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Review

The Current Status of Therapy for Symptomatic Late-Onset Hypogonadism with Transdermal Testosterone Gel

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Abstract

For over 50 years, testosterone therapy has been used for the treatment of hypogonadism. In recent years, there has been an increase in the use of testosterone therapy for men with late-onset hypogonadism, as more convenient and effective modes of application are developed. Testosterone therapy in these men can significantly improve their sense of well-being, and lead to increases in muscle and bone mass, upper body strength, virility and libido [Gruenewald, Matsumoto. J Am Geriatr Soc 2003;51:101; Morales. Aging Male 2004; in press].

However, ensuring that optimal testosterone therapy is achieved in men with hypogonadism remains challenging. Oral delivery of unmodified testosterone is not possible, due to rapid first-pass metabolism and its short half-life. Therefore, different derivatives and formulations of testosterone have been developed to enhance potency, prolong duration of action or improve bioavailability. In addition, several different routes of administration have now been evaluated, including intramuscular injections, oral formulations, transdermal patches, transbuccal systems and transdermal testosterone gel. Despite the broad range of testosterone therapy on offer, each form has its benefits and limitations, and some will suit one patient more than another.

An important concern among clinicians is that testosterone therapy may cause or promote prostate cancer. While current evidence supports the safety of testosterone therapy, androgens are growth factors for pre-existing prostate cancer. Therefore, before therapy is initiated, careful digital rectal examination and determination of prostate-specific antigen (PSA) in serum should be performed, in order to exclude evident or suspected prostate cancer. The first 3–6 months after initiating testosterone therapy is the most critical time for monitoring effects on the prostate. Therefore, it is important to monitor PSA levels every 3 months for the first year of treatment; thereafter, regular monitoring (mostly for prostate safety but also for cardiovascular and haematological safety) during therapy is mandatory.

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1. Introduction to symptomatic late-onset hypogonadism

The decline in androgen production that occurs in a segment of the male population as part of the aging process is sometimes termed the 'andropause'. However, true andropause exists only in those men who have lost testicular function, due to disease or accidents, and those with advanced prostate cancer who are

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subjected to surgical or medical castration. Androgen decline associated with advancing age is known by several terms: partial androgen deficiency of the aging male (PADAM); androgen deficiency of the aging male (ADAM); and, as will be referred to throughout this review, late-onset hypogonadism (LOH). When LOH causes detrimental physiological and mental effects, the syndrome is known as *symptomatic* LOH (SLOH). Aging males with SLOH may benefit from testosterone therapy, but the issues of how and when to treat are complex [2]. In contrast to the consequences of cessation of ovarian function in aging women, the clinical implications of decreasing androgen production in aging men are not unanimously accepted [2]. The most pressing issues with SLOH are diagnosis, treatment and monitoring.

2. Diagnosis of SLOH

2.1. Clinical features

The signs and symptoms of SLOH are numerous and include: a decreased sense of well-being; a decrease in muscle mass, strength, energy and bone mass (potentially leading to osteoporosis); reduced virility, libido and sexual activity; an increased frequency of impotence; and increased sweating, mood changes, fat mass, dry skin and anaemia [1,2]. SLOH may escape clinical diagnosis because not all the signs and symptoms present themselves simultaneously, or because physicians may be unaware that manifestations such as mood disturbances, sexual dysfunction and osteoporosis can be related to low serum levels of testosterone [2]. In addition, the signs and symptoms may have progressed so slowly and subtly over the years that the patient himself may be unaware of their occurrence, or may consider them part of the unavoidable process of aging [2]. Therefore, in order to identify SLOH, it is important to obtain a proper medical history and physical examination. In this context, questionnaires are most suitable as screening tools [3]; their validation as treatment outcome instruments is currently under investigation in several clinical trials.

Many of the manifestations of SLOH can be difficult or impossible to distinguish from other conditions, such as depression or hypothyroidism. Although the presence of one or more signs or symptoms is important, an accurate diagnosis relies on the physician's ability to interpret the symptomatology and biochemical findings that may indicate a possible abnormality in hormone levels. An asymptomatic patient with LOH does not necessarily require treatment. However, a man with evident manifestations of the syndrome and ambiguous biochemical results may be a candidate for testosterone therapy.

2.2. Biochemical features

The basic biochemical evaluation of a suspected case of SLOH includes determination of serum testosterone levels. For consistency and accuracy (due to the circadian pattern of testosterone production) the sample should be taken in the morning. In addition, clinicians should be aware that marked week-to-week variability may occur [4]. There are several test options available, summarized in Table 1. When biochemical hypogonadism is documented, it is advisable to assess

Table 1
Tests available for measuring serum testosterone levels

Test	Method and advantages	Potential limitations
Total testosterone	Automated; widely available; consistent; easy to perform and inexpensive. Satisfactory for initial evaluation	May be misleading: Total testosterone in the presence of elevated SHBG (also seen in healthy aging) may be within the normal range, but a significant proportion of testosterone will not be available at the tissue level
Free testosterone	Measures the fraction of testosterone that is unbound to albumin and globulin. Should be the most accurate index of a man's androgenicity. Accurate results require equilibrium dialysis or ultracentrifugation	Cumbersome, demands expertise and is costly. Rarely performed. If performed by radioimmunoassay, results are notoriously inaccurate
Calculated free testosterone	Measures free testosterone using a formula based on total testosterone and SHBG (see www.issam.ch)	This formula is complicated but easy to perform with the ISSAM method. However, different SHBG assays may alter interpretation
Bioavailable testosterone	Measures circulating testosterone plus testosterone loosely bound to albumin, to provide accurate serum levels of biologically active testosterone	Not automated; requires experience for accurate results
Free androgen index	Simple calculation of total testosterone divided by SHBG	Unreliable and not recommended

SHBG: sex hormone binding globulin.

the hypothalamus–pituitary–gonadal axis function by measuring levels of luteinizing hormone (LH), follicle-stimulating hormone and (optionally) prolactin. Depending on the results, an MRI scan and referral to a specialist may be required.

