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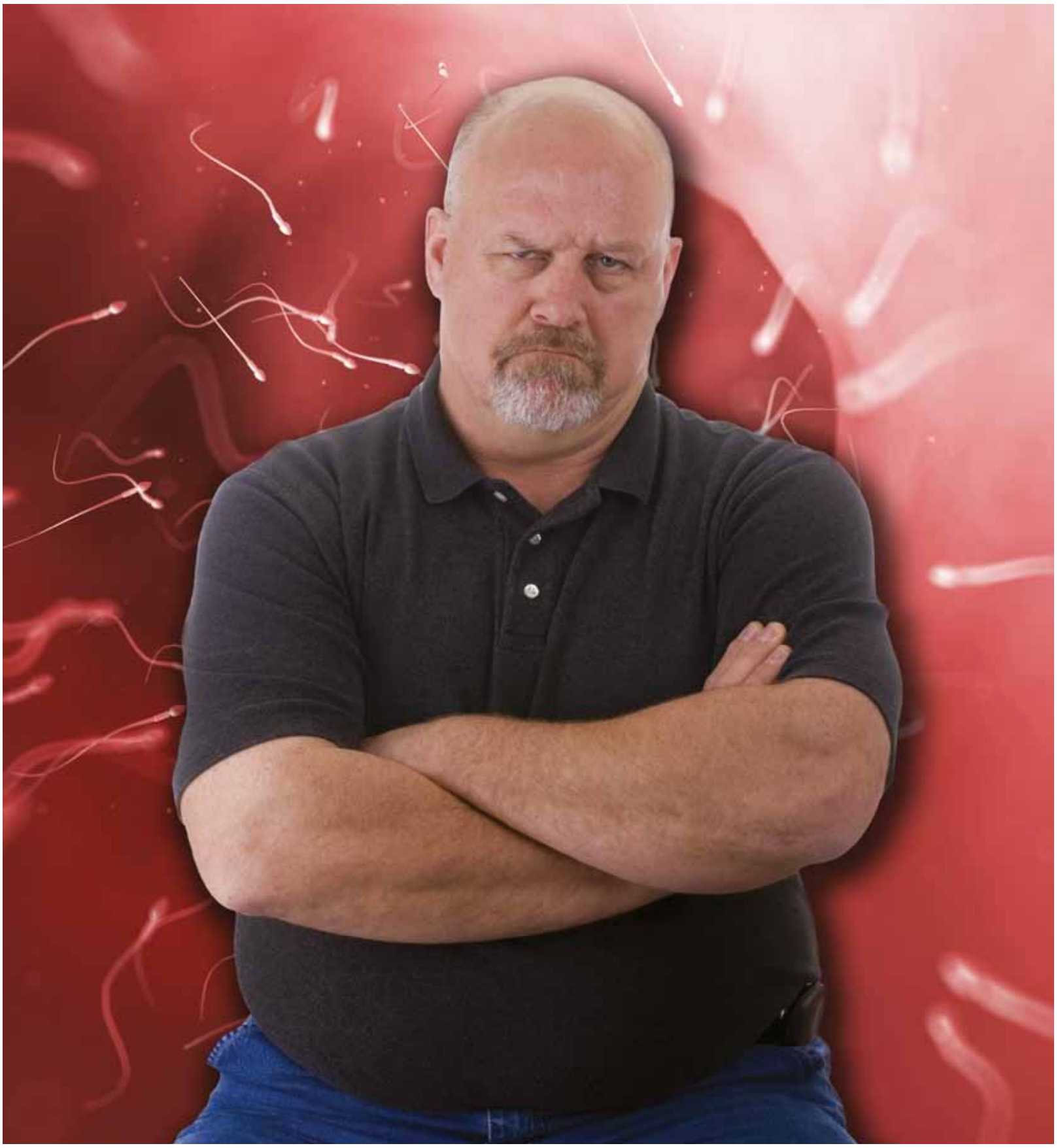

Low testosterone part 1

Introduction

THIS is the first of a two-part series. In part 1, we provide a practical approach to the clinical and biochemical assessment of the man presenting with possible hypogonadism. This will help the GP in the following ways: first, to recognise pitfalls in the evaluation of androgen deficiency; second, to distinguish organic from functional hypogonadism; and third, to decide when, and when not, to consider testosterone treatment. Management of infertility is beyond the scope of this article and will not be discussed.

Part 2 of this series will discuss the management of low testosterone.

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INSIDE

THE AUTHOR

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Background

MALE hypogonadism results from failure of the testes to produce physiological levels of testosterone (androgen deficiency) and a normal number of spermatozoa. It is caused by organic pathology that disrupts one or more levels of the hypothalamic–pituitary–testicular (HPT) axis. The diagnosis of male hypogonadism requires two criteria: first, consistent clinical signs and symptoms of androgen deficiency and/or infertility; and second, clearly low serum testosterone levels on more than one measurement.

Organic hypogonadism

The prevalence of organic hypogonadism in Australia is estimated to be one in 200 men, and GPs will not frequently encounter such men.[1] In organic hypogonadism, clinical features are caused by low testosterone levels (see table 1). In such men, after appropriate diagnostic workup and exclusion of contraindications, testosterone replacement therapy effectively treats signs and symptoms of androgen deficiency and markedly improves wellbeing. However, testosterone treatment does not improve, and indeed may worsen, fertility.

Organic hypogonadism is an important diagnosis not to miss, and there is evidence that this condition is underdiagnosed and undertreated. Australian data have shown that while the birth prevalence of Klinefelter's syndrome is about one in 500, only 50% are diagnosed.[2] This is despite the fact that Klinefelter's syndrome can be easily diagnosed by physical examination, as the cardinal physical sign of small, firm testes is present in virtually every man with this condition.

It should be noted that, in certain scenarios, even functional hypogonadism may be associated with profound androgen deficiency that may require testosterone replacement therapy. One example is patients requiring narcotic analgesia. Opioids often cannot be stopped, but hypogonadism may respond well to testosterone replacement. Data from Australia and elsewhere suggest that organic hypogonadism is underdiagnosed and undertreated, whereas the converse applies to so-called late-onset hypogonadism (LOH).

