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Testosterone replacement therapy: current trends and future directions

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Male hypogonadism is characterized by abnormally low serum testosterone levels associated with typical symptoms, including mood disturbance, sexual dysfunction, decreased muscle mass and strength, and decreased bone mineral density. By restoring serum testosterone levels to the normal range using testosterone replacement therapy, many of these symptoms can be relieved. For many years, injectable testosterone esters or surgically implanted testosterone pellets have been the preferred treatment for male hypogonadism. Recently, newer treatment modalities have been introduced, including transdermal patches and gels. The development of a mucoadhesive sustained-release buccal tablet is the latest innovation, which will provide patients with an additional option. The availability of new treatment modalities has helped to renew interest in the management of male hypogonadism, highlighting the need to address a number of important but previously neglected questions in testosterone replacement therapy. These include the risks and benefits of treatment in different patient populations (e.g. the elderly) and the need for evidence-based diagnosis and treatment monitoring guidelines. While some recommendations have been developed in individual countries, up-to-date, internationally accepted evidence-based guidelines that take into account national differences in clinical practice and healthcare delivery would optimize patient care universally.

Key words: male hypogonadism/testosterone replacement

Introduction

Male hypogonadism can cause significant morbidity and substantial reduction in quality of life. Many of the symptoms of hypogonadism can be improved by injectable testosterone esters, which have formed the cornerstone of treatment since the 1950s. However, in recent years newer therapeutic modalities have been developed with the aim of producing testosterone levels that more closely approximate physiological levels and improve patient acceptability. The advent of these new treatment options has renewed interest in the management of male hypogonadism. This article records the outcome of a meeting of European experts in the field of testosterone replacement, who, through this forum, shared clinical experiences, compared treatment practices across the EU, discussed the potential role of new delivery systems, and identified unmet clinical needs and issues that require further research.

The emerging face of hypogonadism

Male hypogonadism is a clinical syndrome complex defined by low testosterone [i.e. serum total testosterone $< 10-12$ nmol/l ($\sim 2.88-3.46$ ng/ml)] and low sperm production. It may be caused by hypothalamic, pituitary, testicular, or target organ disorders, which can be congenital (e.g. Klinefelter's syndrome) or acquired (e.g. following trauma) in origin (Table I). Male hypogonadism is categorized according to whether pathology occurs at the testicular (primary hypogonadism) or pituitary-hypothalamic (secondary hypogonadism) level (Table I). Primary hypogonadism is characterized by raised levels of

Table I. Some causes of hypogonadism (adapted from Bagatell and Bremner, 1996; Nieschlag, 2000)

Primary hypogonadism
Gonadal defects
Genetic defects
Klinefelter's syndrome
Myotonic dystrophy
Polyglandular autoimmune disease
XX males
XYY syndrome
Noonan syndrome
Anatomical defects
Anorchia (congenital or acquired)
Maldescended testes (cryptorchidism)
Gonadal dysgenesis
Testicular tumours
Varicocele
Sertoli-cell-only syndrome
Defects caused by toxins
Drugs (cytotoxins and spironolactone)
Radiation
Alcohol
Viral orchitis
Hormone and enzyme defects
Androgen insensitivity
Luteinizing hormone (LH) insensitivity
Enzyme defects in testosterone synthesis
General diseases (renal failure, liver cirrhosis, diabetes, etc.)
Secondary hypogonadism
Organic causes
Panhypopituitarism
Idiopathic
Pituitary or hypothalamic tumour
Miscellaneous
Granulomatous disease e.g. sarcoidosis
Vasculitis
Haemochromatosis, transfusion siderosis
Infarction
Trauma, radiation
Hyperprolactinaemia
Isolated gonadotrophin deficiency
Kallmann's syndrome
Idiopathic hypogonadotrophic hypogonadism
Isolated deficiency of FSH or LH
Genetic disorder
Prader–Labhart–Willi syndrome
Laurence–Moon–Biedl–Bardet syndrome
Systemic disorder
Chronic disease
Nutritional deficiency or starvation
Morbid obesity
Drugs
Glucocorticoids, opiates, anabolic steroids
Constitutional cause (delayed puberty)
Mixed primary/secondary hypogonadism
Late-onset hypogonadism

luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in response to diminished testosterone (and estradiol and inhibin B) feedback. Secondary hypogonadism is characterized by low levels of testosterone associated with low or normal levels of FSH and/or LH.

Ageing and hypogonadism

Ageing is also associated with a decline in testosterone levels. Vermeulen and Kaufman (1995) estimate that 7% of men aged 40–60 years have serum total testosterone concentrations of <12 nmol/l (3.46 ng/ml), increasing to 21% of 60–80 year olds, and 35% of men aged >80 years. Age-related low testosterone has features of both primary and secondary hypogonadism, and is associated with decreased total testosterone (i.e. free testosterone plus protein-bound testosterone), decreased free testosterone associated with an increased sex-hormone binding globulin (SHBG) (Harman *et al.*, 2001), decreased secretion of testosterone in response to human chorionic gonadotropin (Nieschlag *et al.*, 1982), and changes in the pattern of LH release (decreased burst amplitude, increased burst frequency, increased burst duration, and increased basal levels) (Veldhuis *et al.*,1992). This 'late-onset hypogonadism' is important since it features many potentially serious consequences that can be readily avoided or treated, and the affected sector of the population is currently expanding in number. Since symptoms of hypogonadism may be similar to those found in other conditions prevalent in older men, such symptoms must always be considered in the context of the full clinical picture and seen in relation to testosterone levels. Because of the complexity of the 'ageing male syndrome', which features multiple co-morbidities, the impact of correcting low serum testosterone levels on the overall syndrome is not yet fully understood and is an area of active research. The possible benefits and risks of testosterone substitution need to be investigated in strictly controlled clinical trials (Institute of Medicine, 2004).