A biochemical evaluation can determine the type of hypogonadism. The classical forms are primary (testicular) and secondary (pituitary or hypothalamic) in origin [2]. LOH is clearly distinct from any form of classical hypogonadism, and is characterized by subtle disturbances at all levels of the regulation of testicular function, which may manifest as a combination of reduced hypothalamic gonadotropin-releasing hormone (GnRH) secretion, increased sensitivity to testosterone feedback at the pituitary and hypothalamic level, and reduced testicular testosterone production [5]. Thus, in LOH, the hypothalamus starts to secrete less GnRH, leading to reduced LH and testosterone production. This reduction in testosterone is enhanced by the increased sensitivity of the pituitary and hypothalamus to the negative-feedback of testosterone. Furthermore, the testicular Leydig cells start to respond less to LH stimulation, reducing the synthesis of testosterone still further [5].

About 15–25% of men above the age of 50 years will experience serum testosterone levels well below the threshold considered normal for men between 20 and 40 years of age. The typical biochemical findings in men with LOH are slightly reduced serum testosterone in the presence of normal levels of gonadotropins [6,7]. Although the results of long-term studies of testosterone therapy have yet to be reported, as a general recommendation, men with LOH should be treated only when clinical symptoms are present that may be potentially corrected by testosterone administration [1,2].

3. Treatment of hypogonadism by testosterone therapy

A firm diagnosis of SLOH should precede testosterone therapy, and should be based on signs and symptoms, the serum levels of hormones, and the knowledge and experience of the physician. By themselves, low levels of testosterone are not necessarily a sufficient reason to initiate treatment. To qualify as a candidate for testosterone treatment, the patient's quality of life must be affected sufficiently that substantial treatment benefits can be expected. Prior to therapy, careful digital rectal examination (DRE) and determination of prostate-specific antigen (PSA) levels in serum should be carried out, in order to assess contraindications and particularly evident or suspected prostate cancer. Treatment may need to be tailored to the manifestations present in each individual case.

3.1. Intramuscular injections

Although often painful, intramuscular injection of testosterone esters, such as testosterone enanthate, has been the mainstay of testosterone therapy for treating all forms of male hypogonadism, for many years. Fatty acid esters of testosterone include propionate, phenyl propionate, cypionate and enanthate. The depot formulations depend upon retarded release of the testosterone ester from the oily vehicle injection. Following release, the esters are rapidly hydrolysed to liberate testosterone into the circulation. The pharmacokinetics of these esters are determined, in part, by side-chain length [8]. Regular intramuscular injections of 250 mg testosterone enanthate (typically every 14–21 days, although doses of 200–400 mg can be administered every 10–21 days [7]), provide adequate long-term testosterone substitution. During more than 50 years of clinical use, testosterone enanthate has proved to be very safe; however, the wide variations in testosterone [9] produced by intramuscular formulations may be responsible for the fluctuations in mood and sexual function reported by many patients. Peak levels occur up to 72 hours after injection, and are followed by a slow decline during the subsequent 1–2 weeks [8,10,11] (Fig. 1). These wide variations in testosterone levels, coupled with the frequency of injections, have prompted the search for better-tolerated delivery modalities.

A newly developed, long-acting, injectable testosterone ester – testosterone undecanoate – overcomes the shortcomings of conventional testosterone injections. Intramuscular injections of 1000 mg testosterone

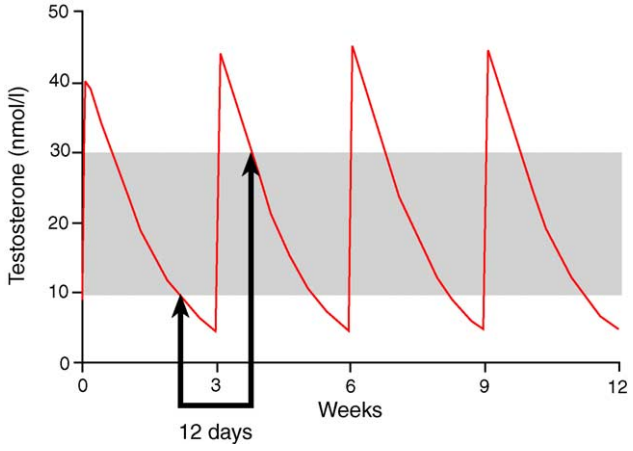

Fig. 1. Pharmacokinetics of intramuscular testosterone enanthate. 250 mg was given as an intramuscular injection once every 3 weeks.

undecanoate dissolved in an oily solution (Nebido®, Schering AG, Germany), given in 12-weekly intervals, restore serum testosterone levels to within the eugonadal range, whilst avoiding non-physiological peaks [12]. Therefore, only four injections per year are required for long-term testosterone therapy. Intramuscular testosterone undecanoate is expected to become available in Europe from 2004 onwards.

3.2. Oral formulations

Oral formulations of testosterone treatments have been developed, in order to avoid the need for injections. However, some of these formulations have proven to be problematic, as absorption can be variable, bioavailability is frequently poor, due to the first-pass effect of the liver, and frequent administration is often required. In addition, 17α-alkylated derivatives may cause hepatotoxicity [2]. Orally active testosterone undecanoate is preferentially absorbed into chylomicrons and thereby avoids the first-pass effect of the liver. However, plasma testosterone levels are generally suboptimal, with erratic bioavailability and occasional gastrointestinal intolerance (oral testosterone undecanoate has to be taken two or three times daily at the end of a meal [8]). Despite these limitations, several controlled studies have demonstrated oral testosterone undecanoate (Andriol®, Organon) to be effective in treating the symptoms associated with reduced serum testosterone levels, resulting in improved bone mineral density (BMD), quality of life, muscle mass, libido and mood [13–15].

