How real is the male menopause?

- What exactly is the 'male menopause'?
- How can it be recognised in practice?
- What is the place for testosterone supplementation?

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The popular term 'male menopause' is a misnomer: men do not experience a relatively sudden cessation of a monthly event. What men do suffer is a steady decline in total testosterone levels from approximately the age of 30 years (see figure 2). 'Andropause' is now a commonly used term for symptoms arising from this, although some authorities prefer 'androgen deficiency in the ageing male' (ADAM).

Whether or not this decline is clinically evident is dependent upon the degree to which testosterone falls in this process, and the sensitivity of the individual to the hormone.[1] The syndrome associated with a low testosterone level (hypotestosteronaemia) has been recognised for as long as castration has been practised, and was first studied in the 1850s.

However, only within the last 20 years, since the introduction of reliable laboratory serum assays, has it been possible to evaluate testosterone levels accurately. We now have a clear knowledge of the range of testosterone levels found

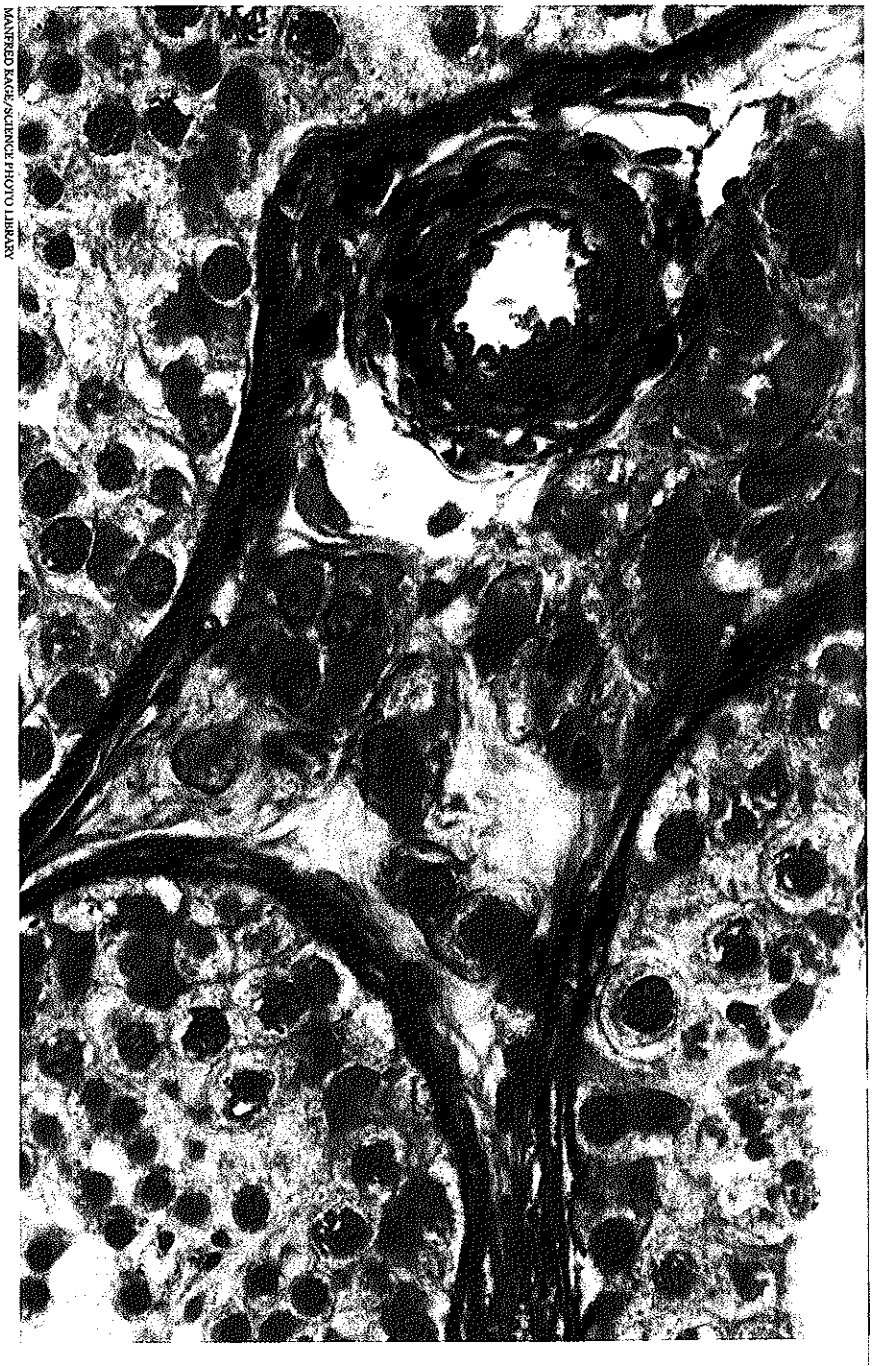

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Figure 1 Light microscopy image of Leydig cells. Declining Leydig cell mass is only one factor in falling testosterone levels with age

in any particular age group[2] (see table 1).

It has been proposed that the prevalence of symptoms attributable to low testosterone is as high as 50 per cent of men over the age of 50 years.[3] It has been famously reported that between four and five million American men are afflicted.[4,5]

•Aetiology The cause of falling testosterone levels with age is multifactorial: there is a decline in Leydig cell mass, dysfunction of hypothalamic-pituitary homeostatic control, low luteinising hormone secretion and loss of circadian rhythm.[6]

