Testosterone replacement therapy

Hypgonadism has important adverse effects on the health and quality of life of affected men, but remains underdiagnosed in clinical practice. This article reviews the physiology, causes and diagnosis of hypogonadism and the potential benefits of treatment with testosterone replacement therapy.

Hypogonadism is a clinical syndrome complex which consists of the presence of symptoms and signs and biochemical confirmation of testosterone deficiency. Testosterone replacement therapy (TRT) is routinely used in clinical practice for the treatment of hypogonadism as a result of either primary testicular or hypothalamic-pituitary failure. There is a higher incidence of hypogonadism in older men. Hypogonadism associated with ageing is now known as 'late-onset hypogonadism' (Nieschlag et al, 2005). It is becoming increasingly recognized that testosterone deficiency is also associated with co-morbid conditions such as coronary heart disease, diabetes, and human immunodeficiency virus (HIV). Osteoporosis is a well-known consequence of untreated hypogonadism. Male hypogonadism is at present underdiagnosed because of the failure of some physicians to consider and investigate the condition. The recent advent of new formulations of TRT is, however, raising the awareness of hypogonadism, since these preparations enable replacement of testosterone so that it closely approximates physiological levels and are more convenient to administer. This article reviews the physiology, causes, diagnosis and management of hypogonadism in light of these developments.

Physiological role of testosterone

In the human male, testosterone has a diurnal variation, with serum levels reaching a peak at 06.00–08.00 hours and a trough at 18.00–20.00 hours. Furthermore, there is a circannual variation since levels are highest in late summer/early autumn and lowest in late winter/early spring. Testosterone production is controlled by the pulsatile secretion of gonadotrophin-releasing hormone (GnRH) from the hypothalamus, which stimulates the pituitary gland to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH) into the circulation. LH then stimulates the Leydig cells of the testis to synthesize and release testosterone. FSH is predominantly involved in testicular growth in puberty and the initiation and maintenance of spermatogenesis. FSH stimulates the release of the hormone inhibin, which exerts a negative feedback on the production of FSH by the pituitary. Testosterone also feeds back on the hypothalamus to inhibit GnRH release (Jockenhövel, 2004).

In adult males, testosterone is important for the maintenance of wellbeing, mood, bone density, muscle mass, erythropoiesis, secondary sexual characteristics and normal sexual function (libido, strength of erection) (Nieschlag et al, 2004). Classically testosterone has been believed to mediate its effects through a direct action on the cell, predominantly genomically via the classic androgen receptor; however, it is being increasingly recognized that it also stimulates more rapid non-genomic mechanisms. Testosterone is metabolized either to the active androgen dihydrotestosterone by the enzyme 5-alpha reductase or to oestradiol by aromatase. The conversion of testosterone to oestradiol is important to maintain adequate bone mineral density (Nieschlag et al, 2004).

In the circulation, 2–3% of testosterone is unbound, approximately 60–80% is tightly bound to sex hormone-binding globulin (SHBG) and 20–40% is weakly bound to albumin (the proportion of testosterone bound to SHBG and albumin varies between individuals). Evidence suggests that free plus albumin-bound testosterone comprises the biologically active (or bioavailable) testosterone available to the tissues (Vermeulen et al, 1996). Total testosterone – which is routinely measured clinically – is therefore made up of all three components (Vermeulen et al, 1996).

Clinical presentation

Symptoms depend on the age at which hypogonadism develops. Hypogonadism of pre-pubertal onset presents clinically as delayed or failed puberty (*Table 1*), while post-pubertal hypogonadism can be more difficult to diagnose, since symptoms may develop slowly and may overlap with features of many systemic conditions.

Table 1. Symptoms/signs of delayed puberty as a result of hypogonadism of pre-pubertal onset

Small testes, penis and prostate (confirm reduced testicular size with a Prader orchidometer)
Undescended testes (cryptorchidism)
Scant pubic and axillary hair
Disproportionately long arms and legs, or short stature
Reduced male musculature
Gynaecomastia
Persistently high-pitched voice
Eunuchoid habitus

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It is therefore important to bear hypogonadism in mind when consulted by any male patient with a history of (Nieschlag et al, 2005):