3.3. Transbuccal systems

A novel delivery system has been developed for testosterone therapy. This formulation—COL-1621 (Striant®, Columbia Laboratories), a testosterone-containing buccal mucoadhesive system—has been shown in preliminary studies to replace testosterone at physiological levels when used twice daily. In short-term studies, the testosterone buccal system produced steady-state testosterone levels comparable with those achieved with 1% testosterone gel [16] and greater than those achieved with a testosterone transdermal patch [17], although issues related to patient comfort and compliance need further evaluation [18]. Thus, the buccal system appears to provide an additional safe and effective option for testosterone therapy in hypogonadal men.

3.4. Sublingual administration

Sublingual administration of testosterone hydroxyl propyl-β-cyclodextrin inclusion complex stimulates episodic androgen release in hypogonadal men. The vehicle enhances testosterone solubility and absorption, but is not itself absorbed. It is administered as a 2.5-mg or 5-mg tablet, three times daily, and is rapidly absorbed by the sublingual route, and quickly metabolised without generating sustained elevation of dihydrotestosterone (DHT) or estrogen [19]. Sublingual administration of testosterone is particularly useful in boys with delayed puberty [8].

3.5. Transdermal patches

In recent years, testosterone administration via the skin has become the focus of attention. As scrotal skin is thin, it absorbs testosterone better than non-scrotal skin. Thus, the first transdermal mode of testosterone application was a scrotal patch, delivering either 4 mg or 6 mg of testosterone daily, which had to be applied once daily on shaved scrotal skin [20–23]. After application of the patch, serum testosterone concentrations rise to the normal range and then decrease slowly over a period of 24 hours. Such administration over 3 years has demonstrated benefits for bone, muscle and erythropoiesis [24]. Although scrotal application provides serum testosterone levels well within the normal range, this method of administration has not been readily accepted, due to the concomitant supraphysiological levels of DHT often observed in patients (scrotal skin contains high concentrations of 5α-reductase [8]) and the unpleasantness of scrotal skin shaving and application.

Adding an absorption enhancer to the patch made application on non-scrotal skin possible [25], but, in a large number of patients, the enhancer gave rise to considerable skin reactions [26,27]. The reservoir patches were generally judged to be too large, uncomfortable, visually obtrusive and noisy [27], and had a tendency to fall off very hairy or sweaty skin. In one study, over 60% of patients using permeation-enhanced patches experienced skin reactions of variable severity [28]. Non-scrotal patches have proven to be safe and effective, and, although more expensive than intramuscular formulations, their ease of administration has made them a more popular and acceptable option for some patients [8]. However, the practical problems associated with the non-scrotal patch, coupled with the frequent irritation of the skin, have generally resulted in a low acceptance of this method of administration.

3.6. Testosterone gel

The problems in finding an effective and well-tolerated method of testosterone administration have led to the development of an ‘open delivery system’, in the form of a 1% testosterone gel, which may be applied to the abdomen, shoulders or upper arms (Testogel®, Schering AG, Germany; AndroGel®, Solvay Pharma-

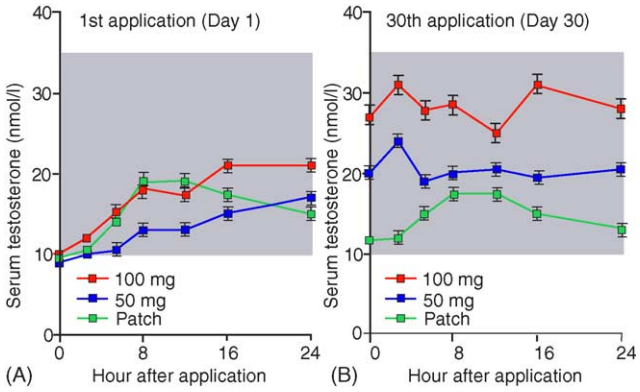

Fig. 2. Pharmacokinetics of Testogel®. Gel was applied daily to the skin as either 5 g or 10 g Testogel® (50–100 mg testosterone). (A) Day 1 pharmacokinetics; (B) Day 30 pharmacokinetics. *Copyright 2000, The Endocrine Society.*

ceuticals; Testim™, Auxilium Pharmaceuticals) [28–32]. In a 6-month study, daily application of 5–10 g of 1% testosterone gel (50–100 mg testosterone) on the skin resulted in serum levels of testosterone (Fig. 2), DHT and estradiol well within their normal ranges [28]. Serum levels of testosterone rose to normal during Day 1, with steady state achieved after 2–3 days. The size of the application site area does not significantly impact on serum levels of testosterone, DHT or estradiol, which can be explained by the rapid permeation of testosterone into the skin following application of testosterone gel. The gel dries within 5 minutes, and showers taken 30 minutes later do not affect the blood levels [6]. In an open, randomized study comparing testosterone gel with the non-scrotal patch, equally good improvements in mood, sexual activity and performance, muscle strength, erythropoiesis and body composition were observed in hypogonadal men [29]. However, patient compliance with gel administration was markedly better than that with patch administration, and considerably fewer cases of skin reactions occurred with the gel.

Since application of the gel is simple, convenient and almost free of local reactions, and does not require injections, many patients prefer this application mode to testosterone patches and intramuscular injections. After cessation of gel application, serum testosterone decreases to baseline levels within 72–96 hours, making testosterone gel highly suitable for the treatment of SLOH, since the effects of treatment can be rapidly reversed if safety problems occur.

The likelihood of gel transfer has been found to be low. After intense skin-to-skin contact between volunteers, one of whom had applied testosterone gel to his forearm, no increase in serum testosterone levels could be found in the other volunteer, in whom endogenous testosterone production had been suppressed using norethisterone enanthate [33].

The benefits that have been observed after application of 1% testosterone gel include improvements in sexual function, mood, muscle strength, body composition and BMD [28,29,34,35]. Improvements in these features persist when treatment is extended up to 3 years [35]. The increases in BMD observed after 6 months of treatment were 1% in the hip and 2% in the spine, and appeared to be dependent on the testosterone level achieved [34]. A randomized, placebo-controlled study with 22 patients has established that 1% testosterone gel, when added to patients' existing antidepressant regimens, is significantly superior to placebo in reducing scores on the Hamilton depression rating scale and the Clinical Global Impression scale, in patients with treatment-resistant depression [36].