Superimposed upon these manifestations is the age-related rise in sex hormone binding globulin (SHBG) synthesised in the liver.[7] Of total testosterone in the blood, most is fixed to SHBG and therefore inert. In consequence the 1–2 per cent of bio-available free testosterone is progressively eroded by ageing.[8]

Testosterone and free testosterone levels are sensitive to a wide range of other aetiological factors. Testicular trauma, orchitis, vasectomy, cryptorchidism and orchidopexy, childhood herniorrhaphy, haemochromatosis, physical and psychological stress, obesity, prolactinoma, chemotherapy, radiotherapy, alcohol abuse, poor nutrition and chronic disease can all adversely affect testosterone levels.

SHBG levels are raised in liver disease, including metastases, in alcohol abuse through raised oestrogen levels, and in thyrotoxicosis. However, it is estimated that the cause of 60 per cent of hypotestosteronaemia and 30 per cent of high SHBG levels is hereditary.[9]

•Clinical features Testosterone is known to have powerful psychological, anabolic and vasodilatory effects. Presentations of hypotestosteronaemia are therefore highly variable (see table 2). The single most common presenting symptom is erectile dysfunction: difficulty achieving and maintaining erections during sexual intercourse. Early morning and nocturnal erections can be preserved.

Overt signs of a low testosterone level are few and occasional: the testes can be atrophic; facial hair can be sparse; central adiposity and loss of muscle mass can be evident; the penis can be reduced in size; pallor can be noticeable; and the skin can be dry and thin.

Secondary sexual characteristics, once established, are not affected by falling testosterone levels.

•Diagnosis As so much depends on symptomatology in the diagnosis of the condition, it is imperative that an accurate history is elicited. Embarrassment can make this surprisingly difficult. Unless the clinician is attuned to the variability of the symptoms, it is only too easy to miss the significance of what the patient is trying to express. ▶

