Male Hypogonadism or Testosterone Deficiency Syndrome: Implications and Management

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Introduction

Male hypogonadism is a condition characterised by subnormal levels of circulating testosterone. It can affect multiple organ systems and have a negative impact on quality of life.[1] The diagnosis of hypogonadism, or testosterone deficiency syndrome (TDS), is based on clinical symptoms and confirmed with biochemical tests.

It is becoming more widely recognised that many men will develop testosterone deficiency syndrome, also known as late onset hypogonadism (LOH) simply as a result of advancing age.[2]

The World Health Organization estimates that by 2025, worldwide, the number of people aged over 65 years will rise from the current figure of 390 million to 800 million.[3] Men who are aged 80 today can expect to live until they are 87,[4] and this means that the incidence of LOH or TDS can be expected to rise. These days we expect quality of life to continue in old age. For men, quality of life is dependent on the ability to remain active, both physically and mentally, and also on their general health. Testosterone is intimately involved not only in sexual function, but also in energy, physical strength, mood, cognition and maintenance of bone mineral density. When testosterone levels are low, all these attributes are altered,[1] resulting in:

- Diminished sexual function, including desire, libido and erectile quality;
- Lethargy, fatigue and sleep disturbances;
- Changes in mood – for example, depression and irritability;
- Decreases in intellectual activity, cognitive function and spatial orientation;
- Increases in abdominal fat and decreases in lean body mass;
- Decreased body hair;
- Decreased bone mineral density, leading to osteopenia, osteoporosis and increased risk of fractures.[1]

In addition, there is a growing body of evidence to suggest that low testosterone levels are associated with an increased risk of developing erectile dysfunction, obesity, type 2 diabetes and cardiovascular disease.[5-9]

A greater awareness of the clinical signs and symptoms of TDS appears to be warranted; however, neither the signs nor symptoms of testosterone deficiency alone are sufficiently conclusive on which to base a clinical diagnosis of TDS, which should be confirmed by biochemical tests documenting consistently low circulating testosterone levels.[10]

Reference values for total and free testosterone[1]

- Normal total testosterone range: 12-40nmol/l
- Intermediate testosterone range: 8-12nmol/l
- Low testosterone: <8nmol/l

- Free testosterone > 0.25nmol/l (250pmol/l) = normal
- Free testosterone <0.18nmol/l (18pmol/l) = low

Prevalence

The signs and symptoms of TDS are often non-specific, or may be ascribed to other conditions, or simply put down to the effects of aging. This may explain why this condition is not diagnosed more often: indeed, it has been described as *"one of the most frequent but also most underdiagnosed endocrinopathies"*.[11]

Estimates of the prevalence of testosterone deficiency vary considerably. It is thought that about five men per 1000 in the UK may be hypogonadal (including those with primary hypogonadism associated with inadequate testicular function).[12] However, the recent European Male Ageing Study (EMAS) suggests that late onset TDS may affect 0.7% of men over the age of 40 years and up to 9.1% of men aged 70-79 years.[13]

The ongoing study has so far collected data from 3369 ageing men in eight European countries on 12 symptoms typical of TDS, together with morning total testosterone and calculated free testosterone. Four symptom domains correlated closely with low testosterone levels:

- Sexual function symptoms (especially the absence of morning erections)
- Decreased physical activity
- Fatigue
- Poor concentration.[13]

These clinical features may therefore help to identify candidates for further investigation or intervention.[13]

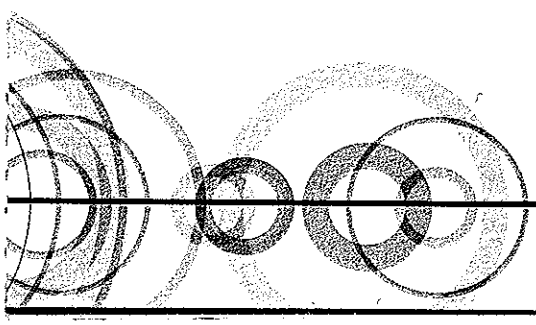
While overall prevalence is difficult to determine, data from the Massachusetts Male ageing Study (MMAS) indicate that the proportion of men with late onset TDS is increasing.[14] Among patients who present with erectile dysfunction (ED), the prevalence of hypogonadism is 18–37%,[5,6,15,16] (this range varies according to whether total or free testosterone levels are measured). Among men with diabetes, one study has shown that 16% have total testosterone <7.5 nmol/l, and approximately 50% had total testosterone <12 nmol/l.[17] A meta-analysis by Ding et al confirmed that men with type 2 diabetes had significantly lower levels of total testosterone than non-diabetic controls (mean difference -2.66nmol/l).[18]

Decline of testosterone levels with age

A declining level of testosterone is significant because of its ubiquitous role in male physiology: it regulates gonadal function, and affects libido, mood, muscle mass, liver function, lipid regulation, bone formation, erythropoeisis and immune function.[19]

Approximately 60% of testosterone is firmly bound to sex hormone binding globulin (SHBG), 38% is loosely bound to albumin and 2% is 'free'. Together, albumin-bound testosterone and free testosterone are considered to be bioavailable.

