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Testosterone replacement therapy - testosterone undecanoate (Andriol)

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TESTOSTERONE REPLACEMENT THERAPY – TESTOSTERONE UNDECANOATE (ANDRIOL®)

PARTIAL ANDROGEN DEFICIENCY IN AGEING MALE (PADAM)

The phenomenon

During the normal ageing process in men there is a gradual decline in testicular function, including a fall in serum levels of total testosterone and of bioavailable testosterone, testosterone not bound by SHBG (Fig. 1) [1, 2]. There is great interindividual variability in the age-related changes in testicular function, and only some men become hypogonadal, as defined by serum total testosterone levels below the normal range for young adult men [3].

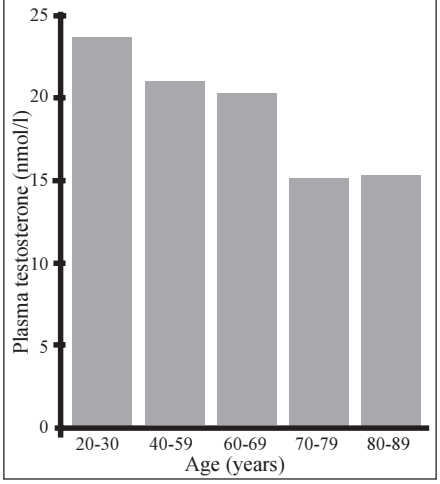
That such a decline in testosterone levels takes place has only been generally accepted very recently and few studies of hormone replacement for older males have been published (Table 1). Reports in the 1960s and 1970s of decreased plasma concentrations in elderly men were followed by a number of publications that did not confirm this. The inconsistencies of these results were attributed to differences in the characteristics of the men studied (eg, health and socio-economic status, smoking, alcohol consumption) and to differences in study design (eg, the time of day at which blood samples were taken). A number of more recent, well-designed studies, however, have shown convincingly that androgen levels do decrease with age [1, 4, 5]. The Massachusetts Male Ageing Study [1] included 415 healthy men and 1294 men with one or more ailments, aged between 39 and 70 years. In both groups of men, free testosterone levels were found to decline by 1.2 % per year, albumin-bound testosterone, by 1.0 % per year and SHBG, the carrier protein that binds 60 % of circulating testosterone, increased by 1.2 % per year. The net effect of these changes was that total serum testosterone levels decreased more slowly (0.4 % per year) than the free or albumin-bound testosterone pools alone. Testosterone levels were 10–15 % lower in the less healthy group of men, which included men with obesity compared with the healthy group but the trends in the two groups did not differ significantly. It has also been found that the circadian rhythm (early morning rise) in serum testosterone levels found in normal young men is markedly attenuated or absent in healthy elderly men [6]. This change makes it even more important to control the time of day at which samples are taken for testosterone measurements.

For some of its biological actions testosterone has to be converted to DHT most of which is produced in a local conversion of testosterone in target organs. Only 20 % of DHT is secreted by the testis; the plasma DHT originates in the main from leakage of DHT from target organs into the general circulation [4]. There have been conflicting reports of the relationship of serum DHT levels with ageing: including reports of decreased levels, unchanged levels and increased levels. In the Massachusetts Male Ageing Study DHT did not show a significant age-related trend. However, the reduction products of DHT, androstanediol and its glucuronide, which are considered to be biochemical indices of androgen action in target organs, were found to decrease with age [1, 4].

There is no established definition of testosterone deficiency in older men. Tremblay and Morales [7] have suggested that patients should be treated for specific indications on the basis of both clinical symptoms and serum testosterone levels. This suggestion is consistent with the views of Tenover [8] who notes that it is probable that the level of testosterone that can be described as a deficiency varies between individuals and between target organs.

Tenover [8] has also pointed out that depending on the definition of hypogonadism, the proportions of men affected differ greatly. If hypogonadism is defined as having a serum testosterone level in the lowest quintile and gonadotropin levels in the highest quintile, about 4 % of men in the 40–70 age range are hypogonadal but if the definition were to embrace men of 55 and over whose serum testosterone levels are below the lower normal range

Figure 1: Changes in plasma testosterone levels with age, based on the data of Vermeulen [2]



for young adults, this would include about 20 %. Further, if the definition were based on unbound or bioavailable testosterone the prevalence might rise to about 50 %.