Co-morbid conditions and concomitant medication

A number of conditions can also be associated with decreased testosterone production. These include diabetes mellitus, atherosclerosis, myocardial infarction, chronic heart failure, chronic renal failure, AIDS, acute exacerbations of rheumatoid arthritis, alcohol abuse, liver cirrhosis and chronic liver disease (Kaufman and Vermeulen, 1997). The use of certain drugs, such as glucocorticoids and neuroleptics, has also been found to be associated with hypogonadism (Kaufman and Vermeulen, 1997). In some cases, testosterone levels may return to within the normal range when these conditions are treated adequately, or drug treatments adjusted.

Clinical features

Male hypogonadism manifests as numerous symptoms, reflecting the many physiological functions of testosterone in men. Because of the central role of testosterone in sexual maturation at puberty, one important determinant of the clinical presentation is whether hypogonadism starts before or after puberty (Table II).

Post-pubertal-onset hypogonadism is commonly associated with decreased muscle mass, decreased libido, erectile dysfunction, oligo- or azoospermia, poor concentration, and decreased prostate size (AACE guidelines, 2002). In older men, the most commonly reported symptoms of hypogonadism are (Morley *et al.*, 2000): decreased libido, erectile dysfunction, lack of energy, decreased strength and/or endurance, deterioration in ability to play sports, falling asleep after meals, deterioration of performance at work, mood fluctuations, height loss.

Table II. Some signs and symptoms of hypogonadism (adapted from Nieschlag and Behre, 2000)

Organ/function	Clinical features of testosterone deficiency	
	Before completion of puberty	**After completion of puberty**
Bones	Eunuchoidal proportions, osteoporosis	Decrease of bone mass, osteoporosis
Larynx	Lack of voice maturation	No change
Hair	Horizontal pubic hair line, straight frontal hairline, sparse beard	No change in pattern, but a reduced density
Skin	Lack of sebum and acne, fine wrinkles	Atrophy, paleness, fine wrinkles
Bone marrow	Anaemia	Anaemia
Muscles	Underdeveloped	Atrophy
Fat mass	Increased	Increased
Penis	Infantile	No change
Prostate	Underdeveloped	Atrophy
Spermatogenesis	Not initiated	Regression
Ejaculate	Anejaculation or small volume	Decreasing volume
Libido	Not developed	Loss
Sexual potency	Not developed	Erectile dysfunction

Diagnosing hypogonadism

Male hypogonadism should be evaluated using a combination of medical history, physical examination and laboratory testing. In older men, the diagnosis of hypogonadism can be complicated by the multiple, non-specific symptoms of the condition that also feature in many other diseases of the elderly. Questionnaires have been developed to assist in the diagnosis of hypogonadism in the elderly (Morley *et al.*, 2000). However, because of the complexity of the ageing male syndrome, these questionnaires lack specificity (Vermeulen and Kaufman, 2002), and the presence of signs and symptoms can only suggest the presence of hypogonadism. Any suspicion should therefore be confirmed with laboratory tests.

The measurement of serum total testosterone concentration is the most commonly used first line test for the biochemical diagnosis of male hypogonadism. The assays to be used need to be under strict quality control and it is advisable to establish normal ranges in each laboratory (Matsumoto and Bremner, 2004; Simoni, 2004). Free testosterone levels may also be important, since changes in SHBG with age may be associated with some of the symptoms of hypogonadism, especially in older men. However, the methods used to measure free testosterone directly by immunoassay are unreliable (Rosner, 2001; Matsumoto, 2002) and it is more advisable to measure SHBG in addition to total testosterone and calculate the free testosterone (Vermeulen *et al.*, 1999; Morley *et al.*, 2002). Especially in older men, free testosterone may be subnormal despite normal total testosterone, since SHBG can be increased.

Defining male hypogonadism according to serum testosterone levels

Serum testosterone levels show a diurnal rhythm, with a decline in the afternoon and evening (Diver *et al.*, 2003). Therefore, to obtain comparable values, blood samples should be taken at the same time each day (preferably in the morning). The lower limit of 'normal' serum testosterone concentration is a matter of some debate, and within the four European countries represented by the authors, the commonly used, or recommended, threshold lower serum testosterone concentration for initiating therapy shows some variation (Table III).

Table III. Commonly quoted threshold serum total testosterone concentrations for considering testosterone replacement therapy

Country	Lower limit of 'normal' serum total testosterone
Germany	10 nmol/l (2.88 ng/ml). When concentrations are between 10 and 12 nmol/l (3.46 ng/ml) additional testing is required (Behre *et al.*, 2000)
France	7.5 nmol/l (2.16 ng/ml)
UK	7.5–8 nmol/l (2.16–2.30 ng/ml)
Spain	~9 nmol/l (2.59 ng/ml)

Studies suggest that a threshold serum total testosterone concentration of 10.4 nmol/l (3 ng/ml) for initiating testosterone replacement therapy may be clinically relevant. In one study of 150 healthy men aged 20–40 years, the mean serum testosterone concentration minus 2.5 standard deviations (i.e. representing $<1\%$ of 'normal' men) was 11.1 nmol/l (3.2 ng/ml) (Vermeulen and Kaufman, 2002). Bhasin *et al.* (2001) suppressed testosterone production with a GnRH agonist in healthy young men, and subsequently examined the effects of restoring testosterone to different degrees. A serum total testosterone concentration of ~10.4 nmol/l (3 ng/ml) was found to maintain fat-free mass; at 8.8 nmol/l (2.53 ng/ml), fat-free mass decreased and fat mass increased; and at >19.8 nmol/l (5.7 ng/ml), fat-free mass increased, and fat mass decreased. In another study, Snyder *et al.* (1999) found that testosterone supplementation only resulted in improved spinal bone mineral density (BMD) in patients with baseline testosterone levels of <10.4 nmol/l (3 ng/ml).

