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Testosterone therapy in the aging male

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Abstract
The decline, with aging, in serum concentrations of biologically active forms of testosterone in men is an indisputable fact and some men will eventually develop symptoms of late-onset hypogonadism (LOH) with its clinical consequences. LOH reduces quality of life and may pose important risk factors for frailty, changes in body composition, cardiovascular disease, sexual dysfunction and osteoporosis. Testosterone supplementation in cases of LOH will restore serum testosterone levels into the physiologic range; will restore metabolic parameters to the eugonadal state, increase muscle mass, strength, and function; maintaine or improve BMD reducing fracture risk; will improve neuropsychological function (cognition and mood); libido and sexual functioning; and enhance quality of life. The ultimate goals, however, are to maintain or regain a high quality of life, to reduce disability, to compress major illnesses into a narrow age range and to add life to years. To achieve these goals men must also adjust their lifestyle to optimize dietary habits, as well as to exercise and to abstain from smoking life-long. Monitoring these patients is a shared responsibility that cannot be taken lightly. The physician must emphasize to the patient the need for periodic evaluations and the patient must agree to comply with these requirements. The physician's evaluation should include an assessment of the clinical response and monitoring must be tailored to the indications and individual needs of the patient.

Keywords: *Late-onset hypogonadism, testosterone, aging, testosterone therapy, obesity, libido*

Introduction

The field of hormonal alterations in the aging male is attracting increasing interest in the medical community and the public at large. Simultaneously, industry has realized the growing importance and enormous potential of a rapidly growing population of males over the age of 50 years which will require special health needs in the first quarter of this century and probably beyond.

Among the many processes of aging, endocrine changes are relatively easy to identify and quantify with the presently available methods for determining hormone levels which are reliable and sensitive. The decline with aging in the serum concentrations of biologically active forms of testosterone in men is an indisputable fact [1–6]. This decline begins earlier than previously appreciated (at approximately age 30 years) and is progressive and relentless. Eventually, if men live long enough (and with a large interindividual variation), serum testosterone levels may fall below the threshold for optimal androgen actions. The question has now turned to whether this decline in testosterone is a physiologic process and should be accepted as 'normal' or as a pathologic process with clinical implications. The pendulum has swung toward a dysfunctional state as there is increasing recognition that age-dependent androgen deficiency has clinical significance. It reduces quality of life and may pose important risk factors for frailty, changes in body composition, cardiovascular disease, sexual dysfunction and osteoporosis. It is increasingly being realized that androgens and their metabolites also have a large number of non-reproductive effects. They are important anabolic factors in the maintenance of muscle mass and bone mass and in non-sexual psychological functioning. The latter are important constituents of wellbeing in old age.

It is quite discouraging that most men and physicians know very little about testosterone or the potential consequences of having low testosterone levels, or about the availability of therapies to substitute testosterone and improve overall health. Interventions such as hormone therapy may prevent, delay or alleviate the debilitating conditions which may result from decreasing hormone levels with aging.

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The understanding of 'androgen deficiency in aging men' among large sections of the medical profession dealing with mature men (i.e. primary care, internists, urologists, etc.) has not kept pace with the developments in the field, and andrology is evolving only slowly as a speciality. A great deal of confusion and misunderstandings exist surrounding the four issues of definition, diagnosis, treatment and monitoring of acquired hypogonadism of the aging male (i.e. late-onset hypogonadism = LOH). The U.S. Food and Drug Administration (FDA) has estimated that 4 to 5 million American men may suffer from hypogonadism, but only 5% are currently treated. The HIM study [7] found that in a sample of 2,162 patients attending primary care centres 836 were found to be hypogonodal, but only 80 (less than 10%) were actually treated.

Definition of late-onset hypogonadism (LOH)

Late-onset hypogonadism (LOH) is a syndrome, characterized by adverse effects on multiple organ systems and decreased quality of life, associated with advancing age and characterized by signs and symptoms of hypogonadism, and a deficiency in serum androgen levels with or without a decreased genomic sensitivity to androgens [8,9]. Considering LOH as a distinct pathophysiological entity is justified by the decreased endocrine capacity of the testes as well as the hypothalamo-pituitary system, thus combining features of both primary and secondary hypogonadism.

Clinical features of late-onset hypogonadism

Aging men often present with a variety of vague, nonspecific symptoms that may be associated with testosterone deficiency. The symptoms of late-onset hypogonadism include reduction of bone mineral density, reduction of muscle mass and strength, abdominal obesity, reduced libido, erectile dysfunction, decrease in body hair and skin alterations reduced haematopoiesis, depressed mood, impaired cognitive function and reduced general well being [8–10].

Bone loss

In men, as in women, the incidence of hip fractures increases gradually with increasing age. In the USA, amongst men aged 65 or more years of age, 4 to 5 per 1,000 break a hip each year [11]. Approximately 20% of these aging men will die within 6 months and only about 40% will recover to their previous level of daily functioning. The root cause of hip fracture in the elderly is reduction of bone mineral density, also described as osteoporosis, which in men is thought to be due, in part at least, to testosterone deficiency [12,13].

Several studies have demonstrated that there is a reduction of bone mineral density, more so of trabecular than of cortical bone, with increasing age in men [14–16]. Although correlations between total testosterone and bone mineral density are generally weak in aging men, studies have shown that there is a clear correlation between bioavailable testosterone and bone mineral density [17–19]. Also the incidence of osteoporotic fractures (preceded by a rapid decline in bone mineral density) has been shown to increase after surgical or pharmacological castration for prostate cancer, leading to extreme hypogonadism [20,21].

A direct link between testosterone deficiency in aging males and hip fracture was demonstrated in a case-control study showing that 48% of subjects with hip fractures were hypogonadal, compared with only 12% of a control group, a difference which was statistically significant [22]. The association between hypogonadism and hip fractures was confirmed in another study in aging men and it was suggested that early diagnosis and treatment of hypogonadism might prevent hip fractures in this aging population [23]. Finally, a retrospective analysis of nursing home residents with a history of hip fracture found that 66% of these men were hypogonadal [24].