The MMAS revealed that total testosterone declines by 1.6% per year (between baseline and follow-up), while bioavailable testosterone declines more rapidly, by 2 – 3% per year.[19] (Figure 1.) This is important because, if men live long enough, their testosterone levels are likely to fall to within the hypogonadal range.



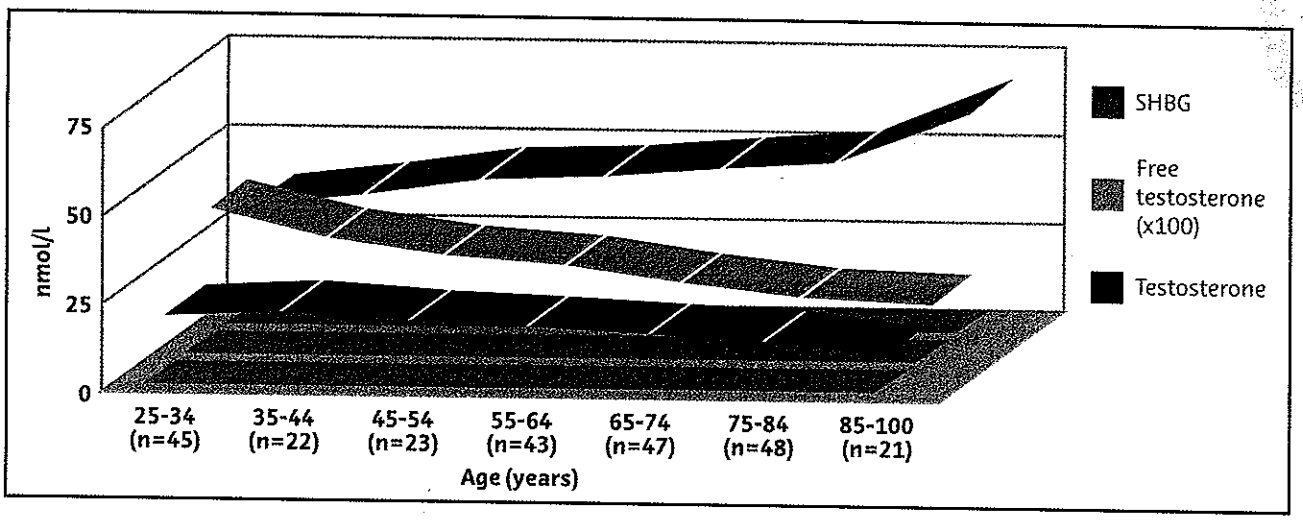


Figure 1. **Rising sex hormone binding globulin (SHBG) and declining free and total testosterone with increasing age.[20]**

Testosterone and mortality

For the first time there is evidence that men with low testosterone levels (<8.7nmol/l) do not live as long as those with normal testosterone levels. This important study showed a strong correlation between low testosterone and significantly increased mortality in men over the age of 40 years: men with initially low testosterone had survival rates significantly lower, and mortality significantly higher, than men with normal testosterone levels. After adjusting for age and morbidity, including coronary heart disease, chronic obstructive pulmonary disease and other clinical conditions, low testosterone levels were associated with increased mortality. (Figure 2.)Even after excluding men who died within the first year, to minimise the effect of pre-existing or acute illness, low testosterone levels continued to be associated with increased mortality.[21]

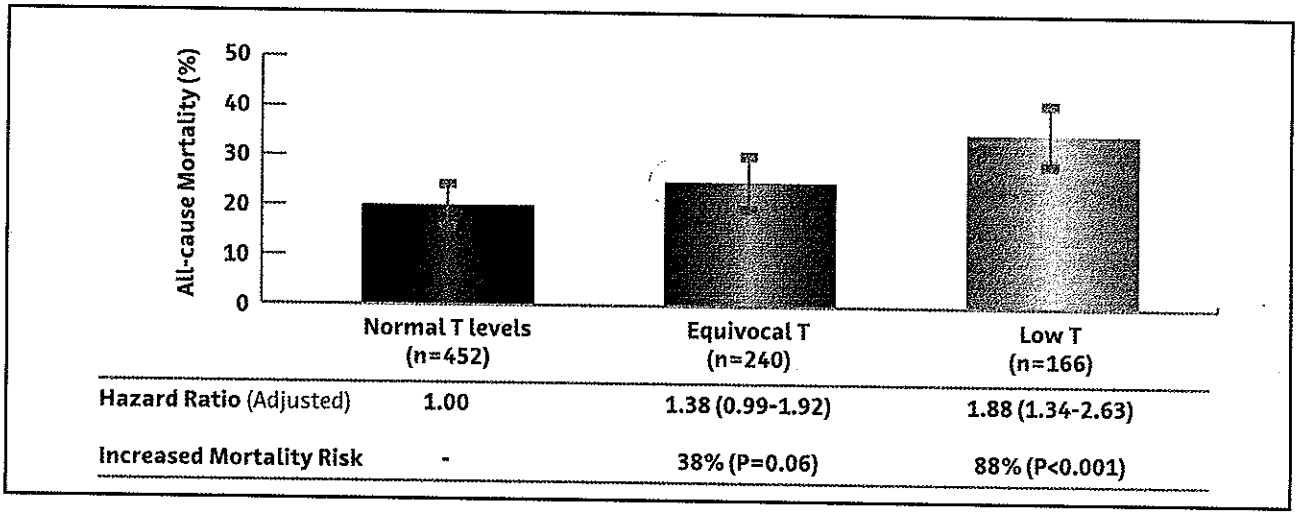


Figure 2. **Relationship between low testosterone and increased mortality risk.[21] Normal testosterone, >8.7nmol/l; equivocal = equal number of low and normal levels; low, <8.7nmol/l.**