Clinical focus

- **Testosterone has powerful psychological, anabolic and vasodilatory effects. Presentations of hypotestosteronaemia are therefore highly variable. The single most common presenting symptom is erectile dysfunction: difficulty achieving and maintaining erections during sexual intercourse. Early morning erections may be preserved**
- **Overt signs of a low testosterone level are few and occasional: the testes can be atrophic; facial hair can be sparse; central adiposity and loss of muscle mass can be evident; the penis can be reduced in size; pallor can be noticeable; and the skin can be dry and thin. Secondary sexual characteristics, once established, are not affected by falling testosterone levels**
- **Essential to the diagnosis is a demonstrably low testosterone level. The reference range for testosterone varies from laboratory to laboratory, and is in itself of little value to the clinician. Ideally the clinician should consult an authoritative table of mean sex hormone levels in healthy men; otherwise it can be reasonably assumed that a testosterone level below a level of around 15nmol/L is of significance. Before age 40, circadian rhythmicity is still evident, and the average of early morning and late afternoon testosterone levels should be taken**
- **Low testosterone levels have been shown to be a risk factor for coronary atherosclerosis and myocardial infarction through disturbance of the clotting mechanism and blood fats. Low testosterone levels are also associated with other risk factors, such as type 2 diabetes, obesity and hypertension**
- **Andropausal men are particularly vulnerable, requiring a sympathetic approach in order to create the trust necessary for effective long-term treatment. Having established a working diagnosis (often unsupported by overt clinical signs), it is necessary to choose a suitable testosterone replacement regime. The success of supplementation can only be measured by improvement in symptoms. The aim should be to obtain a constant serum testosterone level that alleviates symptoms but does not exceed physiological norms for the patient's age**

A full examination should be made, and investigations must include urinalysis, haematology, biochemistry, prolactin, total testosterone, SHBG, PSA and, if considered appropriate, T4 and TSH. LH and FSH levels have little clinical import.[10]

Results that may be significant are a low red cell count and/or a low haemoglobin level;[11,12] also high fasting cholesterol and/or LDL cholesterol; or a high prolactin level, (which can be indicative of a prolactinoma).

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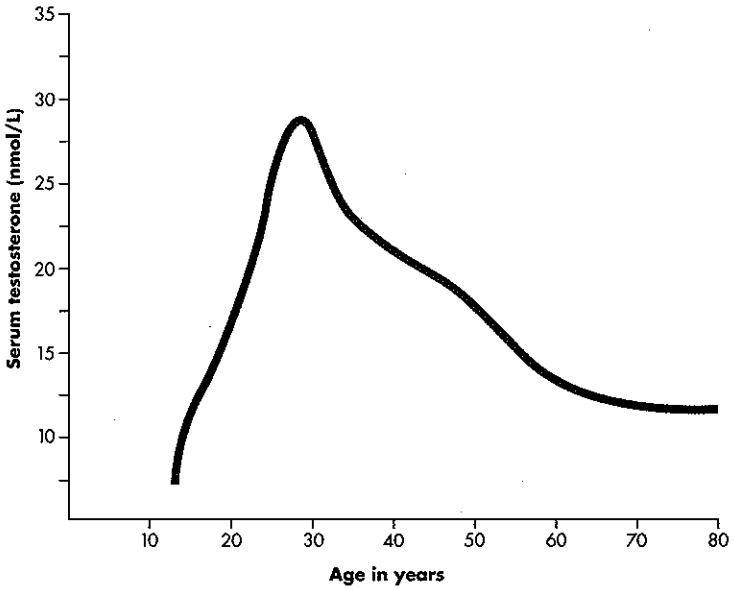
Before age 40, circadian rhythmicity is still evident, and the average of early morning and late afternoon testosterone levels should be taken.[14]

A higher than average level of SHBG is an important finding and should be further investigated (see above). This also applies to disturbed liver enzymes as liver disease and haemochromatosis must be excluded (a serum ferritin level is essential).

•The significance of low testosterone levels Low testosterone levels have been shown to be a risk factor for coronary atherosclerosis and myocardial infarction through disturbance of the clotting mechanism and blood fats.[15] Low testosterone levels are also associated with other risk factors, such as type 2 diabetes, obesity and hypertension.[15]

In older men, cavernosal artery stenosis can be a cause of erectile dysfunction. As there is a direct correlation between cavernosal and coronary artery stenosis, it is important to consider the differential diagnosis in the presence of erectile dysfunction.

Figure 2 Median serum testosterone in relation to age (adapted from Schmidt H[26])



Low free testosterone levels are positively correlated to osteoporosis and there is an increased risk of hip fracture.[16]

Haemochromatosis is a potentially fatal disease that often presents as hypotestosteronaemia due to testicular damage by ferritin.