The mechanisms by which testosterone might affect bone mineral density are not fully known, but one possibility is a direct effect on androgen receptors, or associated cytokines or growth factors. An indirect, but important, effect of testosterone is probably mediated through its aromatization into estradiol [16,25,26]. Reducing plasma levels of the substrate testosterone in aging men results in lower aromatization into estradiol, thereby affecting bone mineral density [27]. Long-term follow-up of men recruited for the Framingham study in the early 1980s revealed that those with the lowest testosterone and estradiol levels at the time of enrolment showed the highest rate of hip fractures [28]. Additional contributing mechanisms are increased mechanical loading via anabolic effects on muscle, via calciotropic hormones, and via renal handling of calcium, phosphorus and vitamin D [29].

Adverse effects on muscle status and body composition

As men grow older, their muscles become smaller and weaker and they develop more adipose tissue in the central and upper parts of the body. This condition of age-related muscle weakness is often referred to as sarcopenia and is associated with impaired functional performance, increased physical disability, increased dependency and increased risk of falls. Potential causal factors include decreased plasma levels of anabolic factors, decreased muscle protein synthesis, nervous system degeneration, as well as the pathological effects of malnutrition and chronic disease. Moreover, results from the New Mexico Aging Process Study have shown that, in relatively healthy aging men, there are significant correlations between total and free plasma testosterone levels and muscle

strength [30]. Significant associations have been reported in men between age, plasma testosterone levels and body composition. Low plasma levels of testosterone and a low testosterone/estradiol ratio are associated with obesity. In addition, associations have been reported between distribution of adipose tissue and testosterone levels: testosterone levels are inversely associated with visceral (or intra-abdominal) adiposity, which was largely independent of the aging process itself [31,32]. The increase of visceral adipose tissue with aging in men results in an increased free fatty acids drain on the portal vein and in turn in an increase of plasma triglycerides, a decrease of high-density lipoprotein cholesterol, impairment of insulin metabolism and reduction of insulin sensitivity [33]. These metabolic effects are thought to contribute to an increased risk of type 2 diabetes [34] and cardiovascular disease and mortality [35].

Recent cross-sectional studies showed that in aging men there are also positive correlations between testosterone and muscle strength parameters of upper and lower extremities, as measured by, amongst others, leg extensor strength and isometric hand grip strength [36]. Moreover, testosterone was positively associated with functional parameters, including the doors test (measuring functionality of the upper extremities) as well as the 6-m walk, 'get up & go' test, and 5-chair sit/stand test (measuring functionality of the lower extremities). In addition, in male nursing home residents a significant relationship was found between testosterone and 'activities of daily living'. Low testosterone levels were associated with a higher degree of dependence [37].

Some studies of testosterone supplementation show improvements in muscle and the distribution of body fat in subjects with hypogonadism [38,39]. These correlations and observations suggest that testosterone is directly or indirectly one of the factors that determine muscle status and body composition. Although the mechanism is unknown, it has been suggested that a key mediator is the nitrogen-retaining effect of testosterone.

Reduced libido and erectile dysfunction

Libido is a poorly understood subjective state shaped by biochemical, psychological and social influences. There is a remarkable increase of libido problems in men with increasing age: a recent study showed that men aged more than 50 years report a threefold increase of the prevalence of decreased libido. Predictors for a deficient libido in men are health and lifestyle factors such as alcohol use, poor health and stress and previous adverse sexual experiences [40]. Decrease in plasma testosterone levels is often implicated in partial loss of libido among aging men. There appears to be a minimum level of testosterone necessary for adequate sexual functioning, above and beyond which additional levels have no effects. Therefore, if plasma testosterone levels in aging men are below this threshold level, low libido is usually prevalent [41]. Moreover, it was demonstrated that, in men, a decrease of bioavailable testosterone (but not of total testosterone) was associated with a decrease of sexual desire and sexual arousal [42]. Recently it was demonstrated that in LOH patients loss of libido occurs when testosterone levels fall below 15 nmol/L, while erectile dysfunction becomes manifest only when testosterone levels drop below 8 nmol/L [43]. These symptom-specific threshold levels have to be taken into account when substitution therapy is initiated.

It is common knowledge that erectile function declines with increasing age. In the Massachusetts Male Aging Study, the incidence increased from 12.4 new cases per 1000 men in the age group 40–49 years to 46.4 new cases per 1000 man-years in the age group 60–69 years. Significant associations with erectile dysfunction were found for low education, diabetes, heart disease and hypertension. In the USA alone, more than 600,000 new cases of erectile dysfunction per year are expected [44]. Many studies have tried to demonstrate a correlation between the known decline in plasma testosterone with increasing age and erectile dysfunction. The relationship between testosterone and erectile function is complex: spontaneous erections are clearly androgen-dependent, whereas erections induced by visual stimuli or fantasies are only partly androgen-dependent [45]. Testosterone is essential for normal erections (probably secondary to its ability to increase nitric oxide release in the corpus cavernosum), the available evidence suggests that hypogonadism alone is rarely the sole cause of erectile dysfunction in aging men. However, studies indicate that approximately 20% of men with erectile dysfunction also suffer from hypogonadism. It is this group of erectile dysfunction patients that can benefit from testosterone therapy [46,47].

Reduced haematopoiesis

Endogenous androgens are known to stimulate erythropoiesis; they increase reticulocyte count, blood haemoglobin levels and bone marrow erythropoietic activity in mammals, whereas castration has opposite effects. Testosterone deficiency results in a 10–20% decrease in the blood haemoglobin concentration, which can result in anaemia [48,49]. Young hypogonadal men usually have fewer red blood cells and lower haemoglobin levels than age-matched controls, whilst healthy older men also may have lower haemoglobin than normal young men. The main androgen involvement in the mechanism of normal haematopoiesis is thought to involve direct stimulation of renal production of erythropoietin by testosterone. Moreover, the latter may also act directly on erythropoietic stem cells [49].