Since there is a 'natural' decline in levels of serum testosterone with age, the relevance of using an age-adjusted lower limit of 'normal' testosterone concentrations is being investigated in longitudinal studies such as the Massachusetts Male Aging Study or the Baltimore Longitudinal Study of Aging (Harman *et al.*, 2001; Feldman *et al.*, 2002) or the European Male Aging Study. Preliminary analyses of these data indicate that any correlations between changes in testosterone levels with age and symptoms are likely to be weak. Until the complete data sets are available, definitive conclusions cannot be made.

Many patients with male hypogonadism are untreated

In general, testosterone deficiency is widely under-diagnosed. Estimates from the United States suggest that as few as 1 in 20 patients are diagnosed and treated (Endocrine Society press release, 2000). A recent analysis of data in the Danish national registry revealed that in this country >70% of patients with Klinefelter's syndrome, the most frequent form of male hypogonadism, remain undiagnosed (Bojesen *et al.*, 2003). This figure is mirrored in the UK where one study showed that three-quarters of the estimated cases of Klinefelter's syndrome in one region (North Thames Congenital Malformation Register) were undetected if not identified prenatally (Abramsky and Chapple, 1997). Other forms of hypogonadism are also likely to be

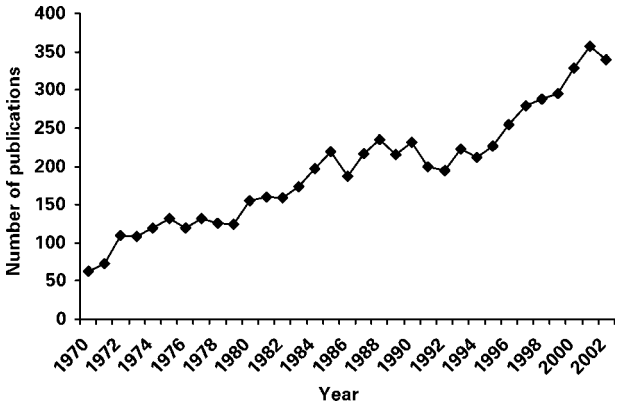

Figure 1. Number of publications identified from PubMed using the search terms 'Testosterone therapy', 'human', and 'male'.

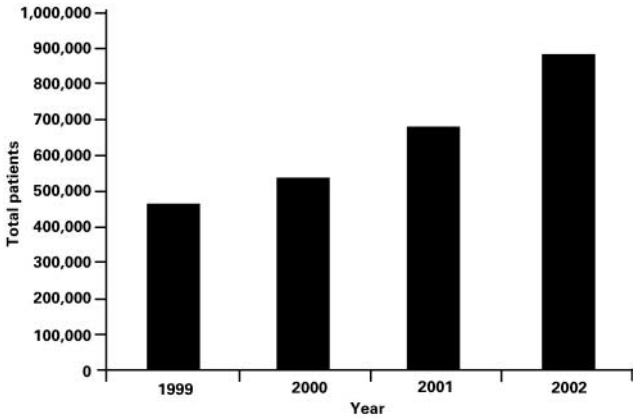

Figure 2. Number of patients treated with testosterone replacement therapy in the USA from 1999 to 2002 (from Institute of Medicine, 2004).

under-diagnosed, possibly due to the taboo surrounding 'maleness' and sexuality, the absence of the patient's experience of the eugonadal state, and/or also due to a lack of awareness among primary physicians. Nevertheless, interest in this field—as illustrated by publication activity (Figure 1) and the number of patients being treated (Figure 2)—has escalated dramatically in the last 15 years. The question remains however whether more hypogonadal patients are being diagnosed and treated, since most of this market growth seems to involve late middle aged men.

Clinical issues in the treatment of male hypogonadism

Clinical benefits

Using testosterone replacement therapy to restore testosterone levels to within the normal range for young adult men [~10–35 nmol/l (2.88–10.00 ng/ml)] can improve many of the effects of hypogonadism. Most importantly, these include beneficial effects on mood and energy levels, thereby improving patients' sense of well-being, sexual function (especially libido, but also erectile function if this is related to hypogonadism), lean body mass, erythropoiesis (improving anaemia if present and due to hypogonadism) and bone mineral density (BMD) (Snyder *et al.*, 1999b, 2000; Kenny *et al.*, 2001; Nieschlag and Behre, 2004). Given the substantial clinical and economic burden that can result from fragility fractures so clearly shown in women, the relationship between testosterone and bone is examined more closely in the following section.

Effects of testosterone on bone

Hypogonadism is the most important single cause of non-idiopathic osteoporosis in men (Francis, 2001). The incidence of all fractures, vertebral fractures and hip fractures increases with age in men as BMD decreases (Melton, 1993; Felsenberg *et al.*, 2002).