Impact of hypogonadism

Sexual function

One of the most frequent reasons for patients with hypogonadism to seek medical advice is because of reduced libido, sexual activity or erectile function. Decreased spontaneous erections, particularly nocturnal and morning erections, can be useful indicators of testosterone deficiency.

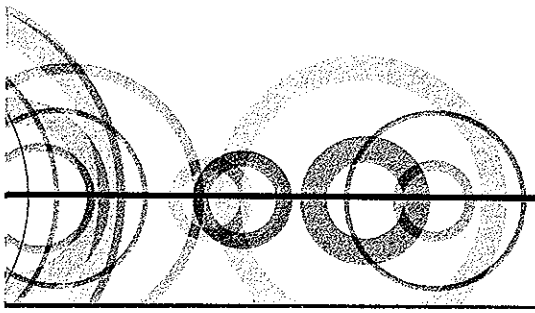
Our current knowledge of testosterone in relation to erectile function is largely based on animal studies, which show that circulating androgens are important mediators of the erectile process, regulating arterial flow and vasodilation. Testosterone also plays a part in regulating nitric oxide synthase, a key modulator of erectile function, and PDE-5 expression and activity.[22] Testosterone also stimulates the central mechanisms of sexual activity, not only libido, but also the transmission of signalling in the spinal cord.[22] A threshold level of testosterone may be necessary for normal erectile function, and because it is involved in the regulation of nitrous oxide synthase, it appears to facilitate the effect of phosphodiesterase type 5 (PDE5)-inhibitors.[23] Approximately 23-50% of men with erectile dysfunction do not respond to PDE5-inhibitors alone.[23] A major risk factor for PDE5-inhibitor failure is hypogonadism. In these patients, the combination of testosterone therapy and a PDE-5 inhibitor has been shown to significantly improve erectile function scores.[24] Improvement in erectile function and libido has also been demonstrated in men with corporal veno-occlusive dysfunction who were treated with long-acting injectable testosterone undecanoate.[25] It is therefore worth investigating all men with ED for testosterone deficiency, especially those who do not respond to PDE5-inhibitors, and populations at increased risk of testosterone deficiency such as those with type 2 diabetes and ED.

Testosterone treatment can result in improvements in sexual function, including sexual performance, motivation, desire and the occurrence of spontaneous erections.[26,27]

Type 2 diabetes

Data from MMAS show that low testosterone is a significant marker for developing type 2 diabetes, and that low SHBG and low testosterone are associated with an increased risk of developing the metabolic syndrome.[28] Studies have also shown that mean testosterone levels are significantly lower (–2.66 nmol/l) in men with type 2 diabetes, than those without[19] and that there is a significant inverse correlation between free testosterone and body mass index (BMI).[29] Populations of men with obesity, type 2 diabetes and hypogonadism show a high degree of overlap: in 2001, the prevalence rate of male obesity represented an estimated 21.4 million people, of whom 6.9 million had type 2 diabetes and 5 million were hypogonadal. (Figure 3).[30]

In addition to restoring erectile function and libido and reducing fatigue, Kapoor and colleagues have recently demonstrated that testosterone therapy reduces insulin resistance and improves glycaemic control in hypogonadal men with type 2 diabetes,[31] and improves metabolic control.[31–33]