Table 2. Classification of hypogonadism

Primary or hypergonadotrophic hypogonadism	Congenital	Klinefelter's syndrome (47, XXY)	
		Noonan's syndrome (male Turner's syndrome, 45 X0)	
		Reifenstein's syndrome (defective androgen receptor)	
		Congenital anorchidism	
		Other syndromes	5-alpha reductase deficiency
			Myotonic dystrophy
			Cryptorchidism
		Rare genetic syndromes	47, XYY syndrome
			Dysgenetic testes
			Androgen receptor defects
	Acquired	Trauma	
		Testicular torsion	
		Orchitis (mumps or bacterial)	
		Radiation treatment or chemotherapy	
		Alcohol abuse	
		Varicocoele	
		Haemochromatosis	
		Liver cirrhosis	
		Human immunodeficiency virus infection	
		Orchidectomy	
Secondary or hypogonadotrophic hypogonadism	Inherited	Kallmann's syndrome	
		Isolated hypogonadotrophic hypogonadism	
		Prader–Willi syndrome	
		Lawrence–Moon–Bardet–Biedl syndrome	
		Isolated gonadotropin deficiency	
		Familial cerebellar ataxia	
		Fertile eunuch syndrome	
	Acquired	Hypopituitarism	
		Pituitary tumour	
		Hyperprolactinaemia	
		Cushing's syndrome	
		Intracranial neoplasm (e.g. craniopharyngioma, meningioma, metastases)	
		Haemochromatosis, transfusion siderosis	
		Head injury	
		Granulomatous disease (e.g. sarcoidosis, tuberculosis, histiocytosis)	
		Hypophysitis	
		Drug abuse (opiates)	
		Vasculitis	
		Radiation	

- Reduced or loss of libido
- Decreased strength of erections leading to erectile dysfunction, including loss of morning erections
- Fatigue – including falling asleep during the day (this may be the main presenting symptom since men may be reluctant to volunteer reduced libido or erectile function)
- Reduced muscle strength and physical endurance
- Changes in mood, including sadness, a tendency to depression, 'grumpiness', reduced spatial awareness or difficulty in making decisions
- Loss of height (as a result of osteoporosis)
- History of fracture
- Excessive sweating
- In marked hypogonadism only: reduced hair growth or frequency of shaving and fine wrinkling of the facial skin similar to that of an ageing woman.

Causes of hypogonadism

Hypogonadism may occur if the hypothalamic–pituitary–testicular axis is interrupted at any level. In primary or hypergonadotrophic hypogonadism (*Table 2*), pathology occurs at the testicular level, and is characterized by low levels of testosterone in association with raised levels of LH and FSH. Secondary or hypogonadotrophic hypogonadism (*Table 2*) is caused by hypothalamic or pituitary disorders that impair gonadotrophin secretion, and is therefore characterized by low levels of testosterone, usually in association with low LH and/or FSH, although some patients may have gonadotrophin levels in the low–normal range. An important cause of secondary hypogonadism is a pituitary tumour. Other causes are listed in *Table 2*.

Hypogonadism associated with normal gonadotrophin levels has been described in the medical literature as either mixed, normogonadotrophic or hypogonadotrophic hypogonadism. This type of hypogonadism has features of both primary and secondary hypogonadism, including decreased total testosterone associated with increased SHBG, which results in decreased free and bioavailable testosterone, decreased secretion of testosterone in response to human chorionic gonadotrophin (hCG) and changes to the pattern of LH release (Nieschlag et al 2004). These pathological changes may be associated with ageing or comorbid conditions (*Table 3*). Hypogonadism occurs in only a minority of older men but testosterone levels show a steady decline with age. Like other forms of hypogonadism, mixed hypogonadism has potentially serious consequences. Hypogonadism associated with obesity also is associated with normal gonadotrophins levels (Kapoor et al, 2005).

Investigations

As stated above, the diagnosis of hypogonadism is based on the presence of clinical symptoms and biochemical evidence of testosterone deficiency. Serum for total testosterone should be taken in the morning, before 10.00 am,

on at least two different days, and the patient should ideally abstain from sexual intercourse the night before as this can lead to a transient increase in the baseline level. Further repeated measurements may be necessary together with measurement of other hormones, e.g. FSH, LH, prolactin or SHBG, when the diagnosis of hypogonadism is in doubt (Nieschlag et al, 2005).

The normal range of total testosterone in the early morning in healthy young men aged 20–40 years is 10–35 nmol/litre (Nieschlag et al, 2005). Although some endocrinologists consider that a value of <8 nmol/litre confirms the diagnosis of hypogonadism, clinical practice varies and there are at present no consensus guidelines in the UK. The American Endocrine Society have published guidelines which give a lower limit of normal total testosterone in healthy young men as 10.4 nmol/litre (Bhasin et al, 2006). However, symptomatic men with total testosterone levels of up to 12 nmol/litre may potentially be hypogonadal (Nieschlag et al, 2005).