Deliberate lowering of testosterone levels following treatment with a gonadotropin releasing hormone (GnRH) agonist for prostate cancer results in bone loss in the lumbar spine, femoral neck, total hip and radius (Mittan *et al.*, 2002); and following orchidectomy for prostate cancer, the incidence of fractures increases dramatically (Daniell, 1997). In hypogonadal men, as well as decreased BMD, the micro-architecture of trabecular bone has also been shown to break down (Benito *et al.*, 2003).

Behre *et al.* (1997) and Zitzmann *et al.* (2002) clearly showed the beneficial effect of testosterone replacement therapy on BMD in hypogonadal men, with improvements over several years. Figure 3 illustrates how the lower age-adjusted BMD in hypogonadal men can be raised to match that of eugonadal men during testosterone replacement therapy (Zitzmann *et al.*, 2002).

The effects of testosterone replacement therapy on the bone of hypogonadal men are so marked that it has been used as a marker of treatment efficacy (although this remains to be formally validated). In hypogonadal patients with osteopenia, increases in BMD should be apparent after 6 months, and progressive increases may continue for 2–3 years (Snyder *et al.*, 1999a).

The mechanism of action of androgens on bone is complex. Testosterone acts on both osteoblasts and osteoclasts via both androgen receptors and, following aromatization, via estrogen receptors. Thus, the conversion of testosterone to estrogens is of crucial importance for maintaining normal bone metabolism (Gennari *et al.*, 2003; Szulc *et al.*, 2003). Table IV shows

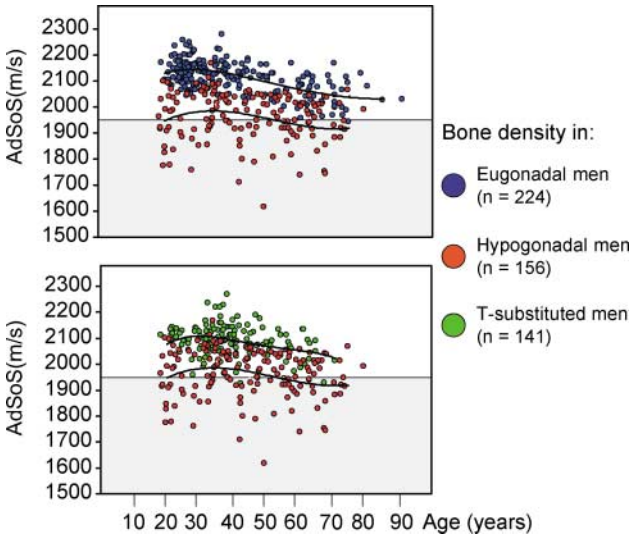

Figure 3. Changes in bone mineral density [amplitude-dependent speed of sound (AdSoS)] in hypogonadal men during treatment with testosterone-replacement therapy (adapted from Zitzmann *et al.*, 2002). Shaded area shows region of increased fracture risk.

Table IV. Effects of testosterone on bone via androgen receptors and estrogen receptors

Androgen receptor-mediated effects	Estrogen receptor-mediated effects
Increased osteoblast lifespan (by increasing proliferation and decreasing apoptosis)	Decreased osteoclast lifespan (by decreasing proliferation and increasing apoptosis)
Decreased early bone turnover	Decreased bone turnover
Increased bone formation	Decreased bone resorption and possible increased bone formation
Increased periosteal apposition of bone	Decreased periosteal apposition of bone
Increased long bone growth	Promotion of epiphyseal closure
Increased bone size	

the main effects of testosterone mediated through the androgen receptor, and indirect effects mediated via estrogen receptors.

Normal bone remodelling is a complex process of coupling between bone resorption and formation. This is mediated through the paracrine and autocrine actions of numerous cytokines in the bone micro-environment. Androgens and estrogens have regulatory effects on much of this cytokine cross-talk (Spelsberg *et al.*, 1999).

In elderly women the effects of low estrogen levels on bones are well established. However, there are fundamental differences in the processes of male and female bone development and maintenance (Seeman, 2001). Thus, areal BMD is higher in men because bone size is greater than in women but there is no sex difference in peak volumetric BMD. During ageing, women lose more long bone by endosteal resorption due to E2 deficiency. Men have greater periosteal apposition in long bones than women, so that net bone loss is less in men than women. In women, trabecular bone loss occurs by loss of complete (number of) trabecular elements at the menopause but ageing men experience continued thinning of the preserved numbers of trabecular units. These sexually dimorphic mechanisms result in the earlier onset of osteoporosis in women.

Falahiti-Nini *et al.* (2002) conducted an investigation where sex steroid production was suppressed in 59 elderly men using a GnRH agonist and an aromatase inhibitor. Patients were randomized to receive testosterone replacement and/or estrogen replacement, or no replacement therapy over 3 weeks. In this study, estrogen was much more effective than testosterone at preventing an increase in bone resorption markers and maintaining bone formation markers. This study suggests that estrogenic metabolites of testosterone are more important than testosterone itself in maintaining bone health. However, other work, using a similar design but treatment for 12 weeks, has not confirmed this, showing testosterone to have significant effects on bone turnover independent of estrogens (Leder *et al.*, 2003). Clearly, more research is required to delineate the relative importance of testosterone and estradiol in male skeletal physiology.