Depressed mood

The prevalence of depressed mood in men appears to increase with aging [50] and a relationship between testosterone levels and mood has been suggested in several studies. Testosterone levels in aging men are inversely correlated with depressive symptoms [51]. In a well-controlled study, it was reported that hypogonadal men have more depressed mood than normal men [52], whereas in the Rancho Bernardo Study a significant association was found between the age-related reduction of bioavailable testosterone and increased depression scores. Moreover, in a subgroup of patients with confirmed clinical depression, bioavailable testosterone levels were 17% lower than in healthy men [53]. The symptom-specific threshold for depression in aging men was found to be 10 nmol/L [43].

Memory loss and impaired cognition

Studies in a mouse model have indicated that the age-related decrease of plasma testosterone levels, which occurs in the SAMP8 strain, is associated with impairment of memory and learning capacity [54]. The relationship between testosterone and cognition (tasks that include spatial attention, visual perception, object identification and visual memory) has been investigated in several studies in aging men and it appears that there is, in general, a U-shaped relationship. This means that both subnormal and supraphysiological plasma levels of testosterone are associated with poor cognitive performance [55]. As a consequence, optimal cognitive performance might be expected with plasma testosterone levels within the normal range.

Screening and diagnosis of late-onset hypogonadism

Screening

Screening for hypogonadism in younger men is usually not necessary as most patients can easily be identified on the basis of their medical history (e.g. Klinefelter's syndrome, Kallman's syndrome, testicular trauma, irradiation, chemotherapy).

Aging men often present with a variety of vague, nonspecific symptoms that may be associated with testosterone deficiency [9]. As it is not cost-effective to screen all these men for low testosterone plasma levels, a number of validated questionnaires have been developed with various degrees of sensitivity and specificity [10]. The validity of the screening questionnaire of Morley [11] was assessed in 316 men aged 40–62 years. This simple questionnaire identifies patients who may have low testosterone levels, with high sensitivity (88%) but a specificity of only 60%. In subjects who are identified by means of this questionnaire, testosterone deficiency should be confirmed by laboratory measurements [9,56]. However, critical review of these tests questions their usefulness in clinical practice because of their low specificity [6].

Diagnosis

The diagnosis of hypogonadism is essentially based on the medical history, measurements of testosterone and measurement of gonadotropins. The clinician should endeavour to discover the underlying pathology of the disease. Diagnosis on the basis of testosterone levels alone may be straightforward in extreme cases. However, in patients with total testosterone in the low-normal range, perhaps with intercurrent chronic illness, the complexities of the circadian and pulsatile rhythms of testosterone secretion can make interpretation difficult.

The generally accepted biochemical definition of androgen deficiency is a repeated value of two standard deviations below normal values for young men [9,10]. In clinical routine, a single sample taken in the morning hours is usually sufficient. Total testosterone is most commonly used but requires awareness that its values may not reflect the amount of metabolically active testosterone fractions. For this reason, measurement of bioavailable or free testosterone may more closely correlate with clinical symptoms.

Since normal ranges vary significantly from laboratory to laboratory, according to the methods used and/or by the assay kits employed [56,57], the results from each patient should be compared with the normal ranges established by each laboratory. When discussing age-related hypogonadism it is often difficult to separate and to distinguish between the natural aging process, aging amplifiers, and acute or chronic illness or intercurrent diseases or iatrogenic causes.

Often-reported causes for late-onset hypogonadism are the aging process itself and intercurrent illness. Testosterone levels decrease progressively with increasing age. It has been postulated that if testosterone levels are relatively high at a younger age, it will take longer before they drop below the normal range. For example, if peak testosterone is relatively low at a young age, an individual may become hypogonadal relatively early in life. However, if the peak testosterone level is relatively high, an individual may remain normogonadal during his entire lifespan.

It has also been postulated that in some cases of late-onset hypogonadism, it is not the aging process itself but the occurrence of disease during the lifespan that is responsible for a (sometimes) irreversible reduction of testosterone levels. In some of these men, the plasma testosterone levels drop below the normal range, rendering such a person hypogonadal.

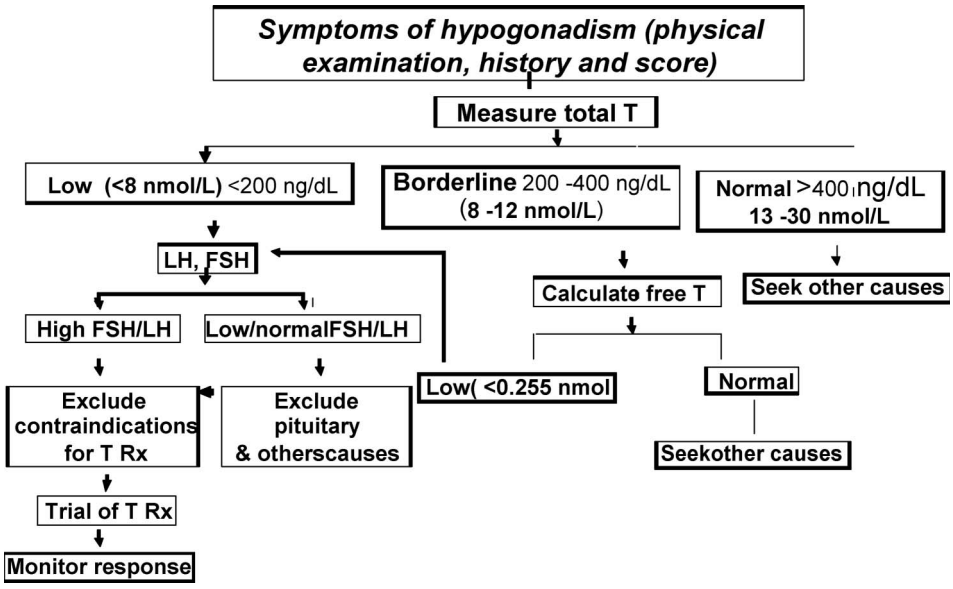

Figure 1. Algorithm for the management of suspected hypogonadism in the aging male.

For the diagnosis of late-onset hypogonadism the following algorithm has been suggested (Figure 1). If the patient's history, signs, symptoms, questionnaire and physical examination make the diagnosis of hypogonadism likely, biochemical tests should be used to confirm the diagnosis prior to initiation of treatment [9].

