressure has been reported (135). The mechanism of this fall in lipids might be related to the decrease in the visceral abdominal fat mass (124) under the influence of androgens, which inhibit lipoproteinlipase activity and increase lipolysis (138, 139) with improvement of insulin sensitivity and mobilization of triglycerides from abdominal fat tissue (140).

As to the influence of androgen supplementation on cardiovascular disease, Alexandersen *et al.* (141) reviewing the outcome of 30 cross-sectional studies in men, reported that most studies suggest either a favorable or neutral effect of normal T levels on cardiovascular disease in men, and they conclude that low androgen levels increase the risk of cardiovascular disease in men.

It should be remembered that the beneficial effects of physiological androgen levels on the lipid profile are limited to aromatizable androgens and that the effects of androgens on the vascular system are not limited to their indirect effects on the plasma lipids, but that T decreases lipoprotein(a) (8) and has complex effects on platelet aggregation (51), blood coagulation, and fibrinolysis, respectively (142, 143). Moreover, it has been shown that administration of T in physiological concentration increases coronary blood flow in patients with coronary heart disease (144, 145), whereas beneficial effects on endothelial function (146) and myocardial ischemia have also been demonstrated (147, 148).

Unfortunately, notwithstanding its favorable effects of T supplementation on the lipidogram, so far no influence on cardiovascular mortality has been reported (45, 46).

In summary, androgen supplementation in aging males with subnormal T levels seems to have beneficial effects on muscle mass and strength, BMD, plasma lipids and insulin sensitivity, mood, libido, and sense of wellbeing, but generally only in men with subnormal (F)T levels; no effects are generally seen above a certain threshold level of T. Moreover, beneficial effects on clinically relevant parameters such as bone fracture rates, falls, infarction rates, or cardiovascular mortality, so far, have not been reported, and the clinical significance of the observed effects remains questionable.

Surveying the data available, on one hand, one is struck by the fact that the beneficial effects of T supplementation are much more pronounced in young hypogonadal males than in elderly men, and, on the other hand, by the fact that although almost a decade has elapsed since the first clinical studies on androgen supplementation in elderly men were published, the number of elderly subjects having participated in controlled studies of androgen supplementation are very limited. We are awaiting eagerly the results of large long-term controlled studies on androgen supplementation in elderly men.

As to the first problem, this might indicate either that the elderly men receiving androgen supplementation had higher T levels at the start than the young hypogonadal men and were not really hypogonadal, which was probably the case in some studies, or that, due to a reduction of their tissue receptors, their possible response to androgens is limited. However, this is less likely as moderately supraphysiological doses appear to induce sometimes polycythemia as well as an atherogenic lipid profile. It is not unlikely that the response to androgen supplementation of the oldest men, who generally have the lowest endogenous androgen levels, would be comparable to the response of young hypogonadal men. Whether higher doses of T via nongenomic effects might be more effective is still an open question. Bhasin *et al.* (149) as well as Young *et al.* (150) observed that supraphysiological doses of T (600 mg/week im) administered for 6

weeks to normal men increased free fat mass, muscle size, and strength.

As to the limited number of studies available, this is probably related to the fear of serious side effects, more specifically, stimulation of the development of an undiagnosed prostatic carcinoma and its possible legal consequences.

Side effects of androgen supplementation. By far the most important possible side effect of androgen supplementation in elderly males is the exacerbation of prostatic disease.

T supplementation in elderly men induces only a minimal increase of the volume of the prostate with, eventually, a modest increase in levels of prostate specific antigen (PSA) (1, 2, 151). Hypogonadal men, treated for many years with T, developed a prostatic volume comparable to that of normal men of similar age (152). Hence, it appears that nonobstructive benign prostatic hyperplasia is not a contraindication for androgen substitution. However, obstructive benign prostatic hyperplasia constitutes a clear contraindication.