Potential effects on the cardiovascular system

Concerns over the effects of testosterone on cardiovascular risk derive from the observation that men have a much higher risk of developing coronary heart disease than women. Over the last 15 years there have been a large number of cross-sectional and some longitudinal studies, all but one of which show either a neutral or an association of low testosterone levels with coronary heart disease (for review, see von Eckardstein and Wu, 2004). It should also be noted that male hypogonadism has been associated with an unfavourable lipid profile, including raised triglycerides, low density lipid LDL-C, and apoprotein Apo-B, and decreased high density lipid HDL-C (Simon *et al.*, 1997) and atherosclerosis (Hak *et al.*, 2002). In studies involving patients with male hypogonadism, the results have, however, been inconsistent. In this patient group, testosterone replacement therapy has been associated with both favourable (increased HDL-C) and unfavourable (decreased HDL-C and increased LDL-C) effects on lipid profile (Sorva *et al.*, 1988; Ozata *et al.*, 1996). Zgliczynski *et al.* (1996) found that in older patients, testosterone replacement therapy decreased LDL-C but had no effect on HDL-C.

Many of the morbidities and conditions associated with low testosterone (such as obesity, type 2 diabetes and hypertension) are also associated with atherosclerosis. It is not clear whether or not low testosterone levels are a contributory cause or a consequence of coronary heart disease. Recently it has been shown that low testosterone levels occur in the metabolic syndrome. Pathophysiological details of these changes in atherosclerosis are still under investigation (von Eckardstein and Wu, 2004).

There have been several recent reports which strongly suggest that testosterone has beneficial effects on vascular reactivity in men with coronary artery disease. Webb *et al.* (1999a) and Rosano *et al.* (1999) demonstrated that a single intravenous large bolus of testosterone improved the ischaemic threshold of eugonadal men with coronary artery disease during exercise, and Webb *et al.* (1999b) showed that intracoronary injection of testosterone at physiologically relevant concentrations induced coronary artery dilatation and increased blood flow in eugonadal men with coronary heart disease. These acute effects of testosterone were mirrored in studies of longer-term testosterone therapy. A randomized, double-blind, placebo-controlled study involving 46 men with chronic stable angina receiving testosterone by transdermal patch (5 mg daily) for 12 weeks (in addition to their normal antianginal therapy) showed that active therapy significantly improved exercise tolerance (time to 1 mm ST segment depression) compared with placebo, an effect that had a weak inverse correlation with baseline bioavailable testosterone levels. This study group was unselected in relation to their testosterone status but about half were hypogonadal (English *et al.*, 2000). A further study (randomized single-blind placebo-controlled crossover) of overtly hypogonadal men with angina, using intramuscular injections of Sustanon 100® fortnightly over 1 month, demonstrated a greater beneficial effect on ischaemic threshold (Malkin *et al.*, 2004).

Testosterone also appears to have a favourable effect in chronic heart failure. Pugh *et al.* (2003) investigated the acute effects of buccal testosterone (60 mg), compared with placebo in 12 patients with chronic heart failure. Testosterone reduced peripheral vascular resistance and improved cardiac index over an 8 h period. In patients with chronic heart failure, a randomized, double-blind, placebo-controlled study of the effects of chronic administration of testosterone using Sustanon 100® fortnightly, over 14 weeks, active treatment resulted in significant enhancement in functional capacity as assessed by the shuttle

walk test and also in mood (Pugh *et al.*, 2004). No adverse effects of testosterone on hematocrit or any other parameter were observed. A longer term study is in progress to investigate these findings further.

Current evidence suggests that testosterone acts as an arterial vasodilator. This is supported by the finding that vascular stiffness in aorta and radial arteries increases in men with prostate cancer treated with a GnRH analogue (Smith *et al.*, 2001). Laboratory studies have shown that testosterone has a direct effect on vascular smooth muscle cells (Jones *et al.*, 2003b) which is endothelium-independent, non-genomic (independent of the classic androgen receptor) and mediated via a calcium channel blocking effect (English *et al.*, 2002; Jones *et al.*, 2003a,c). It has recently been demonstrated that testosterone is a selective and potent inhibitor of vascular L-type calcium channels acting at concentrations within the physiological range (Scragg *et al.*, 2004).

Based on the currently available data, there is no convincing evidence of an adverse effect of testosterone replacement therapy on coronary heart disease or chronic heart failure, and there may be a role for testosterone in the treatment of cardiovascular diseases in men.

Potential effects on the prostate

Testosterone replacement therapy increases prostate volume to that of normal men (with a wide inter-individual variance) (Behre *et al.*, 1994). The final size of the prostate achieved under testosterone substitution is influenced by the androgen receptor gene polymorphism. Hypogonadal men with fewer CAG nucleotide repeats in exon 1 of the gene attain larger prostate volumes than those with more CAG repeats (Zitzmann *et al.*, 2003). In patients with pre-existing prostate enlargement, or urinary flow obstruction, testosterone replacement therapy should be used with caution. However, it remains uncertain whether testosterone substitution is of benefit or will worsen the symptoms in this condition.