A good long-term safety profile has been established for 1% testosterone gel [35]. After approximately 3 years of treatment, levels of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides remained unchanged. As a result, testosterone gel is an appropriate therapy for patients with classical hypogonadism, and for elderly men with SLOH. It offers the flexibility of instant discontinuation, with a consequent decrease in androgen levels, in the event of safety problems.

4. Testosterone therapy in erectile dysfunction

In clinical practice, many men are referred for testosterone therapy because of declining sexual function [37]. Testosterone therapy may benefit patients with underlying hypogonadism, who comprise about 4% of men under the age of 50 years and 9% of men over 50 years with erectile dysfunction (ED) [38,39]. Appropriate hormonal therapy for men with hypogonadism requires an understanding of the normal physiologic regulation of the testes and the pathophysiology of underlying testicular dysfunction. Testosterone is the main sexual hormone in human males, with effects on the brain and the pharmacology and physiology of erectile function. In humans, increasing androgen levels at puberty correlate with the onset of increased sexual desire and the pursuit of sexual activity. Suppression of testosterone in eugonadal adult males leads to reduced sexual desire, sexual activity and erections [40]. However, the suppression of testosterone does not necessarily lead to an immediate hypogonadal state. For example, after castration performed for metastatic prostate cancer, some men can

maintain a reasonable level of sexual activity and function for up to a year after the operation, although castration will eventually lead to sexual dysfunction. Testosterone therapy in hypogonadal men leads to an increase in sexual desire, activity and frequency of erections [40].

Work with rats has provided morphological evidence of the effects of testosterone on the penis [41]. Castration of rats induced apoptosis in specific cells in the corpora cavernosa (erectile tissue) of the rat penis, suggesting that certain cell types are dependent on testosterone for survival. Replenishment of testosterone after castration induced new DNA synthesis in the smooth muscle cells, stroma and blood vessels [42]. In addition, pan-cellular proliferation occurred in the penis in response to testosterone after castration.

Phosphodiesterase-5 (PDE5) inhibitors, such as sildenafil, are dependent on the nitric oxide neurotransmitter system. The efficacy of drugs such as sildenafil may depend on the presence of adequate levels of testosterone. Combination therapy with sildenafil and testosterone in hypogonadal subjects may lead to an improved ability to achieve and maintain an erection [43–46].

A double-blind, placebo-controlled study has been carried out to establish whether testosterone could salvage sildenafil-failure in men with ED and hypogonadism [45]. A total of 75 men with ED for a minimum of 3 months, who failed to respond to sildenafil and who had low to low-normal total testosterone levels (<400 ng/dl), were randomized to treatment with testosterone gel or placebo. All men received sildenafil 100 mg, as needed. Treatment consisted of 50 mg testosterone/day in the form of 1% testosterone gel. The aetiology of ED was either organic or mixed, and ED had persisted for more than a year in 91% of subjects. The majority had either moderate or severe ED. Baseline characteristics were similar in both groups. The mean age was 58.5 years and obesity was common (mean body mass index, 31.44 kg/m^2). Evaluations were performed every 4 weeks.

The primary efficacy outcome was the International Index of Erectile Function. Secondary measurements were sexual desire, orgasmic function, satisfaction (assessed via a questionnaire) and serum testosterone levels.

By Week 4, erectile function was significantly improved in the testosterone group vs. placebo ($p = 0.029$). There were also significant improvements in orgasmic function ($p = 0.009$), overall satisfaction ($p = 0.02$) and the total score of the sexual function questionnaire ($p = 0.011$). Serum testosterone increased in the testosterone group from a baseline level of

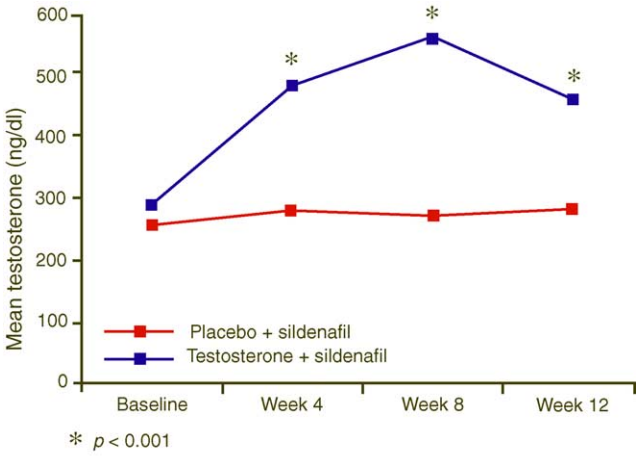

Fig. 3. Testosterone levels in patients treated for erectile dysfunction. Subjects used sildenafil (100 mg) as needed and applied testosterone gel daily (50 mg testosterone) in the form of Testogel® or AndroGel®. *Credited to*: *Shabsigh R, et al.* [45].

300 ng/dl to 500–600 ng/dl ($p \leq 0.001$ compared with placebo; Fig. 3); there was a decrease at Week 12, probably due to patient drop-out. No change was observed in the placebo group. The discovery that a combination of testosterone treatment and sildenafil could improve orgasmic function was an important finding of this study, as monotherapy with PDE5 inhibitors or prostaglandin E1 can only improve vasodilation and erectile function.

These findings are supported by those from an earlier, smaller study, in which 20 hypogonadal subjects were randomized to patch administration of testosterone treatment or placebo, indicating that transdermal administration of testosterone can improve the response to sildenafil [44].

Similar results have been demonstrated by Kalinchenko et al. [43] using sildenafil citrate in combination with oral testosterone undecanoate to treat patients with type 2 diabetes mellitus receiving oral anti-diabetic therapy who had previously failed to respond to therapy with sildenafil citrate alone. In this study of 120 patients (controlled only at baseline), combination treatment restored sexual function, while discontinuation of testosterone undecanoate resulted in the recurrence of ED.