Total testosterone levels <200 ng/dL (7 nmol/L) clearly indicate hypogonadism and that benefits will be derived from testosterone therapy. Total testosterone levels between 200 ng/dL and 400 ng/dL (7–14 nmol/l) should be repeated and followed up by calculation of free testosterone from total testosterone and sex-hormone binding globulin (SHBG) concentrations, or by measurement of free testosterone levels by the dialysis method, or bioavailable testosterone by the ammonium sulphate precipitation method. Calculated free testosterone below 250 pmol/L or bioavailable testosterone <3.8 nmol/l confirms hypogonadism.

A number of systemic disorders may suppress testosterone levels, including hepatic cirrhosis, chronic renal failure, sickle cell anaemia, thalassaemia, haemochromatosis, human immunodeficiency virus, amyloidosis, chronic obstructive pulmonary disease (COPD), rheumatoid, chronic infections, and inflammatory or debilitating conditions. The confirmation of hypogonadism whether it is late-onset (e.g. age dependent) or acquired due to systemic disorders, iatrogenic causes, or environmental conditions merit a trial with testosterone therapy. If a healthy man has a serum testosterone level >400 ng/dL (>14 nmol/l), it is unlikely he is testosterone-deficient, and therefore, clinical judgement should guide the next steps, even if he has symptoms suggestive of testosterone deficiency [9]. Nevertheless, symptom-specific threshold levels should be taken into consideration [43].

Treatment of late-onset hypogonadism

Testosterone therapy

It is common clinical wisdom that a firm diagnosis is desirable prior to embarking on any therapeutic plan. This also applies to the treatment of the hypogonadal man. The goals of treatment are: (1) restoring normal serum testosterone levels into the physiologic range; (2) restoring metabolic parameters to the eugonadal state; (3) increasing muscle mass, strength,and function; (4) maintaining BMD and reducing fracture risk; (5) improving neuropsychological function (cognition and mood); (6) improving libido and sexual functioning; and (7) enhancing quality of life.

Equally important, testosterone therapy can prevent or improve already established osteoporosis and optimize bone density, restore muscle strength and improve mental acuity and normalize growth hormone levels, especially in elderly males [58]. Testosterone therapy should maintain not only physiologic levels of serum testosterone but also the metabolites of testosterone including estradiol to optimize maintenance of bone and muscle mass, libido, virilization, and sexual function. Because some of the manifestations of late onset hypogonadism are shared with other conditions independent of a man's androgenic status, appropriate biochemical confirmation of hypogonadism should be sought out prior to initiation of treatment. In the absence of defined contraindications, age is not a limiting factor to initiate testosterone therapy in aged men with hypogonadism. The purpose of testosterone therapy is to bring and maintain serum testosterone levels within the physiological range. Supraphysiological levels are to be avoided. Prior to initiation of testosterone therapy all patients should have a digital rectal examination (DRE) or an ultrasound assessment of

the prostate and serum prostate-specific antigen (PSA) level should be measured; digital rectal examination (DRE) and PSA are mandatory as baseline measurements of prostate health prior to onset of androgen therapy, the latter should be less than 3 ng/ml and should be repeated at quarterly intervals for the first year and yearly thereafter [9].

Trans-rectal ultrasound (US) guided biopsies of the prostate are indicated only if the DRE or PSA are abnormal. An increase of PSA of more than 0.2–0.5 ng/ml/year in men with a total PSA level less than 2.5 ng/ml/ or a PSA velocity greater than 0.75 ng/ml/year if the total PSA is above 4 ng/ml are indications for a prostate biopsy and withdrawal from testosterone therapy. Testosterone administration should also be discontinued if PSA increases by 2.0 ng/ml at any time or if an increase of 0.75 ng/ml occurs over a two-year period [59]. A meta-analysis of all placebo-controlled trials of testosterone in aging men has revealed that the incidence of prostate carcinoma was not significantly different between the verum and placebo groups, but the prostates of men on testosterone were biopsied much more often than in the placebo group, indicating that physicians are more startled by changes in PSA levels if the patient is on testosterone [60].

Liver function studies are advisable prior to onset of therapy and on a yearly basis thereafter during treatment [10]. A fasting lipid profile prior to initiation of treatment and at regular intervals (not longer than one year) during treatment is recommended.

If there is no history of adverse effects with regard to urinary obstructive symptoms, sleep apnoea, polycythemia (haematocrit $<52\%$), and if no significant increase in PSA is found, patients should continue with testosterone therapy and have a digital rectal examination and a PSA determination, lipid profile, haemoglobin and serum calcium tested at yearly intervals.

The androgen deficiency of the aging male is only partial and consequently only supplementation will be required. Preferably, administration of testosterone should leave the patient's residual testosterone production intact [61].

Adverse effects of testosterone therapy

If taken in proper doses, testosterone has few undesirable side effects [62]. These may concern the prostate, lipid profile and cardiovascular system, haematological changes, sleep patterns, social behaviour and emotional states.

Liver

Reports of liver toxicity manifested by jaundice and alteration of liver function as well as the development of hepatic tumours have been limited almost exclusively to cases in which the alkylated forms of testosterone have been used. These alkylated forms should not be applied and have disappeared from most markets.

Lipids and cardiovascular safety

The relationship between hypogonadism and alterations of the lipid profile remains to be completely resolved. Evidence is emerging supporting the concept that hypogonadism is associated with potentially unfavourable changes in triglycerides and high-density lipoprotein cholesterol and that such abnormalities can be corrected by restoring a physiological androgen milieu [63]. Other studies support the view that low testosterone is a significant risk factor for coronary artery disease [64–66]. Although most recent evidence continues to support the concept of a beneficial effect of androgens in coronary artery disease [33], the relationships between androgens and cardiovascular risk factors are complex and still understood only imperfectly. Similarly, the relationships between serum androgen levels and other lipoprotein sub-fractions have not been fully investigated [67]. Therefore caution is advisable when supplementing androgens in men with significant risk factors for cardiovascular disease.