Concerns over the effects of testosterone replacement on prostate cancer stem from the fact that most prostate adenocarcinomata are androgen-dependent in their early stages. The large majority of patients harbouring foci of prostatic adenocarcinoma are not clinically detected, and, of those that are, the large majority of patients do not die from this disease (Ruijter *et al.*, 1999). Concerns have therefore also been raised over whether raising androgen levels in these patients might alter the phenotype of an otherwise non-aggressive prostatic adenocarcinoma. To date, the most robust study of the correlation between serum testosterone levels and the incidence of prostate cancer is a meta-analysis of three epidemiological studies (Shaneyfelt *et al.*, 2000). This study concluded that individuals with a serum testosterone concentration in the upper quartile of the population distribution have an increased risk of developing prostate cancer. However, this observation has limited relevance to the effects of increasing low testosterone levels to within the normal range and a large, long-term study is required to resolve this issue. Screening for prostate cancer [using prostate specific antigen (PSA) monitoring and digital rectal examination] is recommended before initiating therapy and periodically throughout treatment in younger men and is mandatory in men over 45 years.

Treatment options

According to the World Health Organization Guidelines for Use of Androgens in Men (1992), the ideal testosterone replacement therapy should offer: safety, efficacy, value for money, convenience, a good release profile, dosing flexibility, and effective normalization of testosterone levels.

The ideal testosterone therapy should also replace testosterone to physiologic levels using natural (unmodified) testosterone.

A number of routes of delivery have been used in testosterone replacement therapy over the years (Figure 4). Although these therapies have contributed significantly to alleviating the burden of male hypogonadism, none of them fully satisfy the WHO definition of an ideal therapy (WHO, 1992). In the experience of the authors, the selection of different currently available testosterone preparations, both at national and local hospital formulary levels, appears to be largely based on market forces (i.e. pricing and reimbursement issues) rather than differences in efficacy and safety, or desire to offer patients a choice of treatment, despite the long-term nature of treatment.

Implants

This is the oldest form of testosterone replacement therapy, available since the 1940s and still marketed in the UK. Between three and six pellets of 200 mg unmodified testosterone are

Figure 4. Different testosterone preparations and the years they became available for clinical use: 1940 = subdermal testosterone pellet implants, 1954 = intramuscular testosterone enanthate, 1977 = oral testosterone undecanoate, 1992 = scrotal testosterone patch, 1995 and 1998 = transdermal testosterone patches, 2002 = transdermal testosterone gels, 2004 = buccal testosterone and intramuscular testosterone undecanoate.

implanted subcutaneously every 4–6 months, providing stable physiological levels of testosterone (Handelsman *et al.*, 1990). However, insertion of implants requires minor surgery, can be painful, and extrusion of the pellets is common (Handelsman *et al.*, 1997).

Oral testosterone replacement therapy

Unmodified testosterone taken orally is rapidly inactivated by first-pass hepatic metabolism, making oral therapy an ineffective means of delivering unmodified testosterone. However, the ester testosterone undecanoate (available as Andriol®) is preferentially absorbed into the lymphatic system when taken orally, and hydrolysed *in vivo* to yield native testosterone. While oral therapy is a popular route of delivery, the efficacy of oral testosterone undecanoate is limited because of unreliable oral bioavailability, fluctuating serum levels and short half life, necessitating multiple daily dosing (Behre *et al.*, 2004). Other oral testosterone derivatives include 17α-methyltestosterone and fluoxymesterone, which are associated with hepatotoxicity (De Lorimier *et al.*, 1965; Nadell and Kosek, 1977) and have therefore disappeared from the market in Europe. The dihydrotestosterone (DHT) derivative mesterolone has only partial androgenicity (Nieschlag and Behre, 2004) and is therefore rarely used today.

Intramuscular injections

Intramuscular injections of testosterone esters are the most widely used form of testosterone replacement therapy, probably due to the low cost of treatment and convenience of relatively infrequent dosing. Esterification of testosterone at the 17β-hydroxyl group increases the lipid solubility of these molecules, allowing their use as long-acting depot injections. *In vivo*, these esters are hydrolysed to release native testosterone. The depot effect increases with the length of the ester side chain, so that different testosterone esters have different biological half-lives, and products are available with various durations of action. For example, testosterone propionate requires administration every 2–3 days, whereas testosterone enanthate and testosterone cypionate only require injection every 2–3 weeks.

Intramuscular injections of these testosterone esters are associated with supraphysiological levels of testosterone shortly after administration, and sub-physiological levels towards the end of the dose interval (Behre *et al.*, 2004). Short- and long-acting esters have been combined in attempts to overcome this effect (e.g. Sustanon®), but even higher initial testosterone levels have been reported for these products, without any increase in duration of action (Behre *et al.*, 2004). Deep intramuscular injections are invasive and can cause patient discomfort, although they are usually well tolerated. In a few cases, short episodes of non-productive cough have been observed immediately after the injections. This may be caused by pulmonary microembolism from the oily vehicle (Mackey *et al.*, 1995).

Recently, testosterone undecanoate (previously used orally) and testosterone buciclate have been developed as long-acting intramuscular injections. Testosterone buciclate has been shown to be effective at 12–16 week dose intervals (Behre and Nieschlag, 1992), and testosterone undecanoate in castor oil (Nebido®) has been used at 12-weekly intervals (von Eckardstein and Nieschlag, 2002). This long-acting preparation may not be suitable for the treatment of older men, due to an inability to rapidly withdraw treatment if required should side effects occur, but may be a good choice for younger men (Nieschlag, 1998).