Such improvements indicate that testosterone may be considered for the treatment of ED in men with low to low-normal testosterone levels who have not responded to previous treatment with sildenafil. As recommended at the 2nd International Consultation on Erectile and Sexual Dysfunctions in Paris 2003, it is important to screen men who present with ED for low serum testosterone and hypogonadism, especially if they fail treatment with PDE5 inhibitors or if they are

at-risk populations, such as patients with diabetes, metabolic syndrome or chronic renal failure [47,48].

5. Monitoring during testosterone therapy: prostate safety

One of the greatest concerns among clinicians about testosterone therapy is the fear of causing or promoting prostate cancer. Prostate cancer is one of the most commonly diagnosed cancers in the Western hemisphere; about 50% of men will have microscopic prostate cancer by 70 years of age [49]. Progression to clinical disease is variable, and is linked to both genetic and environmental factors. The most active androgen in the stimulation of the prostate is DHT, a metabolite of testosterone formed by the action of the enzyme 5α-reductase. Androgens are known to stimulate the growth of clinically diagnosed prostate cancer, and testosterone treatment results in severe pain at metastatic bony sites when given to patients with advanced disease [50,51]. However, the action of androgens on the early stages of carcinogenesis is unclear.

In a study to determine the levels of testosterone in patients with and without prostate cancer, it was demonstrated that levels were reduced from normal in patients with high-grade disease, while levels in patients with moderate-grade disease were identical to those in normal controls [52]. In addition, serum levels of total and free testosterone, before and after prostatectomy, were compared in some men with prostate cancer. After prostatectomy, serum levels of both total and free testosterone were significantly elevated, compared with their respective presurgical levels, supporting the possibility that prostate cancer may inhibit serum testosterone levels.

PSA levels are dependent on natural testosterone levels, and are correlated with the risk of prostate cancer. They may therefore provide a suitable marker to monitor the safety of administering exogenous testosterone. An increase in PSA (the velocity) of >1 ng/ml in the first 6 months of therapy or >0.4 ng/ml/year while on therapy is an indication that treatment should be stopped and a biopsy for prostate cancer obtained [53].

DHT has been implicated in causing prostate cancer [54,55]. Finasteride is an inhibitor of 5α-reductase, and thus inhibits the conversion of testosterone to DHT. Finasteride is widely used to shrink the prostate in cases of benign prostate hyperplasia, and a role in prostate cancer prevention is under investigation. A large-scale prostate cancer prevention study has administered finasteride in order to block the conversion of testosterone to DHT [56]. The trial randomly assigned 18,882 men (55 years of age or above), with a normal DRE and a PSA level of ≤ 3.0 ng/ml, to treatment with finasteride (5 mg per day) or placebo for 7 years. Prostate biopsy was recommended if the annual PSA level, adjusted for the effect of finasteride, exceeded 4.0 ng/ml, or if the DRE was abnormal. The prevalence of prostate cancer during the 7 years of the study was 18.4% in the finasteride group and 24.4% in the placebo group. However, high-grade tumours (Gleason grade 7, 8, 9 or 10) comprised a higher proportion of all tumours in the finasteride group than in the placebo group (37% vs. 22.2% of tumours). High-grade tumours occurred in 6.4% of finasteride-treated and 5.1% of placebo-treated patients. These findings indicate that reduced DHT levels under finasteride application may prevent or delay the appearance of prostate cancer; however, this possible benefit must be weighed against an increased risk that the cancers that develop are of high grade.

Overall, the evidence for a role of elevated serum testosterone in the early development of prostate cancer remains inconclusive. In a meta-analysis of 25 studies [57], no correlation between serum testosterone and prostate cancer was found in 15 studies; four studies linked high serum testosterone with prostate cancer and six linked low serum testosterone with prostate cancer. The authors point out that, while there is an association between the levels of DHT in the prostatic tissue at the time of puberty and an increased risk of prostate cancer in young men, it is less clear whether there is a link between testosterone or its metabolites and the incidence of prostate cancer later in life [57].

To date, there is little evidence that testosterone administration elevates PSA beyond normal levels, or at a dangerous rate, in men without prostate cancer. In a study treating 54 hypogonadal men with testosterone intramuscular injections every 2–4 weeks, mean pretreatment PSA was 1.86 ng/ml (median 1.01 [range 0.0–15.80] ng/ml), increasing to a mean level of 2.82 ng/ml (median 1.56 [range 0.0–32.36 ng/ml]; $p < 0.01$) after treatment, with a mean follow-up of 30.2 (range 2.0–82.0) months. In six patients, the PSA level increased above 4.0 ng/ml, and a prostate biopsy was carried out; one of these patients was diagnosed with prostate cancer [58].

Similarly, in another study, 227 hypogonadal men used 1% testosterone gel, as needed, for 3 years. During this time, the mean PSA level remained within the normal range for the majority of patients [35].

A recent review compiled the results of published, prospective studies of testosterone replacement ther-

apy, and found no evidence of an increased prevalence rate of prostate cancer in a total of 461 patients followed for 6–36 months [53].

Further support for the lack of an association between testosterone therapy and the development of prostate cancer comes from a study of men with and without biopsy-defined, high-grade prostatic intraepithelial neoplasia (PIN) [59]. A total of 75 men underwent prostate biopsies, and 55 had benign results (PIN−). However, 20 were found to have high-grade PIN, and therefore might be expected to be at higher risk of prostate cancer. Mean PSA levels were similar in the two groups at baseline (1.53 vs. 1.49 ng/ml). After administration of testosterone for 12 months, PSA levels were elevated slightly in both groups (1.78 vs. 1.82 ng/ml), but only one man (PIN+) developed prostate cancer. These findings indicate that the existence of PIN+ does not necessarily preclude testosterone therapy; however, the number of study participants was small and further investigations are needed.