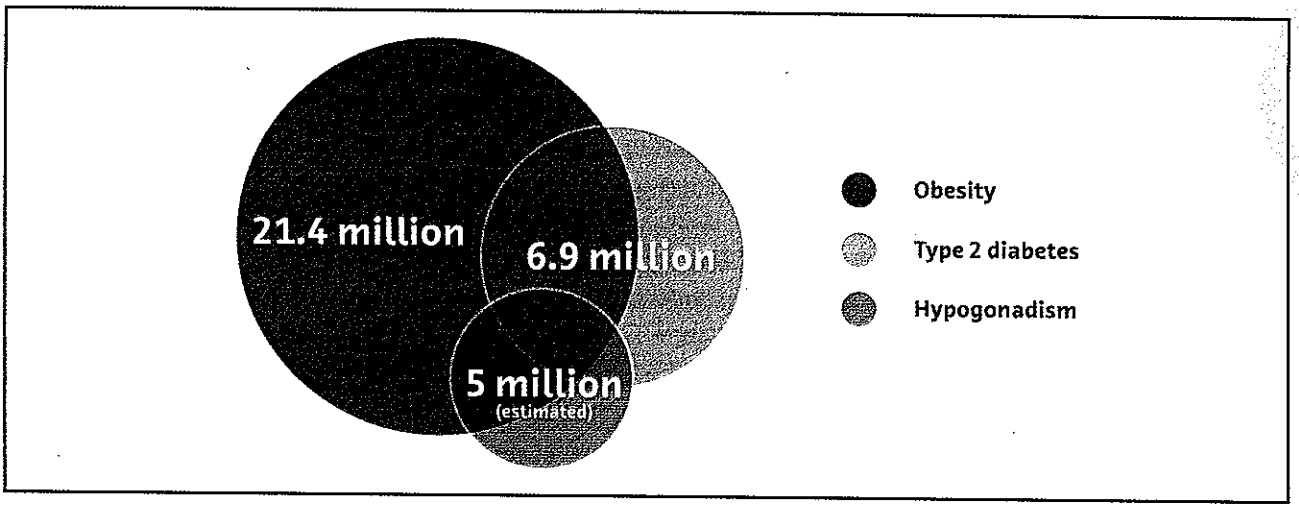


Figure 3. **Populations of men with obesity, type 2 diabetes and hypogonadism show a high degree of overlap. Adapted from Int J Impotence Res 2003;15(Suppl 4):S14-S20.**

Obesity and body composition

An epidemiological study[34] and a study in patients receiving androgen-deprivation therapy for prostate cancer[35] have confirmed the links between testosterone levels and changes in body composition. In the Tromsø study,[34] men with a waist circumference ≥ 102cm had significantly lower levels of total testosterone and SHBG compared with men with an optimal waist circumference of <94cm, (12.3 vs 13.9nmol/l and 48.5 vs 55.1nmol/l, respectively). The lowest levels of total and free testosterone were observed in men with a relatively high waist circumference despite relatively low overall obesity, suggesting that waist circumference may help to predict endogenous testosterone levels.[34]

When men with prostate cancer were given androgen-deprivation therapy, weight, BMI and abdominal subcutaneous fat increased, and percentage lean BMI and muscle size decreased.[35] In contrast, testosterone therapy decreases subcutaneous fat and increases lean muscle mass in men with acquired hypogonadism[36] and decreases visceral fat in obese men with low testosterone levels.[37] Similarly, Dean and colleagues also demonstrated a significant improvement in body composition (increased lean body mass, decreased fat mass and decreased percentage of body fat) with testosterone treatment .[26]

Metabolic syndrome and cardiovascular risk

Low testosterone is associated with the metabolic syndrome (i.e. visceral adiposity, dyslipidaemia and insulin resistance).[9] Conversely, higher total testosterone, bioavailable testosterone and SHBG in aging males are associated with higher insulin sensitivity and reduced risk of the metabolic syndrome, irrespective of insulin and body composition measurements.[9] This is significant in the light of evidence for a substantially increased risk of cardiovascular disease and mortality in men with the metabolic syndrome.[38]

There is also increasing evidence of a strong correlation between hypogonadism and cardiovascular risk. Men with coronary artery disease have lower levels of testosterone than normal controls, challenging the preconception that physiologically high levels of testosterone in men account for their increased relative risk for coronary artery disease.[39] The South Yorkshire Prevalence Study found that nearly a quarter of men presenting for coronary angiography had testosterone levels in the low hypogonadal range, and that about 50% had a total testosterone level <11nmol/l.[39]

Androgen deficiency and fracture risk

Testosterone stimulates bone formation and inhibits bone resorption through multiple mechanisms involving both androgen and oestrogen-receptor mediated processes. A study in more than 50,000 men 66 years or older with a diagnosis of prostate cancer, in whom one group was treated with androgen deprivation, and the other was not, found a significantly increased risk of fracture in the former.[40] Of those men surviving at least 5 years after diagnosis, 19.4% in the androgen-deprived group suffered a fracture, compared with 12.6% in those who were not androgen-deprived (P=<0.001). Furthermore, this study found that the risk of fracture increased with increasing duration of androgen deprivation, suggesting a dose effect.[40]

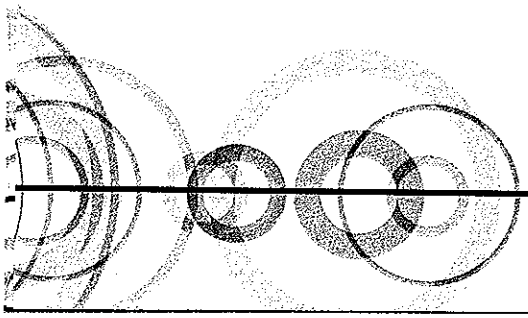
There is a growing body of evidence to support the hypothesis that testosterone therapy improves bone mineral density in hypogonadal men, especially in the spine.[41] This improvement, noticeable after 6 months, persisted in the longer-term (3 years follow-up).[41] Behre et al[42] found that the greatest improvement in BMD was seen in the first year of testosterone therapy but was maintained for the duration of treatment (up to 16 years).