Late-onset hypogonadism

While organic hypogonadism due to proven organic HPT axis pathology (such as pituitary tumour or Klinefelter's syndrome) is a clearly defined disease state, so-called LOH remains a less well-defined and controversial concept (see table 1). The term LOH has been proposed to link observations that older men, especially when obese and suffering from comorbidities, not uncommonly present with non-specific features reminiscent of androgen deficiency. These men have modest reductions in testosterone levels relative to reference ranges based on healthy young men.

By definition, there is no recognisable structural HPT axis pathology. Symptoms may include fatigue, low energy and sexual dysfunction. In addition, some of the somatic features of ageing — such as loss of muscle mass, gain of fat mass and loss of bone density — are reminiscent of those seen in hypogonadal young men. Given this overlap between ageing and hypogonadism, some have posed the question as to whether low testosterone may be a correctable contributor to age-related poor health. However, in older men, these non-specific features and low testosterone may coexist rather than being causally related.

A European study showed that of 39 symptoms commonly attributed to androgen deficiency, only three (reduced sexual thoughts, reduced morning erections and low libido) were clustered with a low testosterone level, and the prevalence of LOH according to this definition was only 2.1%.[3]

It is important to note that in contrast to women who experience a sudden drop of oestradiol around the time of cessation of menses, the age-related drop in testosterone in men is more gradual, about 0.5-2.0% a year from early adulthood onwards. In contrast to women, there is no inflection point or clinical correlate equivalent to cessation of menses and hence no evidence for the existence of andropause. Moreover, the majority of older men have testosterone levels in the normal range.

In many men, so-called LOH may reflect functional suppression of the HPT axis as a result of ill health, representing a eugonadal sick syndrome akin to, for example, the euthyroid sick syndrome (see table 1). Essentially any chronic disease can lead to functional (non-structural) suppression of the HPT axis. Conditions such as type 2 diabetes mellitus, obesity, depression, obstructive sleep apnoea, chronic kidney disease or anorexia nervosa are associated with decreases in testosterone levels between 2nmol/L and 10nmol/L, depending on their severity.[4] In addition, medications to treat chronic illness, in particular glucocorticoids or opioids, can further reduce testosterone levels.

Consistent with this, there is good evidence that age-related accumulation of chronic disease and especially obesity, rather than ageing by itself, largely explains or at least accelerates this age-related decline in testosterone levels. In fact, recent Australian data suggest that healthy ageing by itself may not be associated with marked decreases in testosterone levels.[5] Overall, the evidence suggests that low testosterone is a sensitive biomarker of poor health rather than a causal factor.

Not surprisingly, therefore, there is increasing evidence that this functional HPT axis suppression may be reversible with lifestyle measures, especially weight loss and treatment of comorbidities.

In principle, chronic disease–associated functional HPT suppression may be detrimental, inconsequential or protective to health. If the latter were true, testosterone treatment could be harmful in older men. Although controversial, some studies have reported increased cardiovascular events with testosterone in older men.[6,7] Overall, the long-term risks and benefits of testosterone treatment in older men are unknown because large-scale, adequately powered and designed randomised controlled studies have not been performed.

Recent Australian and global data show marked increases in testosterone prescribing in older men despite this uncertainty. In Australia, the annual expenditure for testosterone products has increased ninefold to $12.7 million over 20 years.[8] In response to this increase in prescribing, coupled with the absence of clinical trial data showing clinically important benefits of testosterone treatment in older men, the criteria for testosterone prescribing on the PBS have been tightened as of 1 April 2015.

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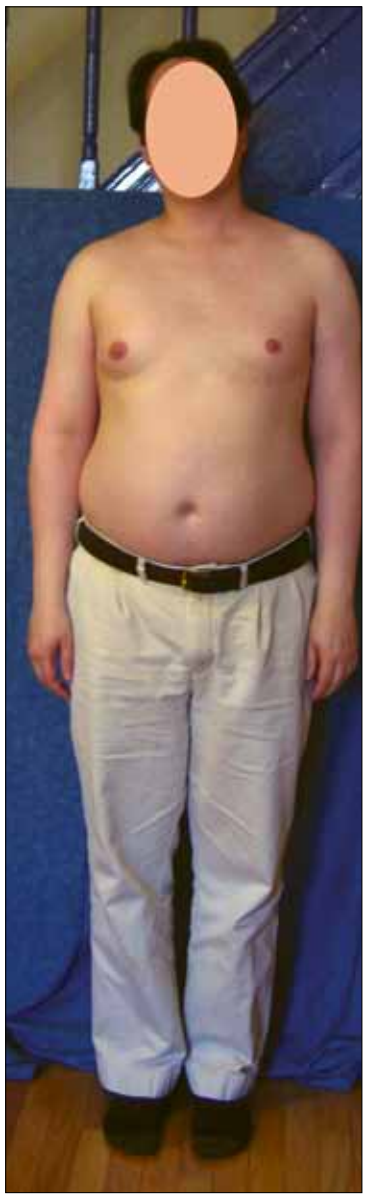
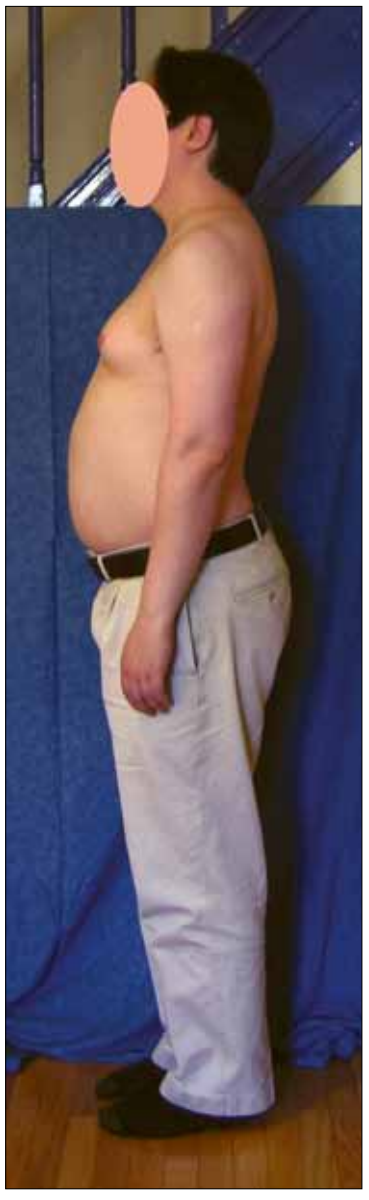