Evidence is emerging that the supplementation of low testosterone levels could be protective against Alzheimer's disease.[17]

Loss of libido and sexual potency can obviously have disastrous effects on interpersonal relationships. Affective symptoms, lack of energy, irritability and fatigue can all adversely affect work performance and home life.[18]

Through loss of muscle mass and strength and increased fatiguability, athletic performance is affected. Low testosterone levels are also associated with deterioration in hand to eye co-ordination and balance.[19]

Poor concentration and short-term memory are frequent features of the reduced cognitive function associated with low testosterone, which may exacerbate feelings of inadequacy and frustration.[20]

The wide diversity of symptoms evidenced gives rise inevitably to diagnostic confusion. Patients are often inappropriately referred to psychiatric departments, and to counselling services. Arterial disease can be overlooked along with a multiplicity of iatrogenic causes, especially those associated with hypotensive agents and antidepressants.

'Low testosterone levels are a risk factor for atherosclerosis and MI'

In the older man frailty exacerbated by low testosterone levels must be the major concern. This may lead to loss of independence, chronic disability and a need for

assisted living or long-term care and an increase in mortality.[14]

●Management Many GPs will not appreciate the clinical significance of testosterone deficiency and therefore it is an under-diagnosed condition. Nevertheless, as with the female menopause, it is eminently treatable within the primary care setting, and as the management of male hypogonadism is relatively straightforward it would seem inappropriate to refer andropausal men to a specialist endocrine clinic.

Andropausal men are particularly vulnerable, requiring a sympathetic approach in order to create the trust necessary for effective long-term treatment.

Having established a working diagnosis (often unsupported by overt clinical signs), it is necessary to choose a suitable testosterone replacement regime. The success of supplementation can only be measured by improvement in symptoms. The aim should be to obtain a constant serum testosterone level that alleviates symptoms but does not exceed physiological norms for the patient's age.

The preparations available for treating low testosterone levels are:

- Testosterone undecanoate capsules;
- Testosterone esters injections;
- Testosterone patches; and
- Testosterone pellets for implantation.[21]

All have their advantages and disadvantages for both the patient and the clinician. Personal experience has shown that testosterone supplementation by implant provides the best control of serum levels and obviates any problems of patient compliance. A degree of skill in administration is required, however.

Meticulous follow-up is imperative. Testosterone levels should be estimated at appropriate intervals to enable the dose to be adjusted.

Occasionally polycythaemia can become evident, which may require on-going venesection. Haemoglobin levels should therefore be checked at least annually, and more frequently if the pre-treatment haemoglobin is in the upper quartile of the normal range.[22]

Although testosterone supplementation has not been shown to be a cause of carcinoma of the prostate,[23] it is essential that testosterone supplementation be stopped if this arises coincidentally. PSA levels must therefore be checked at least annually, and more often if the pre-treatment level is in the upper quartile of the normal range. Clinicians are recommended to follow the WHO guidelines.[24]

'The diversity of symptoms inevitably gives rise to diagnostic confusion'

Advice should be offered on adjustment of lifestyle, which obviously includes management of stress and workload, adjustment of alcohol intake and other substances of abuse, and attention to diet, especially in the overweight or obese.

Referral to a qualified sex therapist should be considered if issues such as taboos, lack of arousal, misconceptions or simply boredom within a sexual relationship are evident.

●Recent developments Sildenafil is mistakenly conceived by many to be the panacea for erectile dysfunction. It is often a surprise to both the clinician and the patient that it is frequently ineffective.

However, we have demonstrated that the efficacy of sildenafil is directly related to testosterone levels: a low testosterone level has been shown to have a negative effect on the production of nitric oxide (NO),[25] the neurotransmitter that initiates dilatation of the sinusoids within the corpora cavernosa in response to arousal stimuli. It is this vasodilatation that facilitates the engorgement of erectile tissue. Sildenafil inhibits the breakdown of NO by phosphodiesterase-5 thus allowing NO to accumulate with resultant improvement in erectile function. Consequently, should the production of NO be critically low due to testosterone deficiency, sildenafil will not work.

Conversely, given an enhanced testosterone level and consequent improved availability of NO, sildenafil works optimally, and, indeed, is an excellent adjunct in overcoming performance-related anxiety during the first months of testosterone supplementation.