In a study in adult males with acquired hypogonadism, testosterone therapy increased spinal BMD by 5% (+/-1%) and trabecular BMD by 14% (+/-3%). Markers of bone formation and resorption decreased significantly over the 18-month duration of the study. In addition, there was a decrease in body fat (14%), subcutaneous fat (13%) and an increase in lean muscle mass (7%).[36]

Improvement in BMD can be achieved with a variety of testosterone formulations, not only quantitatively but qualitatively. Benito and colleagues[43] demonstrated that testosterone therapy (using a gel formulation [Androgel®/Testogel®]) for 24 months resulted in improvements in trabecular architecture, measured by magnetic resonance microimaging, as well as in BMD at the spine (7.4%) and total hip (3.8%). In a 12-month study, testosterone therapy-treated hypogonadal men were found to have a 2.58% increase in BMD at 12 months; greater than the increase observed at 6 months, indicating ongoing repletion of BMD with continuing treatment.[26]

Cognitive function

In healthy men the ability to perform tasks related to spatial cognition is strongly associated with testosterone levels. In hypogonadal men, this ability is reduced. Studies have shown that the administration of testosterone to hypogonadal men enhances glucose metabolism in the areas of the brain that are involved in processing spatial data. Furthermore, in tests measuring visuospatial ability, verbal fluency, perceptual speed and verbal memory, hypogonadal men performed less well than eugonadal men, and that verbal fluency improved following testosterone treatment. These findings support the hypothesis that testosterone levels influence cognitive function.[45]



Potential adverse effects of testosterone treatment

The main concern for clinicians treating men with LOH is that testosterone supplementation will turn an occult prostate cancer into clinically apparent disease. Challenging this well-established paradigm is the observation that the prevalence of prostate cancer in men receiving testosterone therapy is approximately 1%, similar to the prevalence in the general population, and prostate cancer becomes more prevalent at the time of life when testosterone levels decline, rather than when they are at their peak at a younger age.[46] The existence of known or suspected prostate (or breast) cancer remains an absolute contraindication for testosterone therapies.[1] Although androgen-deprivation therapy is the mainstay of treatment for prostate cancer, testosterone therapy *per se* may not be as deleterious to prostate health as previously thought.[47] In clinical trials testosterone therapy has been associated with modest increases in prostate-specific antigen (PSA), but there is no incontrovertible evidence that testosterone therapy causes prostate cancer or benign prostatic hypertrophy.[1] Testosterone therapy in hypogonadal men has been shown to increase prostate volume to a level equivalent to that of men without hypogonadism, but this is not inevitably associated with voiding symptoms.[46]

It is important to note, however, that in the absence of long term data, all patients receiving testosterone therapy should be monitored regularly for changes in PSA, prostate volume and the development, or an exacerbation, of voiding symptoms.[1,46] The International Society for the Study of the Aging Male (ISSAM) recommends baseline measurement of PSA and digital rectal examination (DRE) before initiation of testosterone therapy, at 3-monthly intervals for the first year of treatment, and 12-monthly thereafter.[1]

Regular monitoring of PSA levels and DRE should help to ensure the early diagnosis of most 'unmasked' prostate cancers.[1,46]

Table 1. Potential effects of testosterone therapy, adapted from Rhoden & Morgentaler, N Engl J Med 2004[46]

Effect	Incidence	Action
Lipid alterations	Most studies show no change with replacement doses within normal physiological range	
Erythrocytosis	Wide range of risk dependent on dose and mode of administration	Monitor haematocrit and haemoglobin levels
Benign prostatic hyperplasia	Rarely of clinical significance	Determine voiding history at baseline and monitor urinary symptoms at subsequent reviews
Hepatotoxicity	Associated primarily with long-term administration of methyltestosterone, no longer in routine use	Perform liver function tests in accordance with recommendations in SPC
Sleep apnoea	Infrequent	In patients with pre-existing sleep apneoa, use testosterone therapy with caution
Gynaecomastia	Rare	Usually reversible
Skin reactions	Up to 66% with patch, 5% with gel, rare with injections	
Acne or oily skin	Infrequent	Usually reversible
Testicular atrophy, infertility	Common, especially in young men	Usually reversible on cessation of treatment

Table 2: Pre-referral pathway (general practice/primary care)

Patient presents with symptoms

Erectile dysfunction
Loss of libido
Fatigue, reduced feeling of well-being, depression, loss of concentration, sweats/hot flushes, unexplained anaemia, reduced muscle mass, reduced body hair

General history
Duration of symptoms
Social History (relationships, alchohol, smoking)

Past medical history
Previous testicular injury
Previous head injury
Headache ± visual disturbance
Any chronic illnesses

Drug history
Prescription drugs: eg. ß-blockers, corticosteroids, anticonvulsants
Any 'alternative' remedies?
Any drug abuse?