A person with typical untreated Klinefelter 46,XY/47,XXY mosaic, diagnosed at age 19. Scar from biopsy may be visible on left nipple.
Source: Courtesy Malcolm Gin http://creativecommons.org/licenses/by-sa/3.0/

Table 1: Classical hypogonadism vs functional hypogonadism: A conceptual framework to distinguish the approach to organic and functional hypogonadism

	Organic hypogonadism	Functional hypogonadism (eg, LOH)
Pathophysiology	Proven HPT axis pathology Established disease state	No recognisable structural HPT axis pathology Less well-defined concept Diagnosis of exclusion
Signs/symptoms	Specific: low libido, small testes, gynaecomastia	Non-specific: erectile dysfunction, low energy and mood
Testosterone levels	Unequivocally and consistently low	Borderline low, fluctuating around the lower limit of assay range
Association of low testosterone with symptoms	Causal	Uncertain
Testosterone therapy	Replacement	Replacement/pharmacotherapy
Benefits of therapy	Marked symptomatic and somatic response	Symptomatic and somatic response less likely
Risks of therapy	Low	Unknown

Evidence suggests that low testosterone is a sensitive biomarker of poor health rather than a causal factor.

New eligibility criteria for PBS-subsidised testosterone treatment

To be eligible for PBS-subsidised testosterone treatment, men over 40 who do not have an established pituitary or testicular disorder must have a circulating testosterone level of less than 6.0nmol/L, confirmed by at least two morning testosterone measurements.

Treatment is also subsidised for total testosterone levels between 6.0nmol/L and 15.0nmol/L, provided the LH level is greater than 1.5 times the upper limit of the eugonadal reference range or greater than 14 IU/L.

There are no restrictions for testosterone replacement in men with organic hypogonadism due to an established pituitary or testicular disorder.

PBS-subsidised testosterone therapy can now only by prescribed in conjunction with a specialist endocrinologist, urologist or registered member of the Australasian Chapter of Sexual Health Medicine.

Physiology

TESTOSTERONE, the main circulating androgen, plays critical roles in virilisation and maintenance of the male phenotype. Testosterone production is regulated by the HPT axis. In response to the pulsatile secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus, the anterior pituitary releases FSH and LH (see figure 1).

FSH, in conjunction with intratesticular testosterone, acts on Sertoli cells and seminiferous tubules to promote spermatogenesis. LH stimulates the secretion of testosterone from testicular Leydig cells. Circulating testosterone is largely plasma protein bound: 44% tightly to sex hormone–binding globulin (SHBG) and 54% loosely to albumin, while 2% circulates as free testosterone. The combination of free and albumin-bound testosterone is referred to as bioavailable testosterone.

Testosterone exerts its biological actions via binding to the androgen receptor, leading to gene transcription. Testosterone is not only a hormone but also a prohormone and is converted to both dihydrotestosterone (DHT) and oestradiol. DHT is about 10-fold more potent than testosterone and serves as a local amplification system of androgen action in the prostate gland and the hair follicle.

There is increasing evidence that oestradiol, although circulating at 10-fold lower levels compared with premenopausal women, has important biological actions in men, such as regulation of bone mass, fat distribution and insulin resistance. Both testosterone and oestradiol exert negative feedback on the hypothalamus to restrain gonadotropin secretion in a classical endocrine negative-feedback loop (see figure 1).

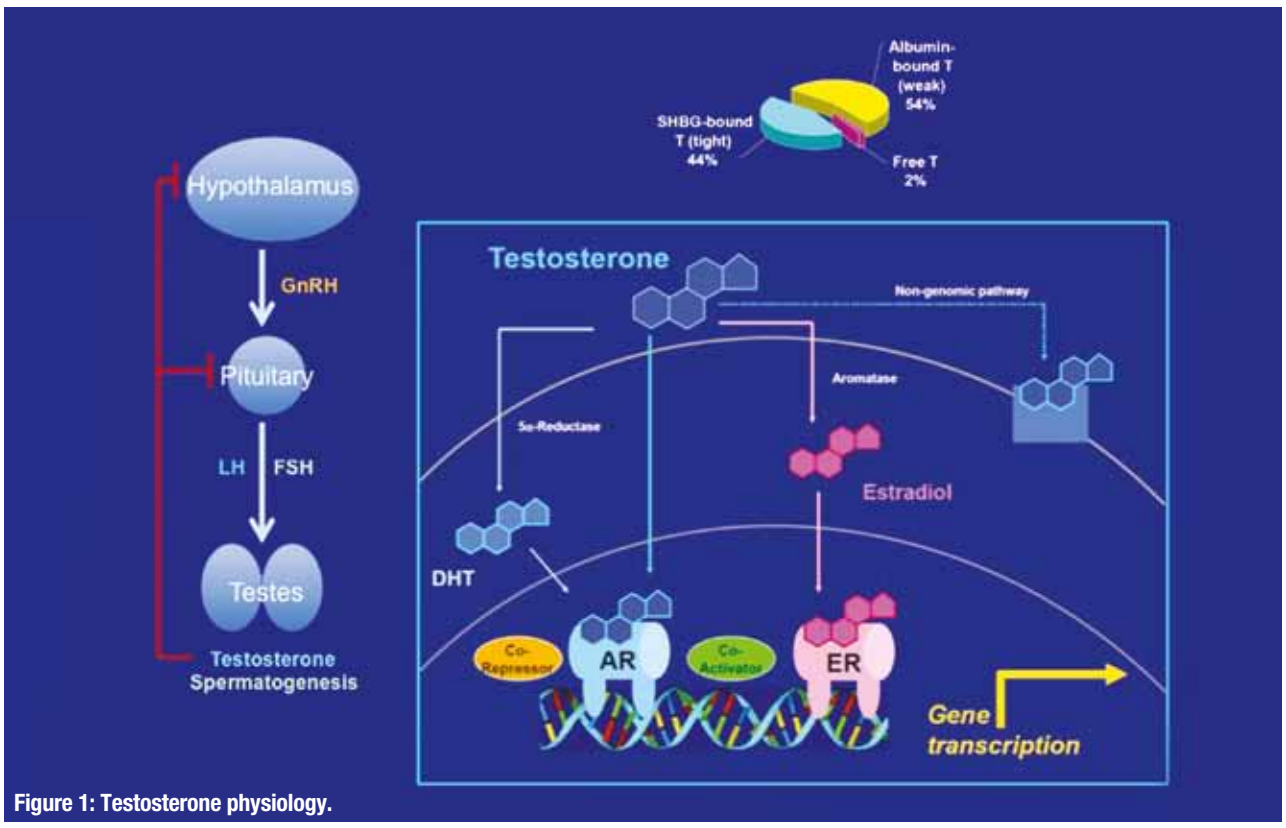


Figure 1: Testosterone physiology.