Because almost all clinical prostatic carcinomas are androgen sensitive, the presence of this prostatic carcinoma is an absolute contraindication for androgen supplementation. Recently, Hoffman *et al.* (153) reported the surprising finding that the levels of FT were inversely correlated with the incidence of prostatic carcinoma, and that low FT levels predicted a more aggressive neoplasm, whereas Kleinman and McKinlay (154), in the Massachusetts Male Aging Study, calculated that the hormone variables (T, FT, DHT, E₂, androstenedione) would only account for 11% of our current knowledge about prostate cancer risk *vs.* 30% for nutrition and 40% for immutable factors (age, height, and family history). In this connection it is interesting to mention that Hardy *et al.* (155) observed an inverse correlation between the length of the AR CAG repeats and the risk of early onset of prostatic cancer.

Whereas in most studies T levels in prostatic CA patients and in normal controls were similar (156), Gann *et al.* (157) in a prospective study involving 222 subjects who, within 10 yr of blood sampling, developed a prostatic carcinoma, matched with 390 controls of similar age observed when hormones and SHBG levels were simultaneously adjusted, an increased cancer risk for patients with high T levels.

A difficult problem constitutes the subclinical prostatic carcinoma, which is very frequent in elderly men (>50% of men over 70 yr old) and which is undetectable by clinical examination or laboratory techniques (PSA; transrectal ultrasonography) but only detectable by prostatic biopsy. Only a small percentage of these subclinical carcinomas will develop to a clinical carcinoma, but it is unknown whether T supplementation might stimulate its growth. There is no evidence that initiation of prostatic carcinoma is influenced by androgens. Whereas there is no geographical variation in the incidence of subclinical carcinoma (158), which is as frequent in the Far East as in Western countries, clinical carcinoma is very rare in the Far East, although (F)T levels are similar or only marginally lower in elderly Japanese men (159, 160). This suggests that physiological T levels would not stimulate a subclinical carcinoma. Nevertheless, the androgen sensitivity of all clinical carcinomas pleads for prudence

as the promotion of subclinical lesions to clinical carcinomas cannot be excluded (161).

The stimulatory effect of T on erythropoiesis is well documented. Whereas a moderate increase in hematocrit in elderly males is possibly beneficial, some studies reported an increase of the hematocrit over 51% (polycythemia) occurring in up to 25% of elderly patients (108, 120), requiring temporary withholding of the treatment and even phlebotomy. Available data suggest that the frequency of this side effect is related to supraphysiological levels (162). As transdermal patches yield T levels within the normal range, this may explain the reported lower frequency of polycythemia with this form of treatment, but more experience is required before to express a definitive opinion.

Whereas sleep apnea has been reported by Matsumoto *et al.* (163), none of the reports on T supplementation in elderly males mentioned the development of sleep apnea, which itself is often associated with lower T levels (164). Nevertheless, it is safe to consider obstructive pulmonary disease in overweight persons or heavy smokers as a relative contraindication.

As already discussed, T supplementation in physiological doses does not seem to induce an atherogenic lipid profile, but, as mentioned, T has also nonlipid mediated effects on the cardiovascular system.

Water and sodium retention generally do not cause a problem, except in patients with heart decompensation, hypertension, or renal insufficiency.

Hepatotoxicity is rare, even after the long-term use of relatively high oral doses of T-undecanoate in oleic acid (TU) (165), but is relatively frequent when synthetic 17 alkylated anabolic-androgenic steroids are used.

Gynecomastia is a benign complication of androgen supplementation, perhaps more frequent in elderly obese men than in young hypogonadal men. It is the consequence of the aromatization of T into estradiol in peripheral fat and muscle tissue.

Finally, T in supraphysiological doses suppresses spermatogenesis, but this should not be of major concern to elderly men.

Contraindications of androgen supplementation. The presence of a clinical prostatic carcinoma is an absolute contraindication for HRT and should be carefully excluded by PSA, rectal examination and, eventually, biopsy before starting any therapy.

Benign nonobstructive prostatic hyperplasia is not a contraindication, but obstructive BPH is. Polycythemia also constitutes a contraindication and the hematocrit should be controlled regularly during HRT. A rare, absolute contraindication is mammary carcinoma in the male as well as a prolactinoma, as their growth may be stimulated by HRT. Dyslipidemia is a relative contraindication requiring careful monitoring of the lipidmia during treatment.