Reasons for the decline in testosterone

Most testosterone is produced by the Leydig cells of the testis (95 %) and its secretion is regulated by the pituitary through the release of LH which is in turn under the control of the hypothalamic luteinizing hormone releasing hormone. There is no clear consensus about the endocrine mechanism of the gradual decline in testosterone levels with age. It seems likely that the lower testosterone levels are the result of changes at many levels of the hypothalamic-pituitary-gonadal axis [9, 10]. That a primary testicular cause is one factor in the decreased androgen levels in elderly men is suggested by the decrease in the number of Leydig cells and the impaired testicular perfusion. The testicular response to gonadotropins is diminished in older men; gonadotropic response to androgen suppression is attenuated and the pulsatility of the gonadotropin-releasing hormone (FSH- and LH-releasing hormone) pulse generator is altered. Co-existing diseases, malnutrition and concomitant medications can also affect serum testosterone levels; in the Massachusetts Male Ageing Study the testosterone levels of the less healthy males were lower [1].

Gooren [4] raised the possibility that ageing might lessen the effects of androgens through a loss of sensitivity to testosterone in target tissues perhaps as a result of changes in receptor number or affinity, or in post-receptor mechanisms. This possibility has not been investigated but it might limit the benefits of androgen supplementation in older men.

Free and bioavailable testosterone

Both free and bioavailable (free and albumin-bound) testosterone levels decline more rapidly with age than do total testosterone levels [2, 11–13]. In the Massachusetts Male Ageing Study plasma free testosterone levels declined by 1.2 % per year, and albumin-bound testosterone declined by 1.0 % per year while total testosterone decreased by only 0.4 % per year [1]. The more pronounced decrease in free than in total testosterone is explained by the age-dependent increase in the binding capacity of SHBG (1.2 % per year). The decline in bioavailable testosterone occurs earlier than the decline in total testosterone [12, 13]. Bioavailable testosterone levels have been found to correlate with a number of age-related cognitive and physical measures [14] and appears to be a more sensitive marker of PADAM than free testosterone.

Effects of the decline in testosterone

Ageing in men is sometimes associated with a cluster of clinical problems including:

- osteoporosis
- muscle weakness and wasting (strength and energy)
- changes in body composition
- decreased body hair
- decreased hematopoiesis
- sexual dysfunction
- memory loss
- decreased general well-being

Some or all of these problems may be related to the decline in testosterone levels or to reduced androgen sensitivity in older men [8, 9]. Other symptoms that have been suggested as possibly due to testosterone deficiency include sweating, hot flushes, insomnia, nervousness, irritability and lethargy, lack of motivation, low mental energy, depressive symptoms, low self-esteem, decreased vigour and physical energy [7].

Osteoporosis

The problem of osteoporosis and hip fractures in elderly men is increasing with the growing numbers of elderly people since the incidence of hip fractures increases with age. In men over 65 years of age, the incidence of hip fractures is about 4 or 5 per thousand [12]. The mortality rate within 6 months after hip fracture in elderly men is 20 % and only 41 % of the survivors recover to their former level of functioning [15, 16].

Several lines of evidence indicate that testosterone levels are a factor in the development of osteoporosis in ageing men. Hypogonadism in elderly white males is associated with an increased risk of minimal trauma hip fracture: in one study involving 17 men with minimal trauma hip fractures and 61 controls, 59% of those with hip fractures but only 18 % of the controls

Table 1: Studies of the use of testosterone supplementation therapy for the treatment of PADAM