Assessment of androgen deficiency

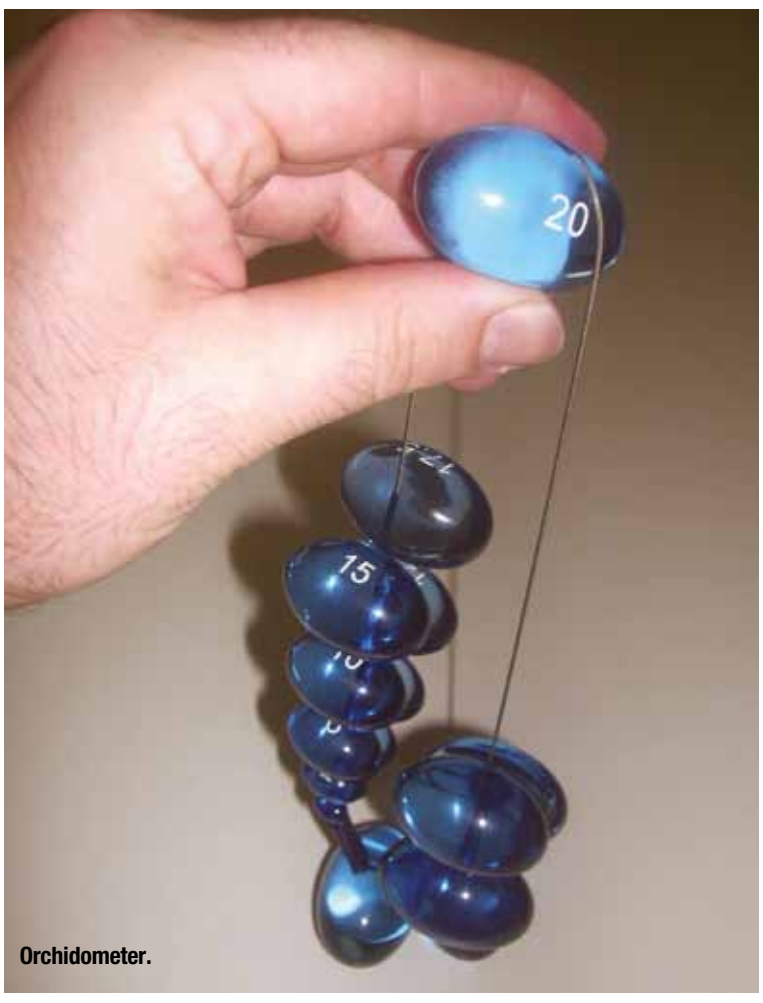
THE diagnosis of androgen deficiency should only be made in men who have consistent signs and symptoms and repeatedly and clearly low serum testosterone levels. Once considered, making the diagnosis of hypogonadism in young, otherwise healthy men is relatively straightforward. However, excluding this diagnosis in obese older men with chronic disease is more difficult.

Clinical evaluation

Given that hypogonadism is primarily a clinical diagnosis supported by consistent biochemical findings, men who present with features suggestive of androgen deficiency should have a thorough history and physical examination to determine the degree of clinically significant androgen deficiency (see table 2).[9,10]

Clinical assessment should be focussed on eliciting the more specific features of androgen deficiency, such as gynaecomastia, recent loss of sexual hair, and decreased testicular volume. Findings denoting prepubertal onset include incomplete sexual development, eunuchoidal proportions and very small testes. Many features — such as fatigue, low libido and reduced muscle bulk — are non-specific and can be caused by almost any chronic disease.

Initial assessment should include the identification of comorbidities that may confound the clinical picture or represent potentially reversible causes — such as obesity, depression, uncontrolled sleep apnoea; or medications, such as opioids or glucocorticoids. Clinical assessment should not miss clues to underlying organic aetiology, such as signs of pituitary dysfunction or mass effect (headache, visual field defect, eye movement disturbance). In addition, features of hypopituitarism or of a hormone-producing pituitary tumour (eg, Cushing's disease) should be excluded. A history of minimal trauma fractures should be elicited.



Orchidometer.

There is no role for testosterone measurement in asymptomatic men.

Biochemical diagnosis

Testosterone levels should only be measured if androgen deficiency is suspected clinically. There is no role for testosterone measurement in asymptomatic men. Total testosterone is the mainstay of biochemical diagnosis of androgen deficiency and the initial diagnostic test. Because any acute illness can decrease testosterone levels, men should be medically stable. Caused by circadian rhythmicity, testosterone levels are the highest in the early morning; therefore, blood samples should be drawn close to 8am. In addition, men should be fasted, given that food intake can decrease testosterone levels abruptly (by up to 25%).

In contrast to, for example, bone density, where age-dependent reference ranges are quite well defined, there is no general agreement on the acceptable normal range of testosterone, especially in older men. This is because there have been

Table 2: Clinical features of hypogonadism

More specific signs and symptoms	Incomplete or delayed sexual development (with prepubertal onset) Reduced libido Decreased spontaneous erections Breast discomfort, gynaecomastia Loss of axillary and pubic hair Reduced shaving Very small (especially less than 5mL) or shrinking testes Infertility or azoospermia Low-trauma fracture or otherwise unexplained osteoporosis on dual-energy X-ray absorptiometry Hot flushes, sweats
Less specific signs and symptoms	Decreased energy levels Diminished physical or work performance Depressed mood Poor concentration and memory Sleep disturbance, increased sleepiness Otherwise unexplained normochromic normocytic anaemia Decreased muscle bulk and strength Increased body fat, BMI

Adapted from references 9 and 10.

relatively few large population-based studies of healthy older men. In addition, testosterone assays are poorly standardised, and reference ranges vary between laboratories. The accuracy of currently used immunoassays is variable, especially in the lower range. One Australian study comparing seven commonly used immunoassays has shown that compared with a liquid chromatography–mass spectrometry-based assay, the current gold standard, testosterone levels at the lower limit of the male reference range differed by as much as 30% between the different immunoassays.[11]

In practice, a normal fasting early morning total testosterone level (somewhat arbitrarily defined as >12nmol/L) is generally consistent with eugonadism and usually does not need to be repeated. If the total testosterone is >12nmol/L, non-specific symptoms will generally not be due to androgen deficiency.