Transdermal patches

Transdermal testosterone patches, which were introduced in the early 1990s, increase testosterone levels to within the normal range, and mimic the normal circadian rhythm of testosterone levels. Initially, scrotal patches were developed (Testoderm®), taking advantage of rapid absorption though the highly vascularized scrotal skin. These patches cover an area of 40 or 60 cm^2, and are applied to the shaved scrotum daily. Scrotal patches may deliver supraphysiological levels of DHT due to 5α-reductase activity in the scrotal skin (Atkinson *et al.*, 1998; Behre *et al.*, 1999). The long-term effects of increased DHT levels on the prostate may be a cause for concern (Shaneyfelt *et al.*, 2000), although no serious side effects have been observed over several years of use.

More recently, non-scrotal patches have been developed (e.g. Andropatch®), which are applied once daily. Non-scrotal systems require an alcohol base to enhance permeation, and this has resulted in skin irritation in ~32% of patients (Jordan, 1997; Parker and Armitage, 1999). Allergic contact dermatitis also occurs in ~12% of patients (Jordan, 1997). Application of triamcinolone acetonide 0.1% under the patch improves local tolerability, but these side effects, and the obtrusive presence of patches on the skin, limits the acceptability of these patches for many patients.

Transdermal gels

Transdermal delivery via hydroalcoholic gels has recently become available (Testogel® or Androtop®; 5 g sachets of gel each containing 50 mg unmodified testosterone). Gel is applied once daily to the torso and upper arms and the dose is titrated to reach ideal levels. Gel formulations provide stable levels of serum testosterone within the normal range, and are not associated with skin irritation in the same way as patch formulations. Transdermal testosterone gels have also been associated with increased serum DHT levels, possibly due to the presence of 5α-reductase in the skin and the need to spread the gel over a large surface area (Swerdloff *et al.*, 2000; Wang *et al.*, 2000). In addition, patients are required to avoid bathing or showering until 6 h after application and precautions are required to minimize the potential for transference of testosterone to partners by skin contact (Testogel® summary of product characteristics) (Rolf *et al*., 2002).

Buccal delivery

Early studies confirmed the feasibility of delivering testosterone replacement to patients across the buccal mucosa (Dobs *et al.*, 1998; Baisley *et al.*, 2002). Buccal delivery avoids first-pass metabolism because venous drainage from the mouth is into the superior vena cava, allowing the use of unmodified testosterone. Following these initial studies using short-acting tablets, recently a sustained-release mucoadhesive buccal tablets, (Striant™ SR), which contains 30 mg of unmodified testosterone has been licensed in the USA and in Europe. This twice-daily buccal tablet is placed in the small natural depression in the mouth above an incisor tooth on either side of the mouth, providing a discreet form of therapy.

Treatment with this tablet restores serum testosterone concentrations to within the normal range within 4 h of application, and steady-state concentrations are achieved within 24 h (Ross *et al.*, 2004). Mean testosterone levels are maintained within the physiological range (Dobs *et al.*, 2004; Korbonits *et al.*, 2004; Wang *et al.*, 2004) similar to that seen in normal young men. Serum DHT levels increase parallel to serum testosterone into the normal range (Dobs *et al.*, 2004; Wang *et al.*, 2004) and not as high as with trans-scrotal patches.

In Phase III clinical trials, 87–97% of patients achieved 24 h time-averaged serum concentrations of testosterone within the normal range (Dobs *et al.*, 2004; Korbonits *et al.*, 2004; Wang *et al.*, 2004). Compared with patients receiving Andropatch® (50 mg at night), patients treated with Striant™ SR were more likely to achieve levels of testosterone within the physiological range (Korbonits *et al.*, 2004). A small 14-day study suggested that the buccal system produced mean steady-state testosterone levels comparable to those with a testosterone gel (Dobs *et al.*, 2004). In these trials, the buccal testosterone tablet was generally well tolerated, with the most common adverse event being application site irritation, although these events were infrequent, usually mild or moderate, and rarely led to treatment discontinuation (Dobs *et al.*, 2004; Korbonits *et al.*, 2004; Wang *et al.*, 2004). This new preparation may be chosen by patients preferring a self-applicable substitution that can be orally administered.

Testosterone therapy in clinical practice

The biochemical goal of testosterone replacement therapy is to achieve physiological testosterone levels with a minimum of adverse effects, using the most convenient route of administration possible for the patient. The many clinical effects of testosterone replacement therapy have been discussed, and all patients should be informed about the expected somatic and behavioural changes that occur during treatment, and the timeframe over which these occur. There are also a number of important parameters that should be monitored throughout treatment.

Somatic effects of therapy

Testosterone therapy normally results in improvements in mood and well-being and thereby results in an improved quality of life. Adverse effects on behavioural patterns during treatment require modification of doses. Within days or weeks of starting therapy, men will notice an increase in libido, improved energy levels and sense of well-being (Morales *et al.*, 1997). Changes in physical appearance (e.g. increases in body weight) and BMD will evolve over 6 months.

Parameters to monitor or to be aware of during therapy

Hematocrit

Almost all studies of testosterone replacement therapy in hypogonadal men have shown a significant increase in hematocrit, due to stimulation of erythropoiesis, which can potentially cause symptoms of hyperviscosity (Hajjar *et al.*, 1997) especially in older patients. Therefore, haemoglobin and hematocrit levels should be checked periodically. If hematocrit levels are abnormally high, the testosterone dose should be reduced or temporarily discontinued until the hematocrit has normalized.

Blood lipids

The impact of androgens on cardiovascular risk and lipids has already been discussed in some detail. In patients who are receiving testosterone replacement therapy, a fasting lipid profile is recommended at yearly intervals.

Prostate

Monitoring of the prostate should be undertaken according to local protocols before and during therapy (e.g. using digital examination, and PSA levels after 3, 6 and 12 months and then at yearly intervals).