Reference	Study design	Type/no. of patients	Daily Testosterone dose/duration	Results	Safety/other aspects
Romanelli et al [34]	Uncontrolled	6 men, low androgen levels and PADAM symptoms, age 53 to 62 years	80 mg TU/day for 8 months	Improved libido and sexual activity, improved well-being and disappearance of symptoms	Some of the effects may be placebo effects
Isidori et al [33]	Double blind placebo-controlled	20 men with PADAM symptoms, age 45 to 75 years	10 men given 80 mg TU/day for 8 weeks	Significant increase in libido, erections	
Janowsky et al [39]	Double blind	Healthy older men aged 60–75 years	Scrotal patches containing 15 mg T for 3 months	Significant enhancement of spatial cognition, but no changes in memory, motor speed, cognitive flexibility or mood	Oestradiol was inversely correlated with spatial cognition
Morley et al [20]	Open, alternately assigned cases (treated) and controls (untreated)	14 men aged 69-89 years with bioavailable T < 70 ng/dl (some impotent)	8 men given 200 mg TE/2 weeks for 3 months, 6 controls	Significantly increased right-hand muscle strength and osteocalcin concentration (suggesting improved osteoblastic function), increased haematocrit	Decreased total cholesterol but no change in HDL cholesterol. Decreased BUN: creatinine ratio. PSA tended to increase
Sih et al [25]	Randomized placebo-controlled	32 men hypogonadal (bioavailable T < 60 ng/dl). Age 58 to 74 years	17 given 200 mg TC every 2 weeks for 12 months	Bilateral grip strength and haemoglobin levels were significantly increased. Leptin levels decreased significantly more in TC group. No significant change in memory	No significant changes in PSA or prostate on DRE. 3 on placebo and 7 on TC withdrew. 3 on TC withdrew because of abnormal haematocrits
Tenover [3]	Double-bllind randomized placebo-controlled crossover	13 healthy men aged 57–76 years with serum T ≤ 13.9 nmol/l	100 mg TE/week im. for 3 months	Lean body mass significantly increased and hydroxyproline excretion decreased suggesting reduced bone resorption. Increased haematocrit	Reduced total and LDL cholesterol. No enlargement or abnormality of prostate but a sustained increase in PSA
Tenover 1998 unpublished	Double-blind randomized	70 healthy men aged 65 to 83 years with morning T < 13 nmol/l	3 groups given 150 mg TE/2 weeks or 150 mg TE + finasteride or placebo for 3 years	Preliminary results. Both T groups showed increased bone density, increased muscle mass and reduced body fat cf placebo group. Further analysis of data will give results for libido and cognition	No increase in serum PSA and no change in the risk of prostate problems. Total and LDL cholesterol reduced. So far not fully analysed, and unpublished
Urban et al [24]	Uncontrolled	6 healthy men aged 67± 2 years with serum T ≤ 480 ng/dl or less	TE injections weekly for 4 weeks. Doses adjusted to keep serum T in the range 500–1000 ng/dl	Increased muscle strength in hamstring and quadriceps, increased fractional synthetic rate of muscle protein. mRNA concentrations suggesting stimulation of IGF-1	

T = testosterone; TC = testosterone cypionate; TE = testosterone enanthate

were hypogonadal [17]. Tenover [8] briefly reviewed several short-term studies (6 weeks to 18 months) which suggest that testosterone supplementation, in the short-term at least, may have benefits for BMD and bone turnover. There is an increased incidence of osteoporosis and related fractures in men after orchidectomy for prostatic cancer [18]. Further, castration or treatment of older men with gonadotropin-releasing hormone analogues can lead to rapid declines in BMD [8]. A few studies have been reported to show a correlation between testosterone levels and BMD while others have failed to demonstrate an age-independent association between testosterone and BMD in men [12].

There are a number of possible mechanisms by which testosterone may affect bones. It may affect them directly via androgen receptors or via cytokines or growth factors. Alternatively the effects of testosterone may be indirect via aromatisation to oestrogens, via an increase in muscle mass and strength (mechanical loading), via calciotropic hormones or via renal handling of calcium, phosphorus and vitamin D.

Increases in bone mineral density were seen in hypogonadal men treated with testosterone supplements for up to 16 years [19]. Most (52) of the 72 patients included in the study were treated with intramuscular testosterone enanthate: the remainder received other formulations including oral TU in three cases. Serum testosterone levels increased to the normal range in all of the treated men. The most significant rise in bone mineral density (trabecular, lumbar spine) was during the first year when it rose by about 26 %. Long-term therapy maintained bone mineral density in the reference range in all cases [19]. The results of the study of the effects of long-term testosterone therapy on bone density in 14 hypogonadal men with Klinefelter's syndrome, mentioned earlier, were much less encourageing [20]. The bone mineral densities of the treated patients were significantly lower than those of normal age-matched controls and there was no correlation between the duration of treatment and bone mineral density.