A low total testosterone, however, needs confirmation because a falsely low level caused by, for example, unrecognised intercurrent illness or assay imprecision at the lower range is more likely than a falsely normal level. Therefore, a diagnosis of androgen deficiency should never be based on a single low testosterone level. Indeed, up to 35% of men with a low testosterone will have a normal testosterone on repeat testing.

Quantification of free testosterone may be helpful when total testosterone is borderline and abnormalities in SHBG are suspected (see table 3). Although equilibrium dialysis is the gold standard, in practice free testosterone is usually calculated by empiric formulae. Importantly, the free androgen index is inaccurate in men and should not be used. Free testosterone can be useful to exclude hypogonadism in men where low total testosterone is due to low SHBG because of insulin resistance in obesity or diabetes. In this context, a normal free testosterone can be reassuring that their non-specific symptoms are not a result of androgen deficiency. However, given that the age-related decline of free testosterone is steeper than that of total testosterone, a low free testosterone should be used with caution to confirm hypogonadism in older men, as the risk of over-diagnosis is substantial because reference ranges are usually based on young men. Even in young men, reported reference ranges for free testosterone vary widely — from 170pmol/L to 310pmol/L in different assays.

Rarely, men can be androgen deficient despite a normal total testosterone. This usually occurs if SHBG is markedly elevated, most commonly in the setting of anti-epileptic treatment or chronic liver disease (see table 3), but these men usually have elevated gonadotropin levels and a clearly low free testosterone.

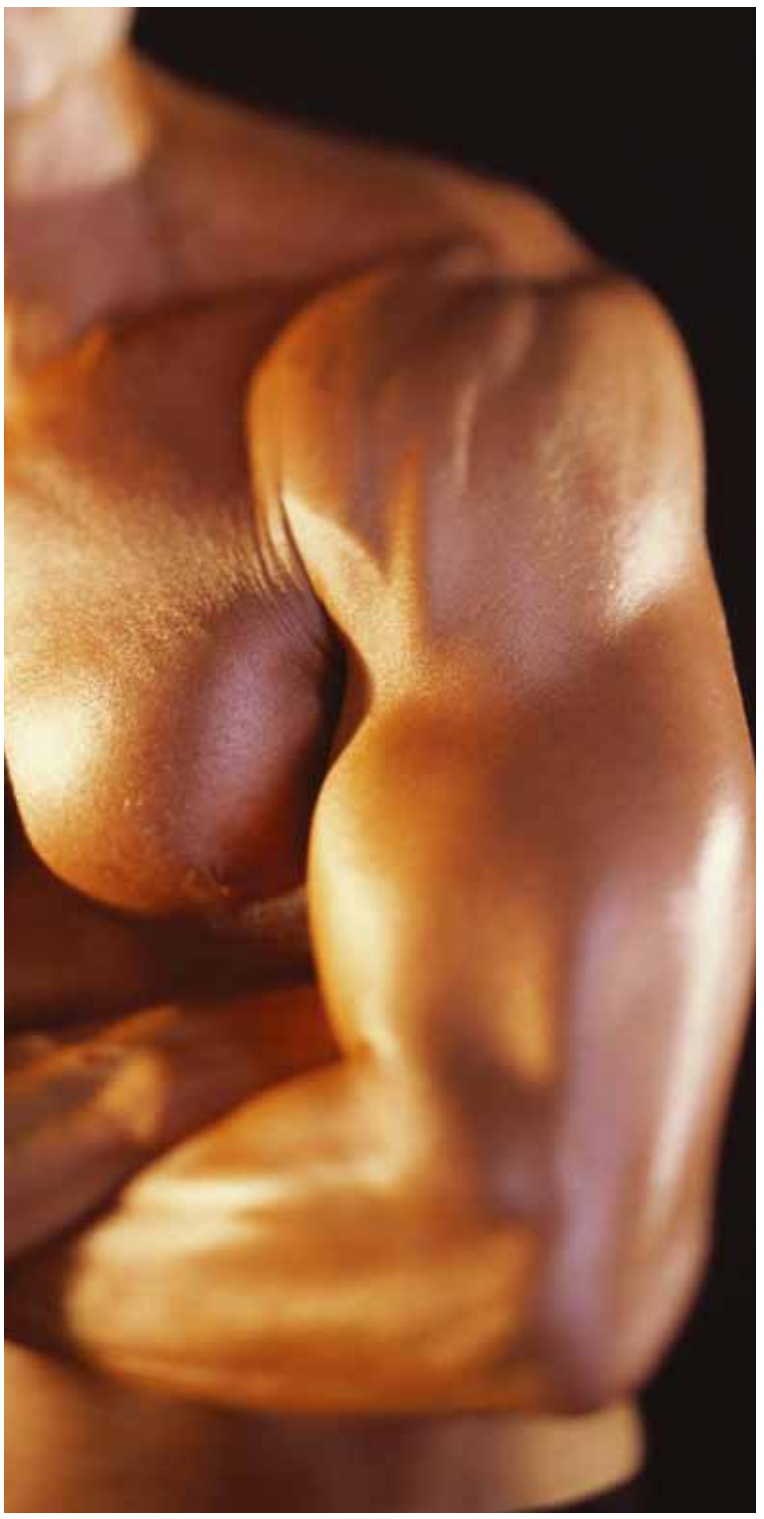
While specific biomarkers of hypogonadism in men are lacking, otherwise unexplained anaemia, reduced bone density or a lower-than-expected PSA can be supportive of clinically relevant androgen deficiency.

In general, a repeatedly low testosterone level is more indicative of hypogonadism the younger, healthier and leaner the man is, but it is much less predictive in obese older men with chronic disease and non-specific symptoms.