Prostate

It is well established that in the absence of sufficient androgens the prostate gland fails to develop. Most studies, however, have shown no significant increases in prostate specific antigen (PSA) or prostate volume following administration of androgens to hypogonadal men [60,68]. Evidence from placebo-controlled studies of men receiving androgen supplementation indicate that the differences between the men on hormones and those on placebo were insignificant in regard to prostate volume, PSA or obstructive symptoms [69,70]. Although testosterone has not been implied in the development of benign prostate hypertrophy (BPH) nevertheless, in the presence of severe lower urinary tract obstructive symptoms, the administration of testosterone may result in the development of urinary retention.

Whether testosterone therapy promotes the development of prostate cancer remains to be elucidated, however, it seems that testosterone could include exacerbation of a pre-existing (sub-clinical) cancer of the prostate. Current evidence indicates that serum levels of sex hormones bear no relationship to the development of prostate cancer and there is either no change or only a modest increase in PSA after testosterone administration [71]. The suspicion of prostate cancer is, however, an absolute contraindication for androgen therapy. On the other hand, prostate biopsies prior to onset of therapy in the absence of an abnormal digital rectal examination

(DRE) or PSA level are not indicated. However, a rapid increase in PSA or the appearance of abnormalities in the DRE is a clear indication for a thorough evaluation of the prostate to rule out the presence of carcinoma. In this situation the administration of testosterone may have served as an early warning to the presence of an occult prostate malignancy [72].

Mood and behaviour

The consequences of testosterone deficiency in mood regulation are widely accepted [73,74] to the point that a hypothesis has been advanced suggesting that perinatal androgen deficiency promotes deficient cognitive development [75]. However, concerns exist regarding the promotion of sexually aggressive behaviour following testosterone administration. Significant behavioural changes can be observed with supraphysiological levels of androgens. Proper treatment, aimed at maintenance of physiological plasma levels, makes this a rare occurrence and certainly not a sufficient cause to withhold treatment [55].

Red blood

The stimulatory effect of testosterone administration on bone marrow has long been recognized even in the presence of advanced malignant disease [76]. Testosterone therapy in older men often can result in a significant increase in red blood cell mass and haemoglobin levels [60]. Haemoglobin levels should therefore be monitored periodically and dose adjustments may be necessary. Rarely must testosterone therapy be discontinued due to polycythemia.

Sleep apnoea

Other possible effects of testosterone treatment include exacerbation of sleep apnoea [77] although hypotestosteronaemia has been cited as a cause of the condition [78]. It is suggested, therefore, that good clinical judgement and caution be employed in this situation.

Benefits of testosterone therapy

In the era of evidence-based medicine, we have to acknowledge that data on hormone supplementation in the aging male is often circumstantial, based on experience in treatment of transitional hypogonadism in young men or in chronic hypogonadism due to disease or experiments of nature. The clinical effectiveness of androgen supplementation in aging men with symptoms of hypogonadism was already described by Werner [79] in 1943 and Heller and Myers [80] in 1944. Since that time publications on testosterone supplementation for symptoms of hypogonadism in aging men have largely been sporadic, mainly case reports and largely outside the context of clinical trials. Most of these observational studies have suggested that, if treatment is to be effective, then selection of patients should be dictated by a measurable reduction of testosterone. However, over the past several years, there has been increasing interest in evaluating whether testosterone therapy might be beneficial for certain older men in preventing or delaying some aspects of aging, and a number of prospective studies on hormone therapy in the aging male were performed. These demonstrated several potential benefits of testosterone supplementation. These included improvements in energy level, lean body mass, strength, and bone mineral density. There also was an improvement in mood, sense of well-being, libido and erectile function.

Marin et al. [81] performed a randomized, placebo-controlled study of 8 months duration with testosterone undecanoate (TU) 160 mg/day in healthy, obese (BMI >25 kg/m^2), middle-aged (>45 yr) men. Their mean plasma testosterone was 16 nmol/l (range 9–21 nmol/l). Body composition was measured by CT-scan. Within 8 months sagittal abdominal diameter decreased from 27.0 to 24.6 cm ($p < 0.01$), whereas with placebo no change was observed. He also reported improved general well-being ($p < 0.05$), feeling of improved energy ($p < 0.01$), cardiovascular safety aspects such as increased insulin sensitivity after glucose load ($p < 0.01$) and reduced fasting glucose ($p < 0.05$). In 1995 Marin [82] repeated the above study in middle-aged men with abdominal obesity using transdermal administration of testosterone, DHT or placebo during 9 months in a double blind design. Treatment with testosterone was followed by an inhibited uptake of lipid label in adipose tissue triglycerides, a decreased LPL-activity and an increased turnover rate of lipid label in the abdominal adipose tissue region in comparisons with the DHT and placebo groups. These effects on adipose tissue metabolism were not detected in the femoral adipose tissue region in any of the groups. Testosterone treatment was also followed by a specific decrease of visceral fat mass (measured by CT scan), by increased insulin sensitivity (measured with the euglycaemic glucose clamp), by a decrease in fasting blood glucose, plasma cholesterol and triglycerides as well as a decrease in diastolic blood pressure. In the DHT group an increased visceral mass was detected. No other changes in these variables were found in the DHT and placebo groups. There were no detectable changes in prostate volume (measured by US), prostate-specific antigen concentration, genito-urinary history or urinary flow measurements in any of the groups.

Morley [4] reported that males who received testosterone had a significant increase in testosterone and bioavailable testosterone concentration, haematocrit, right-hand muscle strength and osteocalcin concentration. They had a decrease in cholesterol (without a change in HDL-cholesterol) levels and decreased BUN/creatinin ratios. These

results were confirmed by Snyder et al. [83] who concluded that increasing the serum testosterone concentrations of normal men >65 years of age to the mid-normal range for young men decreased fat mass, principally in the arms and legs, and increased lean mass, principally in the trunk. They also showed that increasing the serum testosterone concentrations of normal men >65 years of age to the mid-normal range for young men did not increase lumbar spine bone density overall, but did increase it in those men with low pretreatment serum testosterone concentrations (<7 nmol/l) [84].