Results of investigations are particularly difficult to interpret in older men since serum testosterone declines with age at a rate of approximately 1–2% per year (Feldman et al, 2002). One major confounding factor in the diagnosis of hypogonadism is the rise of SHBG levels with age. A greater proportion of the total testosterone is bound to SHBG, which is rendered inactive and therefore the bioavailable testosterone falls. Measurement of total testosterone therefore does not reflect the bioavailable androgen status. In borderline cases, measurement of bioavailable testosterone (which is only available in some research laboratories) or mathematical calculation of bioavailable or free testosterone (using the total testosterone and SHBG levels) is likely to be a better predictor of hypogonadism (Morris et al, 2004).

FSH and LH may also be assessed. Elevated LH and FSH levels are diagnostic of primary hypogonadism, although borderline elevation may be a result of the pulsatile release of gonadotrophins and measurement should be repeated if there is doubt. Low or low normal gonadotrophin levels suggest the possibility of pituitary disease. In such cases, basal production of pituitary hormones should also be assessed. If pituitary disease is suspected, magnetic resonance imaging of the pituitary fossa is mandatory. Normal LH and FSH levels in the presence of a total testosterone level of <10.5 nmol/litre and symptoms are consistent with mixed hypogonadism. Symptomatic men with total testosterone levels of 10.5–12 nmol/litre require careful evaluation and may warrant a trial of TRT. Asymptomatic men should be followed up in the short term as they may have borderline hypogonadism and in time become overtly hypogonadal.

Table 3. Chronic diseases associated with hypogonadism

Cardiovascular disease
Metabolic syndrome
Type 1 and type 2 diabetes
Human immunodeficiency virus
Chronic renal failure
Congestive cardiac failure
Malnutrition
Liver disease

Since hypogonadism may be associated with low bone mineral density – either osteopenia or osteoporosis – and an increased risk of fracture (Isidori et al, 2005), hypogonadal men should undergo scanning with dual energy X-ray absorptiometry at baseline and during follow up. Testicular imaging and biopsy are sometimes needed to investigate for possible anatomical abnormality. Chromosomal analysis should be performed in all men with suspected genetic syndromes resulting in hypogonadism. Fluorescence in-situ hybridization can be used to detect the gene responsible for Kallmann's syndrome.

Testosterone replacement therapy

Treatment of pubertal failure is based on the introduction of low doses of testosterone (usually as intramuscular injections), gradually increasing the dose over 6–12 months to full replacement doses. Alternatively in subjects with secondary hypogonadism, hCG, which has LH-like activity, can be administered subcutaneously twice-weekly, stimulating testosterone synthesis and release from the testis (Jones et al, 1994). The dose of hCG is titrated to provide normal testosterone levels. Testosterone replacement gradually stimulates the development of secondary sexual characteristics. It is important to note that in hypogonadotrophic hypogonadism, which is commonly associated with small testicular size, testosterone does not stimulate testicular growth or spermatogenesis.

An increase in testicular size and the initiation and maintenance of spermatogenesis can be achieved in the majority of men with hypogonadotrophic hypogonadism by treatment with gonadotrophins. In some men hCG therapy alone can stimulate sperm production (Jockenhövel, 2004). The majority of hypogonadotrophic hypogonadal men, however, require combined hCG and FSH therapy. FSH is important for the initiation and maintenance of spermatogenesis and also for testicular growth. FSH (150 iu thrice weekly) and hCG (twice weekly, dose adjusted to give normal testosterone levels) are both given subcutaneously and can be self-administered (Jones and Darne, 1993). A further treatment option is to administer GnRH alone via a pulsatile infusion pump. The success rates of stimulating sperm production in this group have been reported to be 85–90%. Men with primary hypogonadism may have azospermia or oligospermia and do not respond to gonadotrophin therapy.

In hypogonadism of adult onset, improvement in symptoms usually occurs fairly quickly after initiation of TRT (Jockenhövel et al, 2005). Characteristically, patients report improvement in physical wellbeing, energy levels, mood, libido and erectile function (men whose erections do not improve should be investigated for other underlying causes, such as atherosclerosis or psychological problems). TRT also increases Bone mineral density and body composition (greater lean to fat ratio), both of which may continue to improve for several years (Zitzmann et al, 2002).