Table 3: Conditions associated with alterations in SHBG concentrations

Conditions associated with decreased SHBG levels	Conditions associated with increased SHBG levels
Moderate obesity*	Ageing*
Diabetes mellitus*	Hepatic cirrhosis
Nephrotic syndrome	Hyperthyroidism
Hypothyroidism	Use of anticonvulsants
Use of glucocorticoids, progestins or androgenic steroids	Use of oestrogens
Acromegaly	HIV
	Excessive exercise with caloric deficit

Adapted from reference 9 — * common causes



A low total testosterone ... needs confirmation.

Elucidating the cause of hypogonadism

Once the low testosterone value has been confirmed on repeated morning measurements in men with consistent signs and symptoms, the gonadotropins (FSH and LH) should be measured to distinguish between primary or secondary hypogonadism (see figure 2 and table 4). Elevated gonadotropin values denote primary hypogonadism (testicular failure).

If testes are small, karyotype is indicated to evaluate for Klinefelter's syndrome. If fertility is desired, semen analysis should be performed.

Low, or importantly, even inappropriately normal FSH and LH values may indicate secondary hypogonadism due to either pituitary or hypothalamic pathology. The probability of organic pathology is inversely related to BMI, age, number of comorbidities and testosterone level. Therefore, it is essential not to miss underlying pituitary or hypothalamic pathology, especially in young, otherwise healthy men. Guided by clinical assessment, biochemical assessment of pituitary (dys)function may be necessary, and pituitary imaging may need to be considered.

Pathological hyperprolactinaemia or haemochromatosis can cause secondary hypogonadism even in the absence of other clinical features of pituitary disease. Therefore, prolactin and iron studies should be measured routinely in younger men. If there is pathological hyperprolactinaemia — for example, due to a microprolactinoma — the hypogonadism will respond to, and should be treated by, normalising the prolactin level rather than by testosterone therapy.

The majority of obese older men with lowered testosterone will have low/normal gonadotropin levels due to hypothalamic–pituitary inhibition. Evaluation for underlying organic HPT axis pathology is commonly of low yield and should be individualised. In older men, US Endocrine Society guidelines recommend restricting pituitary imaging, in the absence of clinical suspicion, to men with a total testos-

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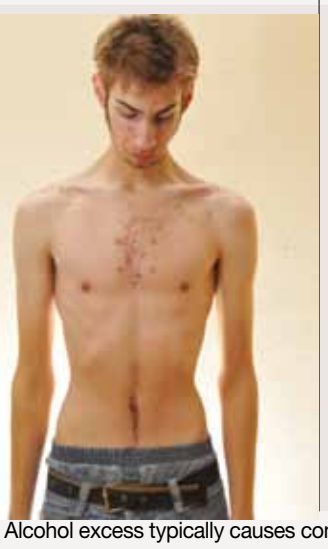
Hypogonadism due to androgen deprivation therapy for prostate cancer

The lifetime incidence of prostate cancer in men is one in six, and more than 50% of men with prostate cancer will receive androgen deprivation therapy (ADT) during the course of their illness, often for several years. ADT reduces sex steroids to castrate levels and is therefore one of the most common contemporary causes of severe hypogonadism. About 3% of the US male Medicare population is receiving this treatment, and the use of ADT in Australia is increasing.

The overall prognosis of prostate cancer is favourable (10-year disease-specific survival rate of over 90%), and most men die with, rather than from, prostate cancer. ADT-associated toxicities are a consequence of the severe hypogonadism and include fatigue, reduced sexual function, anaemia, accelerated bone loss with increased risk of fragility fractures, muscle loss, and visceral obesity leading to insulin resistance and increased risk of diabetes and, although this is still controversial, of cardiovascular events. Therefore, it is important that ADT is only prescribed in situations where there is high-level evidence for benefit, for example, adjuvant to radiotherapy in men with high-risk prostate cancer.

To optimise the risk–benefit ratio of ADT, men receiving this therapy should be monitored and treated for ADT-associated toxicities, including baseline and regular follow-up assessment for bone and cardiometabolic health according to a standardised, evidence-based management plan.[13]

Table 4: Causes of hypogonadism

Primary (elevated FSH/LH)	Secondary (low/ normal FSH/LH)
ACQUIRED Testicular damage Trauma/torsion Orchitis Chemotherapy Autoimmune Varicocele Drugs: • Spironolactone • Ketoconazole	STRUCTURAL Pituitary damage Tumour Surgery Radiation Head trauma Apoplexy/haemorrhage Infiltration (iron overload, sarcoidosis, histiocytosis)
CONGENITAL Klinefelter's syndrome Y-chromosome microdeletions Cryptorchidism Mutations in androgen biosynthesis enzymes FSH/LH-receptor mutations Myotonic dystrophy	GENETIC Isolated GnRH deficiency Kallmann's syndrome (these men have anosmia) Normosmic FSH/LH beta-subunit mutations Prader–Willi syndrome
	FUNCTIONAL Morbid obesity Anorexia/excessive exercise Hyperprolactinaemia Cushing's syndrome or exogenous glucocorticoids Opioids Acute illness Chronic disease End-stage renal failure COPD HIV Type 2 diabetes mellitus Liver cirrhosis Androgen deprivation therapy (GnRH analogues) Anabolic steroids

Alcohol excess typically causes combined primary and secondary hypogonadism.

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terone level of <5.2nmol/L.[9] In the largest study of 313 older men with sexual dysfunction and a mean total testosterone level of 6.6nmol/L, only six patients had a macroadenoma, all of whom had total testosterone levels of 3.6 nmol/L or less.[12]

Men with prior or current anabolic steroid use may present with severe secondary hypogonadism and may deny use even on specific questioning. Suspicious clinical features include truncal acne, muscular build or atrophic testes.

Biochemical clues include a low HDL, low SHBG or a higher-than-expected haematocrit.

Hypogonadism is often associated with mild anaemia due to the erythropoietic actions of testosterone.

Indeed, anabolic steroid use is no longer confined to athletes and is not uncommon among gym attendees. Some men use anabolic steroids simply to enhance physical appearance — to get the six-pack abdomen and sculptured body.

Although perceived to be less common compared with women, excessive exercise and anorexia can lead to functional hypogonadism even in men.