The prospective studies of Arver et al. [85], Tenover [32], Bebb et al. [86], Wang et al. [87] and Wittert et al. [88] performed on elderly men with verified testosterone deficiency confirmed earlier work and indicated that testosterone replacement increases bone density, quality of life and aggression in business, improvement of physical and psychic well-being, libido, a decrease of fat mass, a change in fat contribution and localization as well as a decrease in cardio-vascular accidents. Furthermore Webb et al. [89] demonstrated that short-term intracoronary administration of testosterone, at physiological concentrations, induces coronary artery dilatation and increases coronary blood flow in men with established coronary artery disease.

Morley et al. [90] and Hajjar et al. [91] also observed improved libido after testosterone therapy in hypogonadal elderly men. Since erectile function declines with age due to multifactorial causes, the most prominent of which is impaired penile NO release, erectile dysfunction may not be corrected by testosterone therapy alone unless the local vasodilatory defect is corrected first. It appears from the reported studies that testosterone replacement will enhance libido and contribute to improvement of sexual function in older men co-treated with phosphodiesterase-5 inhibitors (e.g. sildenafil) [46,92]. There may be two different mechanisms by which these effects are mediated: the enhanced production and release of NO, and structural improvement of the penile smooth muscle tissue. Co-treatment with androgens and phosphodiesterase inhibitors also provides the benefits of androgens on other target sites.

Similarly, studies have demonstrated that serum testosterone levels correlates with spatial ability [93–95]. Testosterone suplementation in elderly men also improves spatial ability without changes in memory or verbal fluency [96,97]. There is also evidence available that depressed mood is inversely related to serum bioavailable testosterone levels, and androgen replacement therapy in aging men improved general well-being.

An elegant study by Azad et al. [98] demonstrated that testosterone replacement enhanced cerebral perfusion in the midbrain and superior frontal gyrus (Brodman area 8) at 3–5 weeks of treatment. At 12–14 weeks the study continued to show increased perfusion in the midbrain in addition to the appearance of a newly activated region in the midcingulate gyrus (Brodman area 24). The results of this study provide objective evidence that testosterone and/or its metabolites increased cerebral perfusion in addition to the improvement in cognitive function.

Current generally available treatment options include buccal tablets and oral capsules, intramuscular preparations, both long and short-acting, implantable long-acting slow release pellets, transdermal scrotal and non-scrotal patches and gels [61,99]. Neither injectable preparations nor slow-release pellets reproduce the circadian pattern of testosterone production of the testes. This is accomplished best by transdermal and buccal preparations. The relevance of reproducing a circadian rhythmicity during testosterone therapy remains unknown. However, these short-acting preparations should be preferred since testosterone in circulation will decline immediately after cessation of treatment, should any adverse event (e.g. prostate disease) require discontinuation of testosterone supplementation [9,100]. 17α-methyl-testosterone should no longer be prescribed because of its liver toxicity. Common testosterone preparations and their recommended doses are shown in Table I.

The treating physician should have sufficient knowledge and adequate understanding of the

Table I. Currently available testosterone preparations.

Route of administration	Generic name	Trade name	Dosage
Implants	Testosterone 200 mg	Testosterone implants 200 mg	3–6 implants every 6 months
Intramusclar	Testosterone enanthate 250 mg	Testosterone depot 250	1 ampoule every 2–3 weeks
	Testosterone undecanoate	Nebido	1 ampoule every 10–14 weeks
Oral	Testosterone undecanoate	Andriol Testocaps	2–4 capsules at 40 mg/day
Transdermal	Testosterone patch	Androderm	2 × 5 mg/day
	TTS scrotal	Testoderm	1 membrane/day
	Testosterone gel 25 mg or 50 mg	Testogel Androtop gel	50–100 mg/day
	Testosterone gel 50 mg	Testim	50–100 mg/day
Buccal	Testosterone 30 mg	Striant	1 tablet twice daily

pharmacokinetics as well as the advantages and drawbacks of each preparation.

Testosterone preparations

Testosterone pellets/implants

This is the oldest form of testosterone replacement therapy and has been in use since the 1940s. Pellets of crystalline testosterone are implanted subcutaneously, under local anaesthesia, via a small skin incision usually in the lower abdominal wall using a trocar and cannula. The pellets have a diameter of 4.5 mm and are available in 100 mg (6 mm long) and 200 mg (12 mm long) strengths. A pharmacokinetic study [101] in 14 hypogonadal men implanted with six 200 mg fused crystalline pellets, revealed an initial short-lived burst of testosterone, with a peak concentration for 24 to 48 hours followed by a stable plateau [101]. The pellets provide stable physiological testosterone levels for 4 to 7 months depending upon the dose [102,103]. Each 200 mg pellet releases 1.3 mg of testosterone per day by surface erosion. The pellets diminish in size progressively and continue to dissolve until complete disappearance. There is sustained suppression of plasma LH and FSH, and an increase in plasma levels of E2 without change in SHBG levels. Extrusion of pellets is the most frequent adverse effect and occurs in 10% of implanted pellets [104,105]. Increased physical activity contributes to extrusion of the pellets and those implanted at the hip have a higher extrusion rate than at the lower abdominal wall [106]. Although dependent on the experience of the operator, other rare side effects include bleeding (2.3%), infection (0.6%), and fibrosis. The usual dose is 800 mg (4×200 mg pellets). For dose adjustment testosterone levels are measured before the next implantation. If testosterone is >15 nmol/L or <8 nmol/L, then the dose of the next implant is adjusted accordingly.

The pellets are not expensive and might be suitable for young men in whom the beneficial effects of androgen replacement have been established. Long intervals between treatments are an advantage. Implantation of testosterone pellets is, however, a hospital procedure requiring medical time; minor surgery is needed to remove the implants, if rapid discontinuation of testosterone therapy is necessary. Although popular in the United Kingdom, South Africa and Australia, they are not widely adopted outside these countries.

Oral testosterone undecanoate

An oral preparation that is widely used throughout the world is a non-alkylated testosterone produced through esterification of testosterone in the 17β-position with a medium long-chain fatty acid. This product, testosterone undecanoate (TU) dissolved in oleic acid, has been available since the 1970s [107]. Since 2003 it has been available in a new bioequivalent formulation with castor oil and propylene glycol laurate, improving storage conditions [108,109].