A recent introduction in the USA has been the testosterone gel Androgel, a transdermal preparation that has yet to be licensed in the UK or Europe. It is expensive and personal observation indicates that it may not succeed in elevating testosterone levels sufficiently to alleviate symptoms reliably. ▶

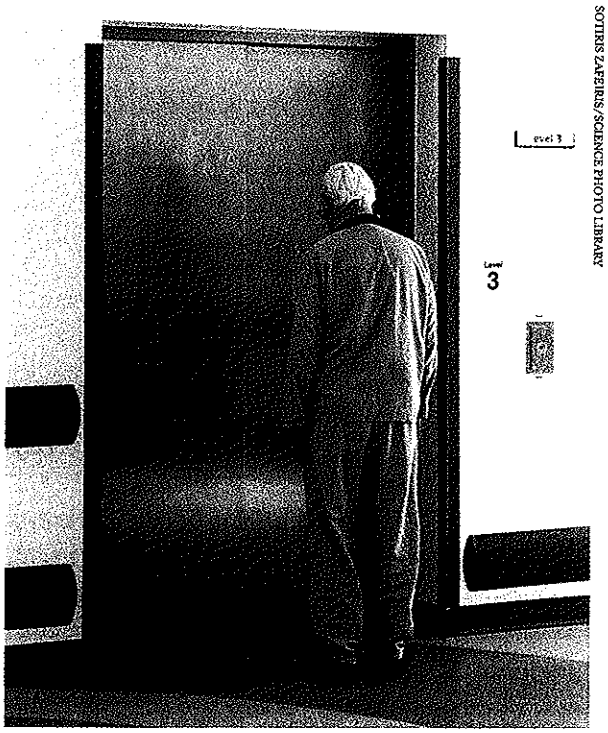


Figure 3
In the older man frailty exacerbated by low testosterone is a major concern, leading to loss of independence, chronic disability and a need for assisted living or long-term care and an increase in mortality

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Table 1 Mean plasma sex hormone levels in healthy men[2]

Age	Testosterone (nmol/L)	Free testosterone (nmol/L)	Sex hormone binding globulin (nmol/L)
25–34	21.38	0.428	35.5
35–44	23.14	0.356	40.1
45–54	21.02	0.314	44.6
55–64	19.49	0.288	45.5
65–74	18.15	0.239	48.7
75–84	16.32	0.207	51.0
85–100	13.05	0.186	65.9

Table 2 Symptoms of hypotestosteronaemia

Frequent

- Loss of libido
- Erectile dysfunction, difficulty achieving and/or maintaining erection
- Diminished nocturnal penile tumescence, early morning erections
- Fatigue and lassitude
- Increased sweating, night sweats
- Depressed mood, anxiety, reduced sense of well-being
- Decline in cognitive function, poor concentration and memory
- Irritability
- Loss of drive and enthusiasm

Occasional

- Urinary frequency, urgency and nocturia
- Disturbed sleep pattern
- Loss of sensitivity of erogenous zones
- Cold and 'shrivelled' penis (most references suggest that secondary sexual characteristics are unaffected)
- Weight gain (central and visceral adiposity), difficulty losing weight
- Loss of muscle mass, weakness
- Decline in athletic performance, hand-to-eye co-ordination, balance
- Ejaculatory dysfunction, premature ejaculation, difficulty ejaculating
- Reduced seminal volume
- Reduced orgasmic sensation
- Dry skin, reduced sebum secretion, decreased skin thickness
- Poor wound healing (including venous ulceration)
- Reduced facial hair growth
- Reduced volume of testes
- Pain or discomfort in testes

Perhaps the most significant advance over the last decade has been increasing public awareness of the andropause and its impact on men's health, and an increasing understanding among physicians that 'impotence' or erectile dysfunction is not an isolated phenomenon as some would have us believe. Rather, it is commonly one of a group of symptoms that constitute the syndrome known as the andropause, a pathological state caused by a low concentration of bio-available testosterone, which is responsive to appropriate intervention and careful and sympathetic management by well-informed clinicians. ■