There is some evidence from studies in older men that testosterone substitution improves BMD. In an open study in which eight men aged 69–89 years with bioavailable testosterone levels below 70 ng/ml were given 200 mg TE every 2 weeks for 3 months, osteocalcin concentrations were significantly increased, suggesting improved osteoblastic function [21]. In a double-blind randomised crossover study of 13 men aged 57–76, treated with 100 mg TE every week for 3 months, hydroxyproline excretion decreased, suggesting reduced bone resorption [3]. Preliminary results from a long-term randomised placebo-controlled trial have shown steady increases in BMD in men treated with testosterone enanthate injections (Tenover, 1998, unpublished). In this latter study, 70 healthy men, aged 65–83 years, with morning total testosterone levels below 13 nmol/l were randomly assigned to receive for 3 years: (1) 150 mg testosterone enanthate intramuscularly every 2 weeks and finasteride (a 5α-reductase inhibitor that prevents the production of DHT) or (2) testosterone plus a placebo pill or (3) placebo injections and pills. After 3 years of treatment, men receiving testosterone with or without finasteride showed an 8 % increase in BMD in the lumbar spine and a 3 % increase at the hip.

Muscles and body composition

Normal ageing in men results in a decrease in muscle mass, a decline in muscle strength and increases in upper and central body fat [8]. Hypogonadal men show similarly reduced lean body mass, decreased muscle strength and increased adipose tissue compared with men with normal testosterone levels. These changes in body composition have been ascribed to lower testosterone levels in both hypogonadal and elderly men. There is no conclusive evidence that testosterone is at the root of these changes in body composition, but young hypogonadal men treated with testosterone replacement have been reported to show increases in lean body mass, muscle size and strength [22]. Further, testosterone has been shown to be associated with muscle mass in animals [23]. It has also been suggested that the ability of testosterone to protect against muscle mass loss may be mediated through insulin growth factor 1(IGF-1), the serum levels of which have been found to fall significantly with age [12, 24].

Several interventional studies suggest that testosterone replacement therapy in older males may enhance muscle strength, increase lean body mass and decrease fat mass (Table 1) [12]. In one open study healthy elderly men treated with testosterone enanthate for 4 weeks showed increased muscle strength in the hamstring and quadriceps muscles, increased fractional synthetic rate of muscle protein and increased IGF-1 mRNA concentrations [24]. Sih et al [25] assessed the effects of testosterone cypionate treatment for 12 months in a placebo-controlled randomized trial in hypogonadal men aged 50 years or above. The testosterone treatment significantly improved grip strength. Sih et al. used grip strength as an indicator of muscle strength and saw encourageing improvement but the effects on lower extremity strength, also an important factor in this age group, were not assessed. There was also a significant increase in right-

Table 2: Published reports of the use of oral testosterone undecanoate (TU) to treat hypogonadism