TU is designed to deliver testosterone to the systemic circulation via the intestinal lymphatic route, thereby circumventing first-pass inactivation in the liver. Therefore it is free of liver toxicity and brings serum testosterone levels within physiological range. The esterification of testosterone with undecanoate renders TU sufficiently lipophilic to be incorporated in chylomicrons formed during the process of lipid digestion in the intestine. These chylomicrons are then transported via the intestinal lymphatic system. Apart from the nature of the ester of testosterone, other relevant factors for the extent of lymphatic absorption are the lipophilic solvent in the capsule [110,111]. Of the 40 mg capsules 63% (25 mg) is testosterone. After ingestion, its route of absorption from the gastrointestinal tract is shifted from the portal vein to the thoracic duct [107,109,111]. For adequate absorption from the gastrointestinal tract it is essential that oral TU is taken with a meal containing dietary fat (23 g lipids) for example: 2 cups of decaffeinated coffee, 2 rolls of bread, 2 slices of cheese, 2 slices of ham, 20 g jam, 20 g butter (460 kcal), or, 48 g carbohydrates and 14 g protein, 1 cup of milk, 2 eggs. Without dietary fat the resorption and the resulting serum levels of testosterone are minimal [111–113]. Maximum serum levels are reached 2 to 6 hours after ingestion [114]. Recent studies show that there is dose proportionality between serum testosterone levels and the dose range of 20–80 mg [114,115]. At a dose of 120–240 mg per day, over 80% of hypogonadal men showed plasma testosterone levels in the normal range over 24 hours. Steady-state testosterone levels in the low normal to subnormal range are reached after three days and result in sufficiently high levels of testosterone for therapy in patients with androgen deficiency with additional advantages of oral administration and easy control of drug dose.

TU is probably best suited to supplement the reduced, but still present, endogenous testicular testosterone production in the aging male with lower than normal, but not deeply hypogonadal levels, of testosterone. Long-term use has been proven to be safe, as demonstrated in a 10-year observation [113].

Oral TU leads to a high DHT to testosterone ratio due to the action of intestinal 5 α-reductase and to a marked decrease in SHBG, caused by excessive androgenic load on the liver via the portal vein. However, the elevation of plasma DHT levels does not seem to have any adverse effects [113,116].

Treatment of hypogonadal men with oral TU resulted in improvements in bone mineral density (BMD), mood, quality of life [115], and sexual function. TU improves body composition [116] by decreasing fat mass and increasing muscle mass.

Buccal testosterone

Another option for testosterone substitution is offered by adhesive buccal tablets (Striant®), which are placed above the incisor tooth on either side of the mouth and slowly release testosterone over 12 h, after which they have to be replaced. If taken twice daily they also provide serum levels in the physiological range and are well suited for longer-term substitution for hypogonadal men [117,118].

Intramuscular preparations

Intramuscular preparations have been the mainstay of androgen replacement therapy since the 1940s. Injectable esters of testosterone have been available for the longest time and their effects are well recognized. They are inexpensive and safe but have several major drawbacks which include: the need for periodic (every 2–3 weeks) deep intramuscular injection, swings in serum levels; initially (in about 72 hours) they result in supraphysiological levels of serum testosterone followed by a steady decline over the next 10–14 days [99,119].

These preparations include testosterone enanthate, cypionate and mixed testosterone esters. Testosterone propionate is rarely used because its short half-life requires administration every other day. After absorption from IM depot, the testosterone esters are hydrolysed to release free testosterone. Testosterone enanthate (TE) (200, 250 mg) causes maximum supraphysiological levels shortly after the injection [120]. Pharmacokinetic simulation of 250 mg of TE given IM every 2 weeks revealed serum testosterone levels at the lower range of normal before the next injection [99]. TE has an elimination half-life of 4.5 days. Injection intervals of three or four weeks are likely to lead to subnormal testosterone levels in the third and fourth weeks. This phenomenon translates into wide swings in mood and well-being – the roller-coaster effect, which is disconcerting and upsetting to both patients and their partners. Supraphysiological peaks of testosterone are responsible for dose-related adverse effects such as polycythemia especially in elderly men [60,121] which revert to normal on withholding therapy and dose reduction. The intermittent supraphysiological levels may result in the development of breast tenderness and gynaecomastia due to conversion of testosterone to E2.

The most widely used parenteral preparations are the 17-β-hydroxyl esters of testosterone, which include the short-acting propionate and the longer-acting enanthate and cypionate. Testosterone enanthate and cypionate esters have identical kinetics [122], and can be administered at the dose of 200–400 mg every 10–21 days to maintain normal average testosterone levels [123]. Higher doses will not maintain testosterone levels in the normal range beyond the three-week limit. Another option is a preparation containing a mixture of four testosterone esters (propionate, phenylpropionate, isocaproate and decanoate), each with a different elimination half-life, which is claimed to prolong the duration of action. These mixed testosterone esters are prescribed on the erroneous assumption that they provide more physiological testosterone levels. These preparations are actually more likely to cause a higher initial supraphysiological peak in testosterone levels.

Appropriate treatment of hypogonadism with injectable esters of testosterone has been shown to improve libido, sexual function, energy levels, mood and bone density if they are caused by an androgen deficiency. Although concern exists about the psychosexual effects of markedly elevated levels of testosterone in serum, evidence indicates that even in eugonadal men, amounts of up to five times physiological replacement doses of testosterone cypionate have only minimal psychosexual effects [124].

A new depot IM injection containing 1000 mg of testosterone undecanoate (TU) in 4 mL of castor oil has recently become available in Europe and some Asian countries.

Parenteral TU is a new treatment modality for androgen replacement therapy. TU IM was originally used in China, dissolved in tea seed oil. Kinetics were improved by using castor oil as a vehicle [61]. Several studies have documented its use in hypogonadal men [125–129]. In short: after two loading doses of 1000 mg TU at 0 and 6 weeks, repeated injections at 12-week intervals are sufficient to maintain testosterone levels in the reference range of eugonadal men. The elimination half-life is 33.9 days and supraphysiological testosterone peaks do not occur. Serum DHT and E2 levels increase in parallel with testosterone levels thus testosterone: DHT and testosterone: E2 ratios do not change. No local adverse side effects at the injection site have been described. It has been argued that this preparation is less suitable for initiation of testosterone treatment of aging men [9]. After the first uneventful year of short-acting testosterone preparations, it may be reasonable to administer long-acting testosterone preparations to elderly men as well.