As mentioned, COPD in overweight or heavy smoking patients often subject to sleep apnea constitutes a relative contraindication.

Modalities of androgen supplementation. The major goal of T therapy is to replace T levels as close as possible to physiologic concentrations (166).

Because orally administered T is almost completely inactivated by its first pass through the liver, the only orally active form is TU that, due its lipophilic side chain, is partly taken up by the lymph and partly escapes hepatic inactivation. The maximal plasma concentration of T is generally observed within 2–3 h, but after 6–8 h levels have returned to pretreatment levels. Hence, TU should be administered 2–3 times daily, preferably with a meal, in a dosage of $2\text{--}3 \times 40$ mg, which generally provides adequate androgen replacement, yielding T levels within the (low) normal range, whereas DHT levels are moderately increased (2–4 nmol/L) (167). However, the absorption is rather variable and the dose required should be determined on the basis of plasma levels and clinical effects. Other orally active synthetic androgen/anabolic steroids are either only weakly active (Mesterolone, Fluoxymesterone) or hepatotoxic due to the presence of an alkyl group in position 17.

The most frequently used pharmaceutical form is the intramuscular administration of the hydrophobic long chain T-esters in oily depot, enanthate and the cypionate at a dose of 200–250 mg/2 weeks. However, this yields transient supraphysiological levels the first 2–3 days after injection, followed by a steady decline to subphysiological levels just before the next injection (168). These fluctuations in T levels are recognized by some of the patients as unpleasant and accompanied by changes in energy, libido, and mood, whereas the transient supraphysiological levels might increase the frequency of side effects (162).

Preliminary studies with im injection of 1000 mg TU indicate that this treatment might yield physiological T levels during 6–8 weeks (169).

Longer acting T esters (4–6 months), such as the buciclate, are not suited for substitution in elderly males as, in case of serious side effects, a rapid withdrawal of T should be possible.

Subcutaneous T pellets (6×100 mg every 4–6 months) provide stable physiological T levels; they are not widely used and not indicated in elderly men. In about 5% of the cases the pellets are extruded, and in a similar percentage a local infection may occur (170–172).

Transdermal scrotal or permeation-enhanced nonscrotal patches, delivering 4–6 mg T per day, provide, after nightly application, physiological T levels both in young and elderly hypogonadal men (116, 162). Peak levels are obtained 2–4 h after application, decreasing afterward to two thirds of peak levels after 22–24 h, mimicking the normal circadian variation of T levels in young adults. The scrotal patches yield supranormal DHT levels (4–5 nmol/L), whereas the nonscrotal patches often cause local irritation. With a second generation torso patch (Testoderm torso patch) this, irritation would be seen less frequently. Besides providing physiological levels in young and elderly hypogonadal men (116), the patches have the advantage that the therapy can be immediately stopped when necessary (162, 173–175) Whether the increased DHT levels have deleterious effects is unknown.

A DHT gel is available (25–50 mg DHT/g) (176) at a dose of 125–250 mg/day, which yields plasma DHT levels comparable to physiological T levels; more recently it has been shown that in healthy elderly males, a lower dose of 32–64 mg/day yields comparable levels (177). DHT cannot be ar-

omatized and, whereas it will not induce gynecomastia, it is probably inactive at the bone level. Wang *et al.* (177, 178) consider that the decrease in E_2 levels by DHT gel treatment may be favorable at the level of the prostate, where estrogens stimulate the proliferation of the stroma.

Recently a 1% hydro-alcoholic T gel has become available in some countries (98, 179, 180). When administered to young or elderly hypogonadal men, 12–68 yr of age, about 9–14% of the T applied was bioavailable and with a daily application of 100 mg/day contained in 10 g gel, the plasma T levels are in the upper normal quartile; DHT levels are only slightly increased. The surface area of inunction has only a slight influence on the T levels achieved. The gels permit an easy adaptation of the dose to the individual needs.