Reference	Study design	Type/no. of patients treated with TU	Daily TU dose/ duration	Results	Safety/other aspects
Bancroft and Wu [48]	Placebo-controlled crossover	8 hypogonadal	160 or 240 mg/day	Erections to films were not affected by treatment but erections to fantasies were significantly improved.	
Conway et al [49]	Comparative prospective randomized crossover	14 hypogonadal	240 mg for 4 weeks	3/14 patients reported adequate effects (libido, potency, muscular strength and general well being).	6/14 had gastrointestinal symptoms but continued treatment.
Franchi et al [50]	Open baseline comparison	42 hypogonadal	80 mg/day for 16 weeks	All patients noticed a "remarkable" increase in sexual, physical and mental activity.	
Franchi et al [40]	Comparison with previous treatment	34 hypogonadal	40–160 mg/day for 8 months	Increase in libido and sexual physical, and/or mental activities. Preferred over TU injectable regimes.	No changes in size and consistency of prostate. No abnormal lab values. No gynecomastia.
Franchimont et al [41]	Baseline comparison	10 hypogonadal	120–240 mg/day for 9 weeks	Increased libido and sexual activity in 9 patients, increased mental activity in 7, physical activity in 2.	
Gooren [29]	Comparison with previous treatment	8 hypogonadal	160–240 mg/day	No difference in sex functions and mood compared with previous testosterone treatment.	One man did not complete, choosing to return to parenteral treatment because of reduced sexual appetite and energy.
Jockenhövel et al [36]	Comparison with other androgen replacements	13 hypogonadal men	160 mg/day for 30 weeks	Increased haemoglobin and haematocrit	
Luisi and Franchi [30]	Double-blind randomised comparison	12 hypogonadal men (TU)	120 mg TU/day for 4 weeks cf 150 mg mesterolone	Significant improvements in libido, erections, ejaculations and mood compared with mesterolone	
Maisey et al [42]	Comparison with previous treatment in 71 patients	76 hypogonadal men (10 dropped out)	80–160 mg/day for 9 weeks (doses modified as needed)	Improvements in sexual function, frequency of intercourse, work efficiency, ability to concentrate and changes in sporting activities.	8(/10) patients dropped out because of side-effects, mainly GI. Sig. rise in plasma testosterone correlating with plasma TU.
Morales et al [51]	Comparison with baseline	23 impotent hypogonadal men	120 mg/day for 60 days+	Measurable improvement in sexual interest in 15. Complete response in 10.	None of conventional biochem. measures correlated with outcome.
O'Carroll et al [45]	Dose-ranging, double-blind	8 hypogonadal men	40, 80, 120 and 160 mg/day in 4 successive 1-month treatments	Dose-response relationship found for frequency of sexual thoughts, arousal accompanying sexual thoughts and well-being. Sleep erections improved significantly.	
Papadimas et al [43]	Comparative (mesterolone) randomized double-blind	9 hypogonadal	120 mg/day for 4 weeks	All 9 reported improved libido and sexual activity. Mental activity improved in 8 patients and physical activity improved in 7.	
Skakkebaek et al [31]	Double-blind crossover comparison with placebo	12 hypogonadal (6 hyper- and 6 hypogonadotrophic)	160 mg/day for 8 weeks	TU had a significant effect on all measures of sexual interest and behaviour. Responses were similar in the two groups.	Rise in plasma testosterone did not reach normal range in some cases. DHT rose more.

Wong et al [20]	Comparison of long-term oral TU with im TE	14 Klinefelter's syndrome	240 mg/day cf 250 mg TE/3 weeks for 2–12 years	No correlation between duration of treatment and bone mineral density. These methods of T replacement don't reverse decline in bone mass in Klinefelter's
Wu et al [52]	Randomized double-blind crossover comparison of TU and placebo	4 Klinefelter's syndrome, low normal testosterone and normal sexual activity	160 mg/day for 8 weeks	Inconclusive results re sexual interest. Increase in circulating DHT more marked than increase in testosterone No effect on mood, energy or erectile responsiveness in the lab.

hand muscle strength in the open study of Morley et al (Table 1) [21]. In the studies of Tenover [3, unpublished 1998] (Table 1), a significant increase in lean body mass was seen in the 3-month study with testosterone enanthate and in the 3-year study there was a 4-kg increase in muscle mass compared with a 3-kg drop in muscle mass in the placebo group. In the long-term controlled study of Tenover (1998) there was also a 16 % reduction in body fat. Testosterone had no significant effect on body composition in the study by Sih et al [25]. The dose-dependency of the anabolic effects of testosterone is, however, unknown so dose could be a contributory factor. Another reason for the discrepancy might be differences in the methods used to measure body composition.

Sexual dysfunction

Several studies have shown that there is an age-related decrease in sexual interest and activity, particularly an increased prevalence of erectile dysfunction [4]. In the Massachusetts Male Ageing Study the combined prevalence of impotence (minimal to complete) was 52 % in men aged 40–70 years [26]. The prevalence of complete impotence tripled from 5 % to 15 %, and that of moderate impotence doubled from 17 to 34 % between the ages of 40 and 70 years. Age was the most predictive variable for impotence. However, heart disease, hypertension, diabetes mellitus, associated medications and psychological troubles all increased the probability of impotence [26]. Of the 17 hormones measured, however, only the androgen metabolite, dehydroepiandrosterone sulphate, showed a strong correlation with impotence. DHT and cortisol showed small effects on minimal impotence only. There was no correlation with impotence for total testosterone, SHBG or any of the androgen metabolites, estrogens, prolactin or the pituitary gonadotropins. Unfortunately, bioavailable testosterone was not measured in this latter study. The classification of men into four impotence categories (no, minimal, moderate or complete impotence) was based on the answers to a questionnaire about sexual activity and erections.