Transdermal patches

Testosterone can be delivered to the circulation through intact skin, both genital and non-genital. Transdermal testosterone therapy closely mimics the variable levels in testosterone production manifested in normal men over the 24-hour circadian cycle. Daily physiological requirement of testosterone of 5–7 mg per 24 hours can be achieved by the trandermal route of delivery. Excipients are generally required to enhance absorption and improve bioavailability. Transdermal testosterone therapy is available both as scrotal and non-scrotal patches and in gel form. They are non-invasive, avoid

first-pass hepatic metabolism, and can mimic diurnal variation seen in eugonadal men [99].

The scrotal patch applied to the scrotal skin contains 10–15 mg of unmodified testosterone per patch, delivering 4–6 mg of testosterone per day [130]. High vascularity, capillaries that extend to the skin surface and the presence of abundant hair follicles contribute to permeability that is five times that of other skin sites. However, the scrotal patch lost its appeal due to inconvenience such as their inability to remain in place and the need for frequent shaving of the scrotal skin.

Transdermal non-scrotal patches have been available since the mid 1990s. These patches deliver 5–6 mg/day of testosterone and produce normal levels of estradiol but, unlike the scrotal patches, result in normal levels of DHT [131,132]. In addition to producing physiologically appropriate serum levels of testosterone, they lower levels of sex hormone binding globulin (SHBG), promote virilization and increase bone mineral density [131]. Moreover, the testosterone patches, as compared to injectable forms, minimize excessive erythropoiesis and suppression of gonadotropins [132,133]. Most common side effects of the body patches are related to the need for enhancers to facilitate absorption; this frequently results in various degrees of skin reactions. Transient erythema and itching are common side effects and can occur in up to 60% of patients [132–134]. Only occasionally do chemical burns appear, which may be prevented with the use of triamcinolone cream.

Transdermal gel

Transdermal delivery of testosterone via hydroalcoholic gel has been available since 2002. The gel is applied thinly on the skin of the torso, shoulders and upper arms once a day and dries quickly. The stratum corneum layer of the skin serves as a reservoir, releasing testosterone into the circulation. Steady state testosterone levels in the mid normal range are achieved after 48 to 72 h with testosterone levels falling to baseline, 96 h after withdrawal of gel application. It has been estimated that 9–14% of the applied gel is bioavailable. Wang et al. [134] suggest that the amount of testosterone absorbed into the circulation depends on the dose of the gel rather than the surface area over which the gel is applied. Thus the formulation of the testosterone gel allows easy dose adjustments (50–75–100 mg testosterone gel) [133,134]. Although mean serum DHT levels tend to be at or above the normal range, the serum DHT: testosterone ratio remains within the normal adult range. E2 levels rise with treatment and are maintained in the normal range. SHBG levels do not show a significant change. For the purpose of dose adjustment testosterone levels can be assessed any time after the application of the gel. The clinical efficacy of transdermal testosterone gel on various androgen-dependent organs has been well documented and is independent of age [135]. Treatment also leads to improvements in sexual function, mood, increase in lean body mass, muscle strength, BMD and decrease in fat mass [136]. A good long-term safety profile has been shown with transdermal gel. Skin irritation is the most common side effect and occurs in 4–5.5% of patients treated with the gel. Any increase in haematocrit tends to occur generally within the normal range. PSA levels also tend to rise, but within the normal range. Serum HDL and LDL cholesterol do not change with treatment. There is a theoretical risk that the gel can be transferred to others through intensive skin contact. Rolf et al. demonstrated that although approximately 50% of the applied dose can be recovered from unwashed skin 8 hours after application of the gel, interpersonal transfer of testosterone is very unlikely, as the alcohol needed for penetration of the skin evaporates in 10 minutes. Washing the skin 10 minutes after application does not influence the pharmacokinetic profile and reduces the risk of contamination of female partners or infants [137]. No increase of serum testosterone was found after intense rubbing of skin with persons whose endogenous testosterone levels had been suppressed.

Transdermal testosterone gel provides flexibility in dosing, with lower incidence of skin irritation compared to non-scrotal transdermal patches. In practice, the gel is well accepted by most patients, although some find the daily application inconvenient. The absorption of testosterone can vary from day to day depending on a wide host of circumstantial factors. This preparation is ideal for treating elderly men in whom treatment may need to be stopped suddenly and for induction of secondary sexual features in younger patients.

A hydroalcoholic gel with a higher testosterone concentration of 2.5% has recently been developed and tested in hypogonadal men over a one-year period resulting in satisfactory substitution. Because of the higher concentration one group could be treated by transscrotal application of the gel and was well substituted [138].

Monitoring of testosterone therapy

Hormonal therapy may be initiated for a variety of indications but treatment is normally lifelong. Monitoring these patients is also a lifetime commitment and is a shared responsibility that cannot be taken lightly. The physician must emphasize to the patient the need for periodic evaluations and the patient must agree to comply with these requirements. The physician's evaluation should include an assessment of the clinical response and monitoring must be tailored to the indications and individual needs of the patient. For example, for osteoporosis, serial BMD determinations are appropriate for

monitoring therapeutic response. In this regard, the studies by Behre et al. [139] provide an elegant and graphic illustration of the effectiveness of chronic testosterone supplementation in increasing bone mineral density and in moving older men out of the range of high fracture risk. For sexual dysfunction, a simple and effective rule of monitoring is that frequently the patient's report is the most reliable indicator of treatment effectiveness [91].

Outlook

Testosterone treatment in men with age-related hypogonadism aims at restoring hormone levels to the normal range of young adults and, more importantly, at alleviating the symptoms suggestive of the hormone deficiency. The ultimate goals, however, 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. To achieve these goals men must also adjust their lifestyle to optimize dietary habits, as well as to exercise and to abstain from smoking life-long.

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