Physical examination
General physical exam
BMI / Waist circumference
Tesicular size/consistency
Secondary sexual hair
Visual fields

Measure serum testosterone levels between 8-10am

Testosterone >12nmol/l
Consider other diagnoses including psychosexual dysfunction

Testosterone ≤12nmol/l
Further tests
Repeat early morning testosterone level plus
Luteinizing hormone (LH)
Follicle stimulating hormone (FSH)
Prolactin
Sex hormone binding globulin (SHBG)

Normal levels
Testosterone (>12nmol/l)
Prolactin
SHBG
FSH/LH

Testosterone 8-12nmol/l and normal levels of
Prolactin
SHBG
FSH/LH

Testosterone 8-12nmol/l
Raised prolactin
Raised SHBG
or FSH/LH
low or high

Testosterone <8nmol/l

Repeat tests
Consider referral if persistent and symptomatic for hypogonadism

Refer to endocrinologist/urologist

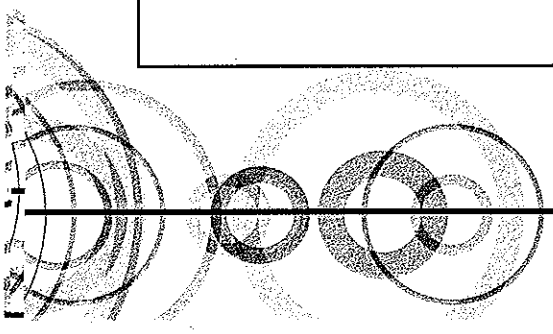
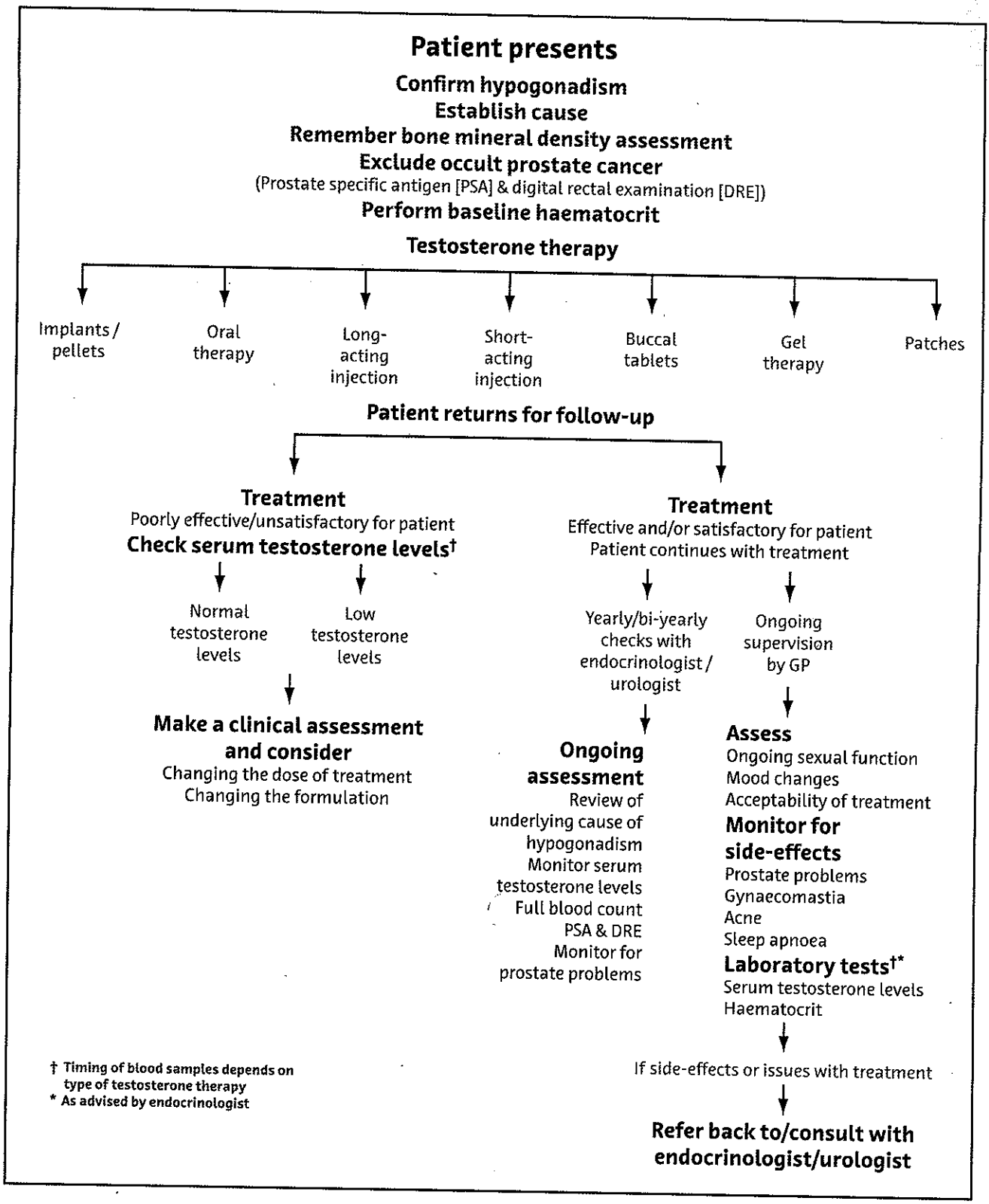