A cross-sectional study of 220 men aged 41 to 93 years showed that total and free plasma testosterone levels declined and gonadotropins increased in parallel with a decline in sexual activity with orgasm, morning erections, sexual thoughts and sexual enjoyment [27]. Decreases in free testosterone and increases in LH correlated significantly with the decline in the measures of sexual functioning (except sexual enjoyment in the case of free testosterone). Hormonal changes seemed to be more closely related to sexual activity and morning erections than to libido. The hormonal factors did not account fully for the age-related decline in sexual functioning. Similarly, in a study of 77 healthy men aged 45–74 years bioavailable testosterone and the ratio of bioavailable testosterone to luteinizing hormone were correlated with several sexual behavioural dimensions: frequency of sexual thoughts and desire, ease of arousal, frequency of sleep erections and strength of coital erections [28]. Total testosterone,

estradiol and prolactin showed few or no such relationships.

Androgen-replacement studies in hypogonadal men indicate that androgens are more important in sustaining sexual desire and sleep-related erections than in maintaining erectile response to external stimuli [4]. In men under 50 years old testosterone levels of about 60 % of the reference values are sufficient to maintain sexual function [4, 29]. Whether this applies to ageing men is not clear.

Studies in hypogonadal men indicate that TU therapy has significant effects on libido, sexual activity and sexual responses such as enjoyment, erections and ejaculation (Table 2) [30, 31]. As noted above, Carani et al [32] treated impotent men (aged 22–50 years) with mild hypogonadism with oral TU (160 mg/day) and found that TU improved sexual function in men with low free testosterone levels but not in those with normal levels although total testosterone levels were similar.

The limited studies carried out so far in older men showing symptoms of PADAM indicate that testosterone replacement with oral TU may have beneficial effects on libido, erections and frequency of intercourse (Table 1) [33, 34]. It seems clear that the prevalence of erectile dysfunction increases with age but the overall picture of the relationship between declining testosterone levels and increasing sexual dysfunction is not yet certain. From the results of the Massachusetts Male Ageing Study there does not appear to be a simple or direct relationship between impotence and androgen levels in ageing men. Other studies indicate that some aspects of sexual functioning are correlated with plasma testosterone levels. The extent to which testosterone replacement in elderly men can improve sexual functioning remains to be clarified.

Decreased hematopoiesis

Androgens are known to stimulate erythropoiesis; they increase reticulocyte counts, hemoglobin levels and bone marrow erythropoietic activity in mammals and castration has the opposite effects. Testosterone stimulates the renal production of erythropoietin and may have a direct effect on erythropoietic stem cells [35]. Young hypogonadal men have lower red blood cell counts and hemoglobin levels than their age-matched controls. Healthy older men tend to have similar or slightly lower hematocrits than normal young adult men [35].

Jockenhövel et al [36] investigated the effects of different forms of androgen substitution on hemoglobin concentrations and hematocrits in 55 hypogonadal men (Table 2). Both hemoglobin levels and hematocrits were significantly increased with oral TU, with T implants and TE injections, whereas no increase was observed in the mesterolone group. Thus for stimulation of erythropoiesis, testosterone levels within the low normal range (as seen with TU) were sufficient. This suggests a possible advantage, from the safety viewpoint, of using TU to treat older men. The authors conclude that it is testosterone and not DHT that stimulates erythropoiesis in a dose-dependent manner. The authors also suggest that blood counts should be monitored during high-dose testosterone substitution since some individuals respond with an exaggerated increase in hemoglobin and hematocrit. The need for such monitoring is emphasized by the fact that in one study, using testosterone cypionate in older men, 3/17 patients dropped out because of abnormally high hematocrits [25].