TRT formulations

Several modes of testosterone delivery are used (*Table 4*), since oral administration does not generally achieve consistent blood levels as a result of first-pass metabolism of the hormone by the liver (Jockenhövel, 2004). Depot testosterone using intramuscular injections or implants as well as transdermal or transbuccal formulations permit sustained release of the hormone into the systemic circulation.

Intramuscular

Until recently TRT has been mainly given by intramuscular injection of short-acting testosterone esters (Sustanon 250, Organon Laboratories, Cambridge (testosterone propionate, testosterone phenylpropionate, testosterone isocaproate, testosterone decanoate)) that usually produces supraphysiological peaks and hypogonadal troughs in testosterone levels, which may result in fatigue, mood swings (particularly depression) and loss of libido. Sustanon 250 is administered every 2–3 weeks. In the author's clinical experience, the troughs and peaks with Sustanon 250 can be lessened by using Sustanon 100 with more frequent injections, i.e. Sustanon 100 every 7, 10 or 14 days.

Intramuscular TRT was also inconvenient for patients because of the need for injections every 2–3 weeks (although some men self-administer their injections, the majority attend their GP's surgery). More recently, a long-acting depot injection of 1000 mg (4 ml) testosterone undeconoate (Nebido, Bayer Schering Pharma, Newbury) has become available and is administered as a deep intramuscular injection into the buttock. After an initial injection and a second (loading) injection 6 weeks later, the injection frequency is once every 10–14 weeks depending on the trough testosterone level (pre-injection) being within the normal range. Nebido is generally well-tolerated and achieves near steady-state, physiological testosterone levels.

With all injectables there is a risk of injection site tenderness.

Transdermal

In the mid-1990s, transdermal delivery became available via skin patches. Andropatch (GlaxoSmithKline, Uxbridge) (testosterone) generally achieves levels of testosterone within the normal range, but the patch is associated with

Table 4. Formulations of testosterone replacement therapy available in the UK

Formulation	Generic (brand if proprietary)	Dosing
Intramuscular injection	Testosterone propionate 20 mg/ml, testosterone phenylpropionate 40 mg/ml and testosterone isocaproate 40 mg/ml (Sustanon 100)	1 ml every 7–14 days
	Testosterone propionate 30 mg/ml, testosterone phenylpropionate 60 mg/ml, testosterone isocaproate 60 mg/ml and testosterone decanoate 100 mg/ml (Sustanon 250)	1 ml every 3 weeks
	Testosterone propionate 50 mg/ml (Virormone)	50 mg 2–3 times weekly (delayed puberty 50 mg weekly)
	Testosterone undecanoate 1000 mg/4 ml (Nebido)	1000 mg every 10–14 weeks after one loading dose of 1000 mg at 6 weeks
Implant	Testosterone 100 mg, 200 mg	100–600 mg; 600 mg usually maintains plasma testosterone concentration within the normal range for 4–5 months
Transdermal gel	Testosterone 50 mg/5 g sachet (Testogel)	50 mg testosterone (5 g gel) applied once daily; subsequent application adjusted according to response in 25 mg (2.5 g gel) increments to maximum 100 mg (10 g gel) daily
	Testosterone 50 mg/5 g tube (Testim gel)	
	Testosterone 10 mg/0.5g metered dose (Tostran 2% gel)	60 mg testosterone (3 g gel) applied once daily; subsequent application adjusted according to response; daily dose should not exceed 80 mg testosterone (4 g gel)
Transdermal patch	Testosterone (approximately 2.5 mg and 5 mg patch/24 hours) (Andropatch)	Initially apply patches equivalent to testosterone 5 mg/24 hours (2.5 mg/24 hours in non-virilized patients) at night. Then adjust to 2.5–7.5 mg every 24 hours according to plasma testosterone concentration
Oral	Testosterone undecanoate (Restandol) 40 mg	120–160 mg for 2–3 weeks, maintenance 40–120 mg daily
Buccal	30 mg testosterone (Striant SR)	One tablet applied to gums twice daily, morning and evening about 12 hours apart

For full details please see relevant summary of product characteristics

a high incidence of local skin reactions (Wang et al, 2000), and patients complain that it is large and visible through some shirts and can be noisy on movement.