Table 3: Post-referral treatment pathway (specialist/secondary care)



Treatment options

The goal of testosterone replacement therapy is to restore 'normal' physiological testosterone levels during treatment, without inducing peaks and troughs in serum testosterone concentration, which patients experience as mood swings, and variability in energy, libido and sexual function.[1] Additional – and equally important – goals are to alleviate symptoms of testosterone deficiency, to induce or restore physiological functions, and to prevent the long-term health risks of testosterone deficiency.[1] A number of different formulations and methods of application/administration are available, and patients should be provided with sufficient information to enable them to make an informed decision on the choice of suitable therapy. The table opposite summarises currently available preparations:

Clinical experience with long-acting injectable testosterone

Treatment for testosterone deficiency syndrome is likely to need to be continued for a period of years rather than months, and therefore patient satisfaction and adherence are important.

In a recent study in 96 hypogonadal men receiving treatment with long-acting injectable testosterone undecanoate (Nebido®), 92% of patients were satisfied with the treatment.[48][Figure 4]

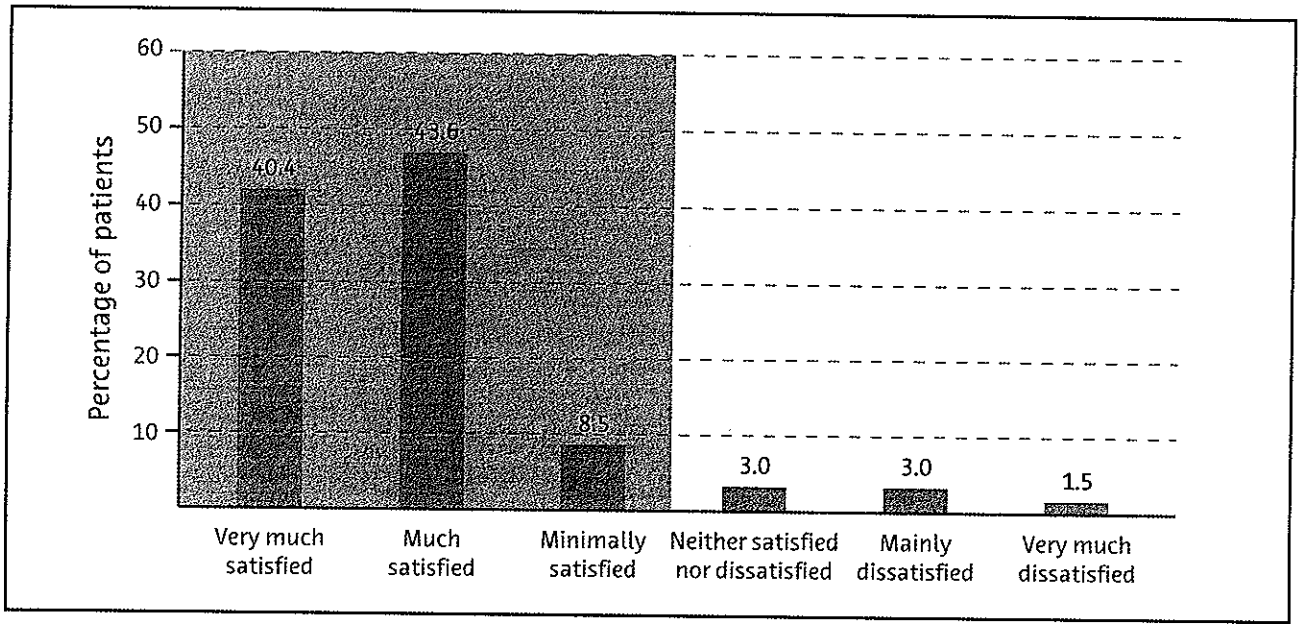


Figure 4. An open-label, prospective, single-arm, multicentre study involving 96 hypogonadal men who received six injections of long-acting testosterone undecanoate showed that 92% were satisfied with their treatment.[48]

This study was an open-label, prospective study to evaluate long-acting injectable testosterone for the treatment of hypogonadal men under conditions resembling real-life clinical practice as closely as possible (ie, variable injection intervals and minimal patient selection).[48] Subjects were men aged 18 – 75 years, with total testosterone levels <10 nmol/l and with no contraindications to testosterone therapy. Following an initial dose of 1000mg long-acting injectable testosterone undecanoate, a second loading dose was administered at 6 – 10 weeks, followed by maintenance doses at 10 – 14 week intervals. Trough concentrations of total testosterone (considered an indicator of the adequacy of substitution) increased from 5.6 ± 3.03 nmol/l at baseline to levels between 9.79 ± 3.96 and 14.02 ± 6.06 nmol/l over the course of treatment.[48] Mean PSA serum concentration increased moderately from 0.81 ± 0.80 ng/ml at baseline to 1.23 ± 1.33 ng/ml after the 6th injection. Assessment of the intensity of androgen deficiency symptoms (using the Aging Males Symptom rating scale[49]) revealed an improvement in the score for sexual symptoms from 13.2 ± 5.0 before treatment to 8.2 ± 3.3 at the end of the study.[48]