Memory loss and impaired cognitive function

There is some evidence that testosterone enhances memory both in mice and in humans although it is not yet clear whether decreasing testosterone levels have a role in modulating age-related cognitive decline [12]. A study in mice has suggested that impaired cognitive functioning in older mice of a particular strain was due to an interaction of ageing and reduced testosterone levels [37]. Testosterone supplementation alleviated impaired learning and memory of a foot shock avoidance task in these mice.

A significant decline in spatial cognition with ageing has also been reported [38]. One study in older men showed an improvement in spatial cognition after 3 months of treatment with testosterone scrotal patches but there were no changes in verbal and visual memory, motor speed, cognitive flexibility or mood (Table 1) [39]. Testosterone supplementation reduced the endogenous production of estradiol and serum estradiol concentrations were inversely related to

spatial cognitive performance. Further evidence that testosterone replacement in older men does not affect memory comes from the study of Sih et al [25]. In this 1-year placebo-controlled study of testosterone replacement therapy (using intramuscular testosterone cypionate) in older hypogonadal men there was no effect on memory. Studies in younger hypogonadal men have suggested that testosterone replacement improves concentration ability or "mental activity" [40–43].

Decreased general well-being

Hypogonadal young men and some older men given testosterone supplementation have variously reported improved mood, improved sense of well-being, decline in anxiety, and improved feelings of energy [3, 44–46]. Treatment with TU of 80 mg/day in elderly men with low plasma testosterone improved general well-being after three months of treatment [34].

Patient selection

Two groups have recently presented their approaches to different aspects of the decision about which patients should be treated for PADAM. Morley [20] has proposed a questionnaire to evaluate the symptoms of androgen deficiency and Tremblay and Morales [7] have published recommendations based on serum concentrations of bioavailable testosterone. A combination of these two approaches seems likely to be helpful.

The questionnaire suggested by Morley et al consists of the following ten questions:

1. Do you have a decrease in libido (sex drive)?
2. Do you have a lack of energy?
3. Do you have a decrease in strength and/or endurance?
4. Have you lost height?
5. Have you noticed a decreased enjoyment of life?
6. Are you sad and/or grumpy?
7. Are your erections less strong?
8. Have you noted a recent deterioration in your ability to play sports?
9. Are you falling asleep after dinner?
10. Has there been a recent deterioration in your working performance?

The validity of this questionnaire as a means of identifying older men with reduced testosterone levels was assessed in 316 men aged 40–62 years. Low bioavailable testosterone levels (< 70 ng/dl) were present in 25 % of these men; the questionnaire identified this group with a sensitivity of 88 % and a specificity of 60 %. In 21 patients treated with testosterone (no details given), scores in the questionnaire improved in 18 patients. The results suggest that the questionnaire may have potential in the assessment which patients should be treated for PADAM.

The recommendations of Tremblay and Morales [7] for the treatment of PADAM include the following guidelines for patients who should be treated:

- Treatment with supplemental testosterone therapy should be given for specific indications to patients with clinical symptoms and physical manifestations of hypogonadism. Laboratory assessment is essential: the diagnosis of hypogonadism should ideally be based on finding levels of serum bioavailable testosterone below the lower limits of normal (2–2.5 nmol/l in Canada) in morning blood samples on two or more occasions. If serum bioavailable testosterone cannot be measured, free testosterone underestimates bioavailable testosterone and may therefore be misleading.
- Patients with suspected secondary hypogonadism (of hypothalamic-pituitary origin) should not be given testosterone until endocrine investigations are complete.
- Before starting testosterone therapy patients should have hematocrit, serum lipid profile and prostate specific antigen determinations and should be given a digital rectal examination.
- Mild benign prostatic hypertrophy is not an absolute contraindication to therapy: patients with few urinary tract obstructive symptoms may be suitable for therapy but those with advanced obstructive symptoms are not.
- Breast cancer, prostate cancer and sleep apnoea are all contraindications to therapy. In the case of breast cancer this is because testosterone treatment may increase oestrogen levels. Patients suspected of having prostate cancer, after digital rectal examination and/or serum prostate-specific antigen measurements, should be fully investigated.