Gynaecomastia

The ratio of estradiol to testosterone usually remains normal during testosterone therapy, but occasionally gynaecomastia develops in patients receiving testosterone therapy, especially testosterone enanthate or cypionate. Dose adjustment may be necessary.

Sleep apnoea

Testosterone treatment can also exacerbate sleep apnoea (Sandblom *et al.*, 1983), although hypogonadism has also been cited as a cause of this condition (Luboshitzky *et al.*, 2002). The development of signs and symptoms of obstructive sleep apnoea during testosterone therapy warrants a formal sleep study and treatment with continuous positive airway pressure (CPAP) if necessary. If the patient is unresponsive or cannot tolerate CPAP, the testosterone must be reduced or discontinued.

Unmet needs in hypogonadism

It is clear that in order to optimize the management of male hypogonadism, several areas need to be addressed. These are summarized below.

Improving diagnosis

The fact that hypogonadism is widely under-diagnosed at the present time means that patients with troublesome symptoms and a reduced quality of life are not benefiting from treatment. This situation could be improved by raising awareness of male hypogonadism among the medical community and patients. Improved education regarding comorbidities, their treatment (e.g. glucocorticoids) and conditions associated with hypogonadism and standard criteria for defining a clinical diagnosis would be of use in this area.

Better treatments

Recently introduced transdermal, intramuscular and buccal testosterone preparations have greatly improved substitution therapy by providing serum testosterone levels in the physiological range. However, new formulations of existing treatment modalities, new modes of delivery or new androgens may further improve the overall acceptability and efficacy of treatments. A wider spectrum of treatment modalities is required so that substitution therapy can be better tailored to the individual needs and requirements of the patients and adjusted to the individual risk profile (e.g. of younger vs older patients).

Determining the role of testosterone replacement therapy in late-onset hypogonadism

There is still much to learn about the 'ageing male syndrome' and the role of testosterone replacement therapy. Fundamentally, the relative importance of low testosterone in this complex syndrome, and the impact of correcting this single parameter upon the multitude of co-morbidities that can affect older men is still not fully understood.

Further research to better quantify the long-term effects of testosterone replacement therapy

It is generally well accepted that restoring testosterone levels to the normal range will improve quality of life parameters in the long term and will provide a range of benefits to muscle, bone and other testosterone-dependent functions. However, the treatment benefits of testosterone replacement therapy need to be more clearly defined. For example, while it is clear that restoring testosterone levels increases BMD, no studies have looked beyond this to see if testosterone therapy decreases the incidence of fractures and whether this benefit would reach a level of clinical significance. Even the threshold serum testosterone level at which treatment is required to avoid morbidity, and its correlation with age, have not been thoroughly investigated.

Our understanding of treatment risk is also at a relatively early stage. In the USA, a planned 6-year study of 5000 men with hypogonadism, to investigate the long-term effects of therapy, was recently rejected by the National Institutes of Health (NIH). In response, the Institute of Medicine of the National Academy of Sciences recommended that endpoints should be defined and tested in well-powered short-term studies before undertaking large long-term studies. Potential adverse effects on the prostate and the cardiovascular system are concerns for this type of therapy. Although evidence to date suggests a favourable balance of risk to benefit, unequivocal proof of this would require a large number of participants in long-term studies (Institute of Medicine, 2004).

Evidence-based guidelines

There are a number of guidelines available for treating male hypogonadism. These include the World Health Organization (WHO) Guidelines for the Use of Androgens in Men (1992); The Endocrine Society of Australia Consensus Guidelines for Androgen Prescribing (2000) (Conway *et al.*, 2000); the Andropause Consensus Recommendations arising from the Second Annual Andropause Consensus Meeting (2001) (available through the Endocrine Society web site); the International Society for the Study of the Aging Male (ISSAM) (Morales and Lunenfeld, 2002); Consensus Guidelines from several German Societies (Weidner *et al*., 2001); and the American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the Evaluation and Treatment of Hypogonadism in Adult Male Patients (2002).

However, there are no widely accepted international guidelines for the diagnosis and treatment of male hypogonadism. This, in part, may reflect the national variations in health systems and gaps in knowledge. Nevertheless, given the increasing awareness of male hypogonadism and recent pharmaceutical innovations, the medical community would benefit from up-to-date guidelines that reflect the expanding evidence base.

Conclusions

Male hypogonadism and its treatment is a rapidly evolving area. Patient and doctor awareness has been increasing in recent years and as a result, greater numbers of patients are being treated. In parallel with this, testosterone replacement therapy itself has evolved, and a number of novel delivery systems such as transdermal patches and transdermal gels have become available as potential alternatives to established treatments such as subcutaneous implants, intramuscular injections and oral preparations. The mucoadhesive sustained-release buccal tablet is the latest new development that will offer patients further choice.

While male hypogonadism has previously been underdiagnosed, the apparently increasing incidence and expanding range of treatment options may facilitate greater awareness of the condition among both the medical community and patients. Many questions in the treatment of hypogonadism remain unanswered, and there is a need for active research to fully unravel further information in areas such as late-onset hypogonadism and the potential benefits and risks of testosterone replacement therapy in these men. The development and implementation of widely accepted and adopted diagnosis and treatment guidelines will provide a substantial improvement in patient care and ensure consistency of management in different countries. It is hoped that many of these challenges will be addressed in the near future to the greater benefit of hypogonadal patients.

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