Other T formulations, such as bio-degradable T microspheres (181) or cyclodextrin complexed sublingual formulations (182, 183) are under experimentation.

Monitoring androgen supplementation. During treatment, the eventual development of side effects should be carefully monitored by 6 monthly rectal examinations of the prostate, PSA, and hematocrit and plasma lipid determinations. Any increase of PSA by more than 0.75 ng/ml in two consecutive controls or a PSA level abnormal for age (>4 ng/ml) (184) requires further examination and eventually biopsy, whereas any increase of the hematocrite above 51% requires reduction of the dose or temporarily arrest of the treatment.

Further developments

A major problem in the evaluation of the need of androgen supplementation is the absence of clinically useful biological parameters of androgen action, which would enable more exact evaluation of the androgen requirements of elderly men. Such parameters are urgently needed to identify objectively elderly men in need of androgen supplementation.

The biological effects of T are mediated by T itself (in muscle for example), by its 5α reduced metabolite, dihydrotestosterone, formed locally in target tissues (skin, external genitalia, and prostate) and by estradiol (bone and central nervous system). Local formation of DHT will stimulate prostatic growth and eventually prostatic carcinoma. Hence more organ selective androgens, specific AR modulators (SARMS) (185), with a desired profile of activity, stimulating only the desired organs (for example bone) without affecting other organs, would be a useful addition to our therapeutic arsenal. 17α methyl-19-nortestosterone, which does not undergo 5α reduction but does undergo aromatization and appears to be 10 times as active as T at the feed back, but only twice at the prostate level, is the first of such SARMS (186, 187) to provide adequate replacement in hypogonadal men (188). The existence of 2 forms of AR (AR-A and AR-B) (189) with different tissue distribution might contribute to the development of other SARMS.

Finally, we urgently need more carefully designed, well controlled, long-term, large-scale studies of HRT in healthy elderly men with subnormal T levels. These should permit an objective balance between the benefits and risks of HRT and, eventually, permit a wider application of HRT in elderly men.

General conclusions

Aging is unavoidable and physiologic, but the large interindividual disparity in the pace of development and progression of signs and symptoms of aging, suggests that the development of this symptomatology can be delayed and that a high quality of life can be maintained until a very advanced age, in other words that it is possible to add life to years. Being aware of these possibilities, more and more elderly men (and women) will seek medical help to achieve these goals.

Many signs and symptoms of aging in males are reminiscent of the symptoms of young hypogonadal men. These symptoms are often significantly (albeit often weakly) correlated with T levels. Therefore, although these symptoms have a complex origin it may be reasonably assumed that the age-associated decrease in T levels is in part responsible for these symptoms. As shown in almost all studies, androgen supplementation in elderly men with subnormal T levels, has favorable, albeit often modest, effects on most of the symptoms, such as muscle mass and strength, fat mass, BMD, mood and general well-being. Therefore, it seems logical to consider that in elderly men with subnormal T levels and clinical symptoms suggestive of androgen deficiency, hormone replacement therapy in combination with physical activity (resistance training) and adequate nutrition will result in an optimal increase in muscle strength, BMD, and general sense of well-being.

However, data on clinical effects of androgen substitution, such as cardiovascular morbidity and mortality, falls and bone fracture rates are so far not available.

The major contraindication for androgen supplementation is the presence of a prostatic carcinoma.

Whereas interest in androgen supplementation in the aging male is certainly increasing, the number of controlled studies as well as the number of patients involved, remains disappointingly low, and available data are too limited to permit a definitive balance between risks and benefits. Hence, we cannot recommend routine androgen supplementation in elderly men and this treatment should still be limited to patients with both symptoms suggestive of androgen deficiency and with subnormal T levels, after careful exclusion of contraindications.

The promising results obtained so far may nevertheless raise the hope that, when more research will have been performed, it will be possible to define accurately the indications for androgen supplementation and identify the elderly to profit most of the treatment. Hormonal therapy then, together with adequate physical activity and a healthy life style might delay the aging process, prevent disability, and contribute to maintain the elderly as well integrated members of society and enable them to enjoy the highest quality of life.

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