Testosterone gels (Testogel, Bayer Schering Pharma, Newbury (testosterone), Testim gel, Ipsen, Slough (testosterone), Tostran 2% gel, ProStrakan, Galashiels (testosterone)) have significantly changed the treatment of hypogonadism, since these are much less visible and have a much lower incidence of skin reactions than patches (Wang et al, 2000). Physiological levels are achieved in the majority of men and treatment with testosterone gels improves aspects such as increasing Bone mineral density (Wang et al, 2000; Steidle et al, 2003). Some men, however, do not like the daily administration of the gel, as they have to wait for it to dry before dressing

Buccal

A further option is a buccal tablet (Striant SR, Ardana Bioscience, Edinburgh (testosterone)), which has a novel microadhesive formula allowing the tablet to adhere to the upper gum above the lateral incisors. The tablet is applied twice daily and achieves testosterone levels within the normal range (Ross et al, 2004). It is important that patients receive education concerning the application process.

Oral

Also available are tablets (Restandol/Andriol, Organon Laboratories, Cambridge (testosterone undecanoate)), which are taken in 40–60 mg doses three times per day with a fatty meal.

Subdermal

Finally, some centres in the UK use testosterone implants, which last for about 4–6 months, although the procedure is time consuming and there is a risk of infection and extrusion of the pellets (Handelsman et al, 1997).

Monitoring testosterone replacement therapy

Since testosterone acts on a range of organs, a number of potential adverse events have been associated with TRT (*Table 5*). These have been reviewed (Rhoden and Morgentaler, 2004), and many are rare or infrequent, while others can be reduced by careful baseline assessment and monitoring at follow-up visits.

The main concern among doctors relates to the potential adverse effects of TRT on the prostate, although there is no substantive evidence to support this. In hypogonadal men, prostate volume on ultrasonography increases significantly during TRT but only to a level equivalent to that of men with normal testosterone levels (Rhoden and Morgentaler, 2004). However, objective and subjective measures of urinary symptoms do not change significantly, possibly because of the poor correlation between such symptoms and prostate volume (Rhoden and Morgentaler, 2004). There is no objective evidence that TRT increases the risk of prostate carcinoma, but no large, sufficiently powered studies have been performed to exclude this risk. Suspected or known prostate cancer consequently remains a contraindication to TRT.

Prostate carcinoma should as far as possible be excluded before initiating TRT. It is recommended that both serum prostate-specific antigen (PSA) is checked and digital rectal examination of the prostate are performed and both are normal especially in subjects aged 45 years or more. Some authorities also recommend transrectal ultrasound since an occult prostate carcinoma that is not associated with elevated PSA or abnormal digital rectal examination may potentially become apparent

Table 5. Side effects potentially associated with testosterone replacement therapy

Risk	Current evidence
Cardiovascular disease	Neutral or possible benefit
Lipid alterations	Generally no change with physiological replacement
Erythocytosis	Requires monitoring as risk varies according to mode of administration and greater likelihood with supraphysiological T levels
Fluid retention	Rarely clinically significant
Benign prostatic hyperplasia	Rarely clinically significant
Prostate cancer	Remains controversial, but requires long-term monitoring
Hepatotoxicity	Limited to oral agents
Sleep apnoea	Infrequent
Gynaecomastia	Rare and usually reversible
Skin reactions	High incidence with patch, low with gel and rare with injections
Acne or oily skin	Infrequent
Testicular atrophy or infertility	Common especially in young men. Usually reversible on cessation of treatment

Adapted from Rhoden and Morgentaler (2004)

(Morales and Lunenfeld, 2002). However, this is not routinely performed in most centres. Regular surveillance of the prostate is mandatory for all patients, especially those aged over 45 years, and it has been recommended that PSA and digital rectal examination should be performed at 3-monthly intervals for the first year and annually thereafter in these patients. If PSA becomes elevated and repeat levels continue to rise, TRT should be stopped and the patient referred for a urological assessment.

Haemoglobin and haematocrit should also be monitored at similar intervals to PSA, as improved erythropoiesis with TRT can cause these values to rise and there is a risk of polycythaemia if testosterone levels remain supraphysiological. The decision as to whether or not to stop TRT has to be made on the benefit of TRT to the patient, the degree of polycythaemia and other relevant co-morbid conditions. Sleep apnoea should also be borne in mind as a potential, though rare, side effect as this may be associated with TRT especially in men with risk factors such as obesity or chronic respiratory disease. Male breast carcinoma is also a contraindication to the use of TRT.

Future of TRT

There is an urgent need for professional education regarding identification of men with testosterone deficiency. Hypogonadism may present in a range of specialties, such as endocrinology, urology, orthopaedics, psychiatry, cardiology, diabetology, medicine for the elderly, as well as general practice. Once suspected, the patient should be referred to an endocrinologist or andrologist for further evaluation, diagnosis and treatment.