Testosterone therapy in hypogonadal men can increase the prostate size to that observed in normal men of the same age [60], but does not appear to cause a rapid increase in prostate size or to be associated with the development of benign prostatic hyperplasia [61,62].

In summary, in most studies of testosterone therapy in hypogonadal men, the PSA level rises to that seen in eugonadal men, at a rate that is not considered dangerous. To date, there is no evidence that testosterone therapy induces prostate cancer in elderly men. However, testosterone is a growth factor for an existing prostate cancer, so pre-existing prostate cancer is an absolute contraindication for therapy. Men should be screened prior to therapy, and in the event of confirmed prostate cancer, elevated PSA levels and/or a suspect DRE, therapy should be withheld. The first 3–6 months after initiating testosterone therapy is the most critical time for monitoring effects on the prostate, as this is when a subclinical carcinoma is most likely to manifest itself. Therefore, it is strongly recommended that PSA levels are carefully monitored every 3 months for the first year, and then yearly thereafter, during testosterone therapy [47]. If PSA levels increase more rapidly than 0.4 ng/ml/year, testosterone treatment must be stopped and further investigations, such as biopsy, performed [47]. If levels remain stable, the intervals between testing can be extended. Testosterone levels should be monitored frequently during therapy until normal values are attained, and less frequently thereafter. Ideally, prostate volume, residual urine volume and DRE analyses should be carried out every 12 months.

6. Monitoring during testosterone therapy: cardiovascular and haematological safety

There is evidence suggesting that hypogonadism is a risk factor for hyperlipidaemia, unfavourable changes in high-density lipoprotein cholesterol, and coronary artery disease [63–68]. Therefore, restoring the androgen balance may protect against these abnormalities [63,68]. However, the relationships between androgens and cardiovascular risk factors are complex and not fully understood. Thus, caution is advisable when administering testosterone to men at high risk of cardiovascular disease. It is recommended that a fasting lipid profile is obtained prior to the initiation of treatment and at regular intervals (no longer than 1 year) during treatment [7].

Testosterone therapy in older men often results in significant increases in red blood cell mass and haemoglobin levels [69]. Therefore, dose adjustments or phlebotomies may occasionally be necessary. In rare cases, testosterone treatment may have to be discontinued, due to polycythaemia. Thus, regular (no longer than 1 year) haematological assessment is recommended during testosterone treatment [7].

7. Conclusions

The ability of testosterone therapy to alleviate the signs and symptoms of SLOH, together with the development of convenient and active modes of administration, will lead to increased treatment of the aging male population. However, evidence to establish the risks and benefits is still emerging and large-scale, long-term trials are needed [70].

Transdermal preparations have provided an important advance in testosterone therapy, removing the need for regular injections or thrice-daily tablets. Although safe and effective, transdermal patches are often associated with skin irritation, which can reduce patient compliance and, increasingly, open administration using testosterone gel is being favoured as an alternative form of testosterone therapy. A single daily application of gel can rapidly restore testosterone to physiological levels, which remain stable for 24 hours; conversely, cessation of treatment allows levels to fall rapidly, which is important if treatment needs to be stopped.

Restoring testosterone to physiological levels does not appear to increase the risk of prostate cancer. However, pretreatment screening must eliminate the possibility of an existing carcinoma, and the subject must be monitored carefully during therapy.

References

[1] Gruenewald DA, Matsumoto AM. Testosterone supplementation therapy for older men: potential benefits and risks. J Am Geriatr Soc 2003;51:101–15 discussion 115.

[2] Morales A. Andropause (or symptomatic late-onset hypogonadism): Facts, myths and controversies. Aging Male 2004; in press.

[3] Heinemann LAJ, Saad F, Thiele T, Wood-Dauphinee S. The Aging Males' Symptoms rating scale: cultural and linguistic validation into English. Aging Male 2001;4:14–22.

[4] Morley JE, Patrick P, Perry 3rd HM. Evaluation of assays available to measure free testosterone. Metabolism 2002;51:554–9.

[5] Jockenhoevel F. Male Hypogonadism. Bremen: UNI-MED Verlag AG; 2004.

[6] Jockenhovel F. Testosterone supplementation: what and how to give. Aging Male 2003;6:200–6.

[7] Morales A, Lunenfeld B. Investigation, treatment and monitoring of late-onset hypogonadism in males. Official recommendations of ISSAM. International Society for the Study of the Aging Male. Aging Male 2002;5:74–86.

[8] Hameed A, Brothwood T, Bouloux P. Delivery of testosterone replacement therapy. Curr Opin Investig Drugs 2003;4:1213–9.

[9] Mackey MA, Conway AJ, Handelsman DJ. Tolerability of intramuscular injections of testosterone ester in oil vehicle. Hum Reprod 1995;10:862–5.

[10] Nieschlag E, Cuppers HJ, Wiegelmann W, Wickings EJ. Bioavailability and LH-suppressing effect of different testosterone preparations in normal and hypogonadal men. Horm Res 1976;7:138–45.

[11] Schurmeyer T, Nieschlag E. Comparative pharmacokinetics of testosterone enanthate and testosterone cyclohexanecarboxylate as assessed by serum and salivary testosterone levels in normal men. Int J Androl 1984;7:181–7.

[12] Eckardstein S, Nieschlag E. Treatment of male hypogonadism with testosterone undecanoate injected at extended intervals of 12 weeks: A phase II study. J Androl 2002;23:419–25.

[13] Kohn FM, Schill WB. A new oral testosterone undecanoate formulation. World J Urol 2003;21:311–5.

[14] Park NC, Yan BQ, Chung JM, Lee KM. Oral testosterone undecanoate (Andriol) supplement therapy improves the quality of life for men with testosterone deficiency. Aging Male 2003;6:86–93.

[15] Morales A, Johnston B, Heaton JP, Lundie M. Testosterone supplementation for hypogonadal impotence: assessment of biochemical measures and therapeutic outcomes. J Urol 1997;157:849–54.