Table 4: Treatment options for testosterone deficiency syndrome

Testosterone preparation			Features	Considerations
Long-acting injection	**Nebido®** Bayer Schering Pharma 1000mg every 10-14 weeks	Testosterone (T) undecanoate	Physiological pharmacokinetic profile Infrequent dosing (Approximately 4 injections per year to maintain physiological testosterone levels)	Injection site reactions
Short-acting injections of testosterone [T] esters in oily solution	**Sustanon®** Organon 100mg, 250mg every 2-3 weeks	T propionate, T phenyl-propionate, T isocap-roate, T decanoate (250mg only)	Inexpensive and widely used	Injection site reactions 2-3 weekly injections Fluctuating testosterone levels between injections outside physiological range
	Testosterone enanthate Cambridge Laboratories 250mg every 2-3 weeks	T enanthate		
	Virormone® Ferring 50mg, 2-3 times a week	T propionate		2-3 injections per week
Patches	**Andropatch®** GSK 2.5mg, 5mg once daily to unbroken skin on back, abdomen, upper arms or thighs	Testosterone	Non-invasive, Physio-logical pharmacokinetic profile, once daily administration mimics natural diurnal variation in testosterone levels	Skin irritation New application site every 24 hours
Implants / pellets	Testosterone implant non-proprietary, Organon 100mg, 200mg 2-3 pellets, every 4-5 months	Testosterone	Physiological pharmacokinetic profile, Long-acting (4-5 months)	Insertion (subcutaneously under local anaesthetic) Extrusions occur in 5% of patients Risk of infection Possible scarring
Oral (capsules)	**Restandol®** Organon 40mg (dose: 1-3 capsules a day)	Testosterone undecanoate	Oral administration	Low bioavailability Variable testosterone levels Administration with dietary fat recommended
Buccal (mucoadhesive tablets)	**Striant®** Ardana 30mg (twice a day)	Testosterone.	Buccal delivery achieves physiological pharmacokinetics	Twice daily dosing Tablet can become dislodged
Gels	**Testogel®** Bayer Schering Pharma 1% gel in 5g sachets (dose: 5-10g per day)	Testosterone	User friendly Physiological pharmacokinetic profile High patient compliance	Daily application Testosterone transfer to partner
	Testim® Ipsen			
	Tostran® ProStrakan 2% gel in metered dose canister (60g) (dose: 3g once daily)			

Clinicians should refer to the summary of product characteristics for each individual product before prescribing

Schubert et al[50] have also demonstrated that long-acting injectable testosterone undecanoate provides consistent testosterone therapy that maintains trough serum total testosterone levels within the physiological range. This open-label, active-controlled, randomised prospective trial compared the pharmacokinetic profile of long-acting injectable testosterone undecanoate with that of testosterone enanthate. Injecting a dose of 1000mg long-acting injectable testosterone at 10 – 14 week intervals was found to be sufficient to maintain normal testosterone levels in hypogonadal men without causing frequent oscillations outside the physiological range in serum testosterone levels, as observed with short-acting testosterone injections.[50]

The treatment was well tolerated with few adverse events or changes in clinical laboratory parameters.[50] In other studies, testosterone undecanoate did not result in clinically significant increases in PSA in any patients.[51] There may be some concerns about the injection volume of 4ml, but during this two-year study, local adverse side effects at injection site were not significant, and none of the patients expressed any complaints.[50] The long-acting preparation with a 4 ml volume was as well tolerated as the testosterone enanthate injection with a smaller volume.[50] None of the patients opted to switch back to testosterone enanthate during the follow-up period.[50]

A more recent study supports the finding that after an initial dose followed by a second loading dose after 6 weeks, only four injections a year are required (once on stable maintenance treatment). This regimen might therefore be attractive for men requiring permanent testosterone therapy.[48]

Conclusion

Testosterone plays an essential part in the regulation of sexual function, body composition and bone metabolism in men,[1] and has been shown to decline with age.[2] Testosterone deficiency syndrome is becoming more prevalent with our aging population,[14] and we are beginning to understand more fully that this not only has a significant impact on quality of life, but that it is also associated with increased risk of developing erectile dysfunction, obesity, type 2 diabetes, and cardiovascular disease.[5-9] Thus, a higher index of suspicion for hypogonadal signs and symptoms in ED and type 2 diabetes patients groups may be justified. The diagnosis should be confirmed by measuring morning serum testosterone levels.

A wide range of testosterone formulations are available, including gels, patches, oral, implants and injections. Currently, short-acting injectable testosterone is the most frequently used preparation for testosterone therapy in hypogonadal men, requiring injections at 3-weekly intervals (approximately 17 injections per year). Testosterone undecanoate (Nebido®) is a longer acting formulation that requires less frequent injections (approximately four a year to maintain physiological testosterone levels) and so may be a useful option for some patients.[48]

Testosterone therapy has been shown conclusively to improve the symptoms of hypogonadism, or as it is now known, testosterone deficiency syndrome. With the variety of preparations now available, clinicians have a genuine choice enabling them to select the most appropriate treatment for the individual patient.