Androgen deficiency treatment given to men with prostate cancer is the most common contemporary cause of severe hypogonadism in older men and requires dedicated assessment and management.[13]

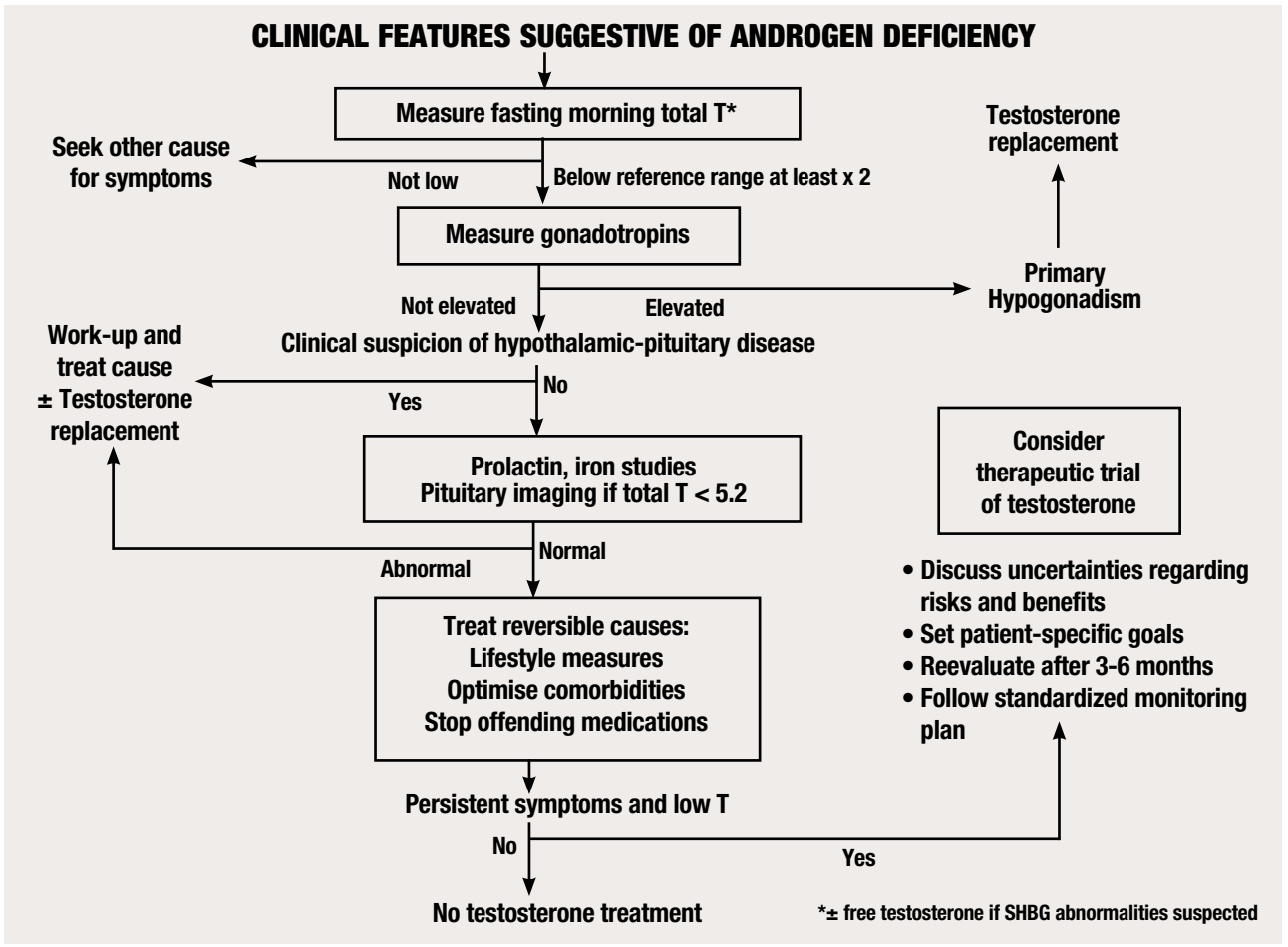
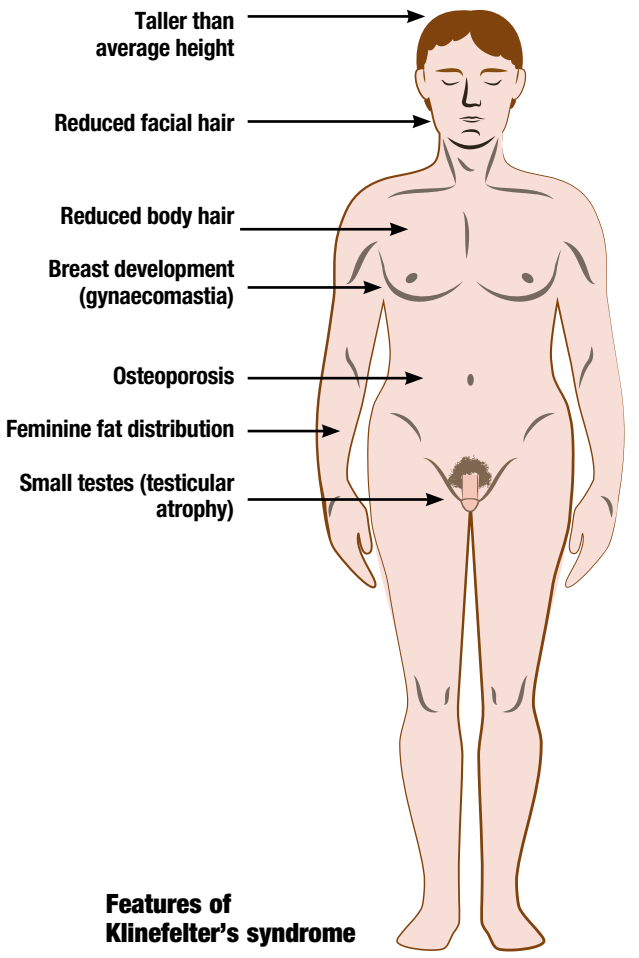


Figure 2: Hypogonadism: Diagnostic approach and management.



Case studies

Case study one

TONY, aged 55, has been diagnosed with metabolic syndrome. He is referred for cardiometabolic risk optimisation, not for andrological assessment. He has been unable to engage in lifestyle modification measures, which he attributes to lethargy, muscle weakness and depressive moods. On specific questioning, he reports poor libido.

Physical examination reveals gynaecomastia, reduced sexual hair and reduced muscle bulk. Testes are 12mL bilaterally (normal is greater than 15mL) without lumps. Visual fields and eye movements are normal.