[16] Dobs AS, Matsumoto AM, Wang C, Kipnes MS. Short-term pharmacokinetic comparison of a novel testosterone buccal system and a testosterone gel in testosterone deficient men. Curr Med Res Opin 2004;20:729–38.

[17] Korbonits M, Slawik M, Cullen D, Ross RJ, Stalla G, Schneider H, et al. A comparison of a novel testosterone bioadhesive buccal system, striant, with a testosterone adhesive patch in hypogonadal males. J Clin Endocrinol Metab 2004;89:2039–43.

[18] Ross RJ, Jabbar A, Jones TH, Roberts B, Dunkley K, Hall J, et al. Pharmacokinetics and tolerability of a bioadhesive buccal testosterone tablet in hypogonadal men. Eur J Endocrinol 2004;150:57–63.

[19] Stuenkel CA, Dudley RE, Yen SS. Sublingual administration of testosterone-hydroxypropyl-beta-cyclodextrin inclusion complex simulates episodic androgen release in hypogonadal men. J Clin Endocrinol Metab 1991;72:1054–9.

[20] Findlay JC, Place V, Snyder PJ. Treatment of primary hypogonadism in men by the transdermal administration of testosterone. J Clin Endocrinol Metab 1989;68:369–73.

[21] Bals-Pratsch M, Knuth UA, Yoon YD, Nieschlag E. Transdermal testosterone substitution therapy for male hypogonadism. Lancet 1986;2:943–6.

[22] Korenman SG, Viosca S, Garza D, Guralnik M, Place V, Campbell P, et al. Androgen therapy of hypogonadal men with transscrotal testosterone systems. Am J Med 1987;83:471–8.

[23] Ahmed SR, Boucher AE, Manni A, Santen RJ, Bartholomew M, Demers LM. Transdermal testosterone therapy in the treatment of male hypogonadism. J Clin Endocrinol Metab 1988;66:546–51.

[24] Snyder PJ, Peachey H, Berlin JA, Hannoush P, Haddad G, Dlewati A, et al. Effects of testosterone replacement in hypogonadal men. J Clin Endocrinol Metab 2000;85:2670–7.

[25] Dobs AS, Meikle AW, Arver S, Sanders SW, Caramelli KE, Mazer NA. Pharmacokinetics, efficacy, and safety of a permeation-enhanced testosterone transdermal system in comparison with bi-weekly injections of testosterone enanthate for the treatment of hypogonadal men. J Clin Endocrinol Metab 1999;84:3469–78.

[26] Meikle AW, Arver S, Dobs AS, Sanders SW, Rajaram L, Mazer NA. Pharmacokinetics and metabolism of a permeation-enhanced testosterone transdermal system in hypogonadal men: influence of application site–a clinical research center study. J Clin Endocrinol Metab 1996;81:1832–40.

[27] Parker S, Armitage M. Experience with transdermal testosterone replacement therapy for hypogonadal men. Clin Endocrinol Oxf 1999;50:57–62.

[28] Swerdloff RS, Wang C, Cunningham G, Dobs A, Iranmanesh A, Matsumoto AM, et al. Long-term pharmacokinetics of transdermal testosterone gel in hypogonadal men. J Clin Endocrinol Metab 2000;85:4500–10.

[29] Wang C, Swerdloff RS, Iranmanesh A, Dobs A, Snyder PJ, Cunningham G, et al. Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. Testosterone Gel Study Group. J Clin Endocrinol Metab 2000;85:2839–53.

[30] Wang C, Berman N, Longstreth JA, Chuapoco B, Hull L, Steiner B, et al. Pharmacokinetics of transdermal testosterone gel in hypogonadal men: application of gel at one site versus four sites: a General Clinical Research Center Study. J Clin Endocrinol Metab 2000;85:964–9.

[31] McNicholas TA, Dean JD, Mulder H, Carnegie C, Jones NA. A novel testosterone gel formulation normalizes androgen levels in hypogonadal men, with improvements in body composition and sexual function. BJU Int 2003;91:69–74.

[32] Marbury T, Hamill E, Bachand R, Sebree T, Smith T. Evaluation of the pharmacokinetic profiles of the new testosterone topical gel formulation, Testim, compared to AndroGel. Biopharm Drug Dispos 2003;24:115–20.

[33] Rolf C, Knie U, Lemmnitz G, Nieschlag E. Interpersonal testosterone transfer after topical application of a newly developed testosterone gel preparation. Clin Endocrinol Oxf 2002;56:637–41.

[34] Wang C, Swerdloff RS, Iranmanesh A, Dobs A, Snyder PJ, Cunningham G, et al. Effects of transdermal testosterone gel on bone turnover markers and bone mineral density in hypogonadal men. Clin Endocrinol Oxf 2001;54:739–50.

[35] Swerdloff RS, Wang C. Three-year follow-up of androgen treatment in hypogonadal men: preliminary report with testosterone gel. Aging Male 2003;6:207–11.

[36] Pope Jr HG, Cohane GH, Kanayama G, Siegel AJ, Hudson JI. Testosterone gel supplementation for men with refractory depression: a randomized, placebo-controlled trial. Am J Psychiatry 2003;160:105–11.

[37] Hayes FJ. Testosterone–fountain of youth or drug of abuse? J Clin Endocrinol Metab 2000;85:3020–3.

[38] Morales A, Heaton JP. Hormonal erectile dysfunction. Evaluation and management. Urol Clin North Am 2001;28:279–88.

[39] Buvat J, Lemaire A. Endocrine screening in 1,022 men with erectile dysfunction: clinical significance and cost-effective strategy. J Urol 1997;158:1764–7.