The recommendations of Tremblay and Morales [7] also include

guidelines for the assessment of patients who are being treated:

- In the early phase of treatment patients should be assessed every 3 months. At these times, the response to therapy should be assessed, a digital rectal examination should be done and, if the patient is over 40 years old PSA should be determined. If the PSA level is above 4 ng/ml the patients should be examined by a urologist.
- Patients who remain stable may subsequently be assessed every 6 months when their lipid profiles, hemoglobin levels and hematrocrits may also be considered.
- Clinical response is a better guide to the dose required than are serum levels of bioavailable testosterone which may fluctuate considerably (depending on the treatment) (In the case of oral TU, doses should be adjusted on an individual basis).

Testosterone undecanoate treatment in PADAM

So far there have been few studies of the use of oral TU to treat PADAM: small groups of older men were studied; the studies were of less than 12 months' duration and the outcomes reported were limited and varied. However, taken together with the results of studies of the use of oral TU in other indications, such as hypogonadal states in men of all ages, these limited studies add weight to the view that the potential of oral TU as an option in the treatment of PADAM should be explored.

An uncontrolled study was carried out in six men, aged between 53 and 62 years [34]. The men presented with decreased libido and potency, insomnia, palpitations, poor efficiency at work, impaired concentration and memory, irritability, mild depression, apathy and low circulating androgen levels, and without apparent prostatic pathology. The men were given 80 mg TU orally/day for 8 months. Five of the six patients had not had intercourse for some time and the other made infrequent generally unsuccessful attempts at intercourse. Plasma testosterone levels rose steadily during the treatment period from a mean of 131.5 to 283.3 ng/dl after 7 months. Plasma levels of DHT and estradiol also rose steadily while FSH and LH declined during the treatment period. By the third month of treatment all patients reported an improved general feeling of well-being and disappearance of complaints. Libido also increased and four of the six reported having intercourse. Further improvements occurred subsequently and all of the patients and their partners were very satisfied with the treatment.

In a double-blind placebo-controlled study oral TU also showed promising results in men affected by PADAM [33]. Half of the group of 20 men, aged 45 to 75 years were given 80 mg TU/day for 8 weeks while the other ten received placebo. There were significant increases in plasma testosterone concentrations in the treated group, compared with the control group both 4 and 8 weeks after the start of treatment. After 8 weeks the men in the treated group showed significant increases in both libido and erection scores compared with the placebo group. There was also an increase in the score of ejaculation but this was not statistically significant.

The potential risks of testosterone treatment of older men are elevation of red blood cell count, exacerbation of sleep apnoea, fluid retention, exacerbation of benign or malignant prostate disease and increased risk of cardiovascular disease.

Bhasin and Tenover [47] expressed concern at the high dropout rate in the study of Sih et al [25] using testosterone cypionate. Three men dropped out because of increases in hemoglobin reflecting the fact that older men seem to show more marked increases in hemoglobin than do younger men in response to testosterone injections. Clearly there is a need to monitor hemoglobin and hematocrit levels as was also suggested by Tremblay and Morales [7].

Concerns about prostate enlargement, prostate cancer and coronary heart disease risk are clearly greatest for older men. Existing safety reports are mainly for younger men (and the numbers involved are relatively small) but in the case of TU they are encourageing. The use of testosterone supplementation in older men will need careful ongoing monitoring of all aspects of safety.

In conclusion, oral TU does not appear to induce prostate enlargement beyond that seen in

eugonadal men of the same age. As with other testosterone formulations, however, prostate cancer is an absolute contraindication to the use of TU. The effects of oral TU on lipid and lipoprotein profiles are not yet clear but the evidence so far suggests that TU often has generally favourable effects, particularly by reducing total cholesterol. Finally, oral TU does not appear to have any detrimental effects on liver function.

Conclusions

- TU has the advantage over other preparations that it is easy to administer since it can be taken orally. Dose flexibility and the possibility to immediate interruption of treatment are easy for patients themselves.
- As a result of its lymphatic absorption, TU administration results in variable serum testosterone levels within the lower normal range, depending on the daily dose administered.
- There is evidence that testosterone therapy may have benefits for some older men (PADAM): TU appears to be a potentially effective, safe, easy-to-use treatment, worth considering for this purpose.
- There is no evidence that oral TU has negative effects on the liver or the prostate.
- Ongoing safety monitoring is essential particularly if TU is used in older men in whom the risks, for example with respect to the prostate, are greatest.

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