At present, awareness of classical primary and secondary hypogonadism is low – a community survey concluded that 75% of men with Klinefelter's syndrome, a relatively common inherited hypogonadal condition, remain undiagnosed (Bojesen et al, 2003). All too often, patients with comorbid conditions such as diabetes and coronary heart disease believe that their loss of libido is caused by these disorders rather than their testosterone deficiency. Fatigue may therefore be the only presenting feature volunteered by the patient, and other symptoms may be revealed only after taking a proper history.

Late-onset hypogonadism has also been not well understood previously. It is now becoming an internationally recognized syndrome. The definition of late-onset hypogonadism is 'a clinical and biochemical syndrome associated with advancing age and characterized by typical symptoms and a deficiency in serum testosterone levels. It may result in significant detriment in quality of life and adversely affect the function of multiple organ systems' (Nieschlag et al, 2005). Recommendations regarding its investigation, treatment and monitoring have been issued by the International Society for Andrology, International Society for the Study of the Ageing Male and European Association for Urology (Nieschlag et al, 2005). This terminology has now superseded such terms as the andropause and ADAM (androgen deficiency of the aging male).

TRT increases bone mineral density, muscle strength, lean body mass, libido and sexual satisfaction, decreases body fat and improves serum lipid profiles in older men in clinical studies (Jockenhövel, 2004). It is, however, essential that biochemical confirmation supports clinical symptoms of late-onset hypogonadism. According to the US National Institute of Aging, studies conducted to date have been too small to address potential long-term adverse effects, and there are risks in extrapolating benefit from epidemiological studies in light of the lack of correlation between such data and the outcomes of clinical trials of hormone replacement therapy in women (Advisory Panel on Testosterone Replacement in Men, 2001). The National Institute of Aging therefore recommends the urgent initiation of large, placebo-controlled clinical trials of TRT lasting 3–5 years and including frail men aged over 75 years, as well as healthy men aged 50–75 years who are currently the more likely recipients of TRT for late-onset hypogonadism.

Finally, the results of small pilot clinical trials suggest that in future TRT may help to improve some cardiovascular risk factors and symptoms in testosterone-deficient men with angina (English et al, 2000; Malkin et al, 2004), congestive cardiac failure (Pugh et al, 2004;

KEY POINTS

- Hypogonadism is a clinical syndrome complex consisting of the presence of symptoms, with or without signs, and biochemical confirmation of testosterone deficiency.
- Hypogonadism is under-diagnosed, and hypogonadal men may present in a range of hospital specialties and in general practice.
- Symptoms depend on the age at which hypogonadism develops.
- There are at present international but no UK guidelines; however, symptomatic men with total testosterone levels of 8–12 nmol/litre may be hypogonadal and require further evaluation.
- Men with suspected or confirmed hypogonadism should be referred to an endocrinologist or other appropriately trained clinician for treatment and follow up.
- New formulations of testosterone replacement therapy are more convenient to administer and enable replacement of testosterone so that it closely approximates to physiological levels.

Malkin et al, 2006) and type 2 diabetes (Kapoor et al, 2005, 2006). Other studies indicate that TRT may also be a useful adjuvant treatment for hypogonadal men with refractory depression (Pope et al, 2003), Parkinson's disease (Okun et al, 2002), HIV (Bhasin et al, 2000), and erectile dysfunction unresponsive to phosphodiesterase-5 inhibitors alone (Shabsigh et al, 2004). Larger and longer-term studies are needed before testosterone is used specifically for these conditions. However, TRT is indicated for the treatment of hypogonadism in the absence of contraindications.

Conclusions

Improved TRT preparations have enabled the replacement of testosterone more closely mimicking normal physiological levels in hypogonadal men. The lack of specificity of the presenting symptoms of hypogonadism may not direct the clinician to measure testosterone levels. A greater awareness of the possibility that men may have hypogonadism should increase the diagnosis of men suffering with this condition. Once a diagnosis is made or suspected the patient should be referred to an endocrinologist or appropriately trained clinician for treatment and follow up. The lack of long-term data in relation to the association of hypogonadism with ageing and co-morbid states means that clinicians must provide patients with an unbiased account of the possible risks and benefits of TRT, so that men make a truly informed decision before committing themselves to long-term hormonal therapy. **BJHM**

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