[40] Shabsigh R. Hypogonadism and erectile dysfunction: the role for testosterone therapy. Int J Impot Res 2003;15(Suppl 4):S9–S13.
[41] Shabsigh R. The effects of testosterone on the cavernous tissue and erectile function. World J Urol 1997;15:21–6.
[42] Shabsigh R, Raymond JF, Olsson CA, O'Toole K, Buttyan R. Androgen induction of DNA synthesis in the rat penis. Urology 1998;52: 723–8.
[43] Kalinchenko SY, Kozlov GI, Gontcharov NP, Katsiya GV. Oral testosterone undecanoate reverses erectile dysfunction associated with diabetes mellitus in patients failing on sildenafil citrate therapy alone. Aging Male 2003;6:94–9.
[44] Aversa A, Isidori AM, Spera G, Lenzi A, Fabbri A. Androgens improve cavernous vasodilation and response to sildenafil in patients with erectile dysfunction. Clin Endocrinol Oxf 2003;58:632–8.
[45] Shabsigh R, Kaufman JM, Steidle C, Padma-Nathan H. Randomized study of testosterone gel as adjunctive therapy to sildenafil in hypogonadal men with erectile dysfunction who do not respond to sildenafil alone. J Urol 2004;172:658–63.
[46] Arver S, Dobs AS, Meikle AW, Allen RP, Sanders SW, Mazer NA. Improvement of sexual function in testosterone deficient men treated for 1 year with a permeation enhanced testosterone transdermal system. J Urol 1996;155:1604–8.
[47] Morales A, Buvat J, Gooren LJ, Guay AT, Kaufman J-M, Tan HM, et al. Endocrine aspects of sexual dysfunction in men. J Sexual Medicine 2004;1:69–81.
[48] Lue TF, Giuliano F, Montorsi F, Rosen RC, Andersson K-E, Althof S, et al. Summary of the recommendations on sexual dysfunctions in men. J Sexual Medicine 2004;1:6–23.
[49] Swerdloff RS, Wang C. Androgens and aging in men. Exp Gerontol 1993;28:435–46.
[50] Schroder FH. EORTC Genitourinary Group: prostate cancer studies. Prog Clin Biol Res 1990;357:73–81.
[51] Fowler Jr JE, Whitmore Jr WF. The response of metastatic adenocarcinoma of the prostate to exogenous testosterone. J Urol 1981;126: 372–5.
[52] Zhang PL, Rosen S, Veeramachaneni R, Kao J, DeWolf WC, Bubley G. Association between prostate cancer and serum testosterone levels. Prostate 2002;53:179–82.
[53] Rhoden EL, Morgentaler A. Risks of testosterone-replacement therapy and recommendations for monitoring. N Engl J Med 2004;350:482–92.
[54] Flores E, Bratoeff E, Cabeza M, Ramirez E, Quiroz A, Heuze I. Steroid 5alpha-reductase inhibitors. Mini Rev Med Chem 2003;3:225–37.
[55] Occhiato EG, Guarna A, Danza G, Serio M. Selective non-steroidal inhibitors of 5 alpha-reductase type 1. J Steroid Biochem Mol Biol 2004;88:1–16.
[56] Thompson IM, Goodman PJ, Tangen CM, Lucia MS, Miller GJ, Ford LG, et al. The influence of finasteride on the development of prostate cancer. N Engl J Med 2003;349:215–24.
[57] Slater S, Oliver RT. Testosterone: its role in development of prostate cancer and potential risk from use as hormone replacement therapy. Drugs Aging 2000;17:431–9.
[58] Gerstenbluth RE, Maniam PN, Corty EW, Seftel AD. Prostate-specific antigen changes in hypogonadal men treated with testosterone replacement. J Androl 2002;23:922–6.
[59] Rhoden EL, Morgentaler A. Testosterone replacement therapy in hypogonadal men at high risk for prostate cancer: results of 1 year of treatment in men with prostatic intraepithelial neoplasia. J Urol 2003;170:2348–51.
[60] Behre HM, Bohmeyer J, Nieschlag E. Prostate volume in testosterone-treated and untreated hypogonadal men in comparison to age-matched normal controls. Clin Endocrinol Oxf 1994;40:341–9.
[61] Meikle AW, Arver S, Dobs AS, Adolfsson J, Sanders SW, Middleton RG, et al. Prostate size in hypogonadal men treated with a nonscrotal permeation-enhanced testosterone transdermal system. Urology 1997;49:191–6.
[62] Kenny AM, Prestwood KM, Gruman CA, Marcello KM, Raisz LG. Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels. J Gerontol A Biol Sci Med Sci 2001;56:M266–72.
[63] Zmuda JM, Cauley JA, Kriska A, Glynn NW, Gutai JP, Kuller LH. Longitudinal relation between endogenous testosterone and cardiovascular disease risk factors in middle-aged men. A 13-year follow-up of former Multiple Risk Factor Intervention Trial participants. Am J Epidemiol 1997;146:609–17.
[64] Phillips GB, Pinkernell BH, Jing TY. The association of hypotestosteronemia with coronary artery disease in men. Arterioscler Thromb 1994;14:701–6.
[65] Uyanik BS, Ari Z, Gumus B, Yigitoglu MR, Arslan T. Beneficial effects of testosterone undecanoate on the lipoprotein profiles in healthy elderly men. A placebo controlled study. Jpn Heart J 1997; 38:73–82.
[66] Crook D. Androgens and the risk of cardiovascular disease. Aging Male 2000;3:190–5.
[67] Gooren LJG. Visceral obesity, androgens and the risk of cardiovascular disease and diabetes mellitus. Aging Male 2001;4:30–8.
[68] Jockenhovel F, Bullmann C, Schubert M, Vogel E, Reinhardt W, Reinwein D, et al. Influence of various modes of androgen substitution on serum lipids and lipoproteins in hypogonadal men. Metabolism 1999;48:590–6.
[69] Jockenhovel F, Vogel E, Reinhardt W, Reinwein D. Effects of various modes of androgen substitution therapy on erythropoiesis. Eur J Med Res 1997;2:293–8.
[70] Liverman CT, Blazer DG, editors. Testosterone and aging. Committee on assessing the need for clinical trials of testosterone replacement therapy. Institute of Medicine of the National Academies. Washington (DC): The National Academies Press; 2004.