Tony's morning fasting total testosterone is 4.4nmol/L, with an assay-specific reference range (RR) of 10-27.6nmol/L, and it is 3.9nmol/L on repeat. LH is inappropriately normal, 1.8 IU/L (1-10), suggesting secondary hypogonadism. Prolactin is mildly raised, 637m IU/L (86-324), more suggestive of pituitary stalk compression than of a prolactinoma. Pituitary function is otherwise normal, as are iron studies. Pituitary imaging is not performed.

In addition, he has mild anaemia, a haemoglobin of 12.6g/dL (13-18) and osteopenia (lumbar spine T-score of 2.2 and femoral neck T-score of 1.7) — all further clues to androgen deficiency, with the typical trabecular-predominant bone loss a sign of chronicity. MRI of the sella turcica shows a 16mm pituitary cyst with anterior displacement of pituitary tissue.

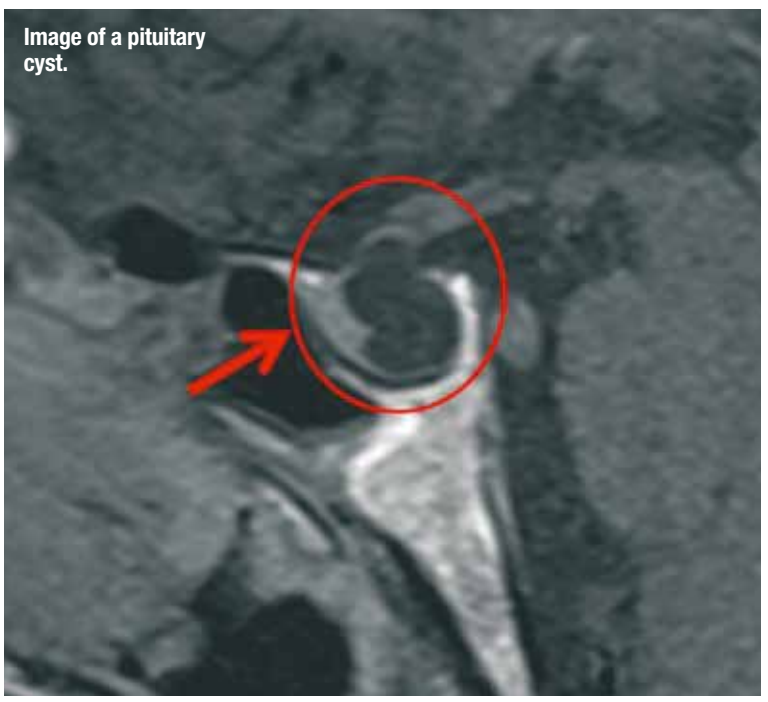


Image of a pituitary cyst.

Physical examination reveals gynaecomastia, reduced sexual hair and reduced muscle bulk. Testes are 12mL bilaterally, without lumps.

He has no desire for paternity, so testosterone therapy is initiated, with testosterone gel to ensure tolerance, and subsequently changed to IM testosterone undecanoate with therapeutic trough levels. Tony has marked improvements in libido and energy, which enable him to lose weight. His metabolic syndrome and anaemia resolve and strength improves. On follow-up MRI, the pituitary cyst remains stable and visual fields remain normal.

Case study two

Andrew, a 28-year-old competitive amateur cyclist, presents with fatigue, loss of strength and libido, and poor exercise recovery. Further history reveals heavy training (up to 30 hours a week), and he admits to dieting to be as light as possible. He reports 15kg of weight loss over the preceding 18 months.

Physical examination shows a BMI of 20.3kg/m^2 — low for an athlete. There are no physical signs of androgen deficiency, and his testes are 20mL bilaterally.

There are no signs of a pituitary mass lesion. Andrew has profound central hypogonadism, with a total testosterone of 2.6nmol/L, repeated 1.9, (RR 10-27.6) and low gonadotropins: LH 0.2 IU/L (RR 1-10) and FSH 0.7 IU/L (RR 1-10). Thyroid function tests suggest a euthyroid sick pattern: TSH 1.24 IU/L (RR 0.5-5.0), a free thyroxine of 11.2pmol/L (11-21) and a free triiodothyronine of 3.2pmol/L (RR 4.7-72.2).

This, and his raised SHBG of 78nmol/L (RR 17-56), is consistent with a stress response due to overtraining and caloric deficit. He has mild anaemia, with a haemoglobin of 12.4g/dL (RR 13-18), and a high HDL of 1.9nmol/L — findings opposite to what would be expected with anabolic steroid use.

With counselling and weight gain, his gonadal axis reactivates and his anaemia and euthyroid sick pattern resolve, confirming the diagnosis of functional hypogonadism caused by overtraining and caloric deficit.

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Conclusion

IN men, testosterone, the principal circulating androgen, has essential reproductive functions in establishing and maintaining the male phenotype. It also plays important anabolic roles in somatic tissues, such as muscle and bone.

Organic hypogonadism is an important diagnosis not to be missed and an important differential to consider in the man presenting with, for example, otherwise unexplained weakness, anaemia or osteoporosis. Hypogonadism is a clinical diagnosis based on a combination of consistent signs and symptoms, confirmed by repeatedly and consistently low morning fasting testosterone levels. Once the diagnosis of hypogonadism is made, an individualised diagnostic workup is required to establish the cause, and it is essential that this is done before testosterone treatment is considered.

Importantly, testosterone treatment does not improve, but instead compromises, fertility. Organic pathology with underlying pituitary or testicular disease is more likely to be present in younger, leaner, otherwise healthy men who present with more specific clinical features and markedly low testosterone levels. In contrast, in the majority of obese older men with comorbidities presenting with less specific clinical features and more modest testosterone reductions, there is no recognisable pituitary or testicular pathology.

In these older men, low testosterone is a robust biomarker of poor health and should prompt assessment for comorbidities. Indeed, erectile dysfunction is usually due to vascular disease and therefore a strong predictor of future cardiovascular events. Making a distinction between organic hypogonadism and so-called late-onset hypogonadism has important implications for management in these men, which will be discussed in part 2 of this series.

References
Available on request from howtotreat@cirrusmedia.com.au

How to Treat Quiz

Low testosterone part 1
— 26 June 2015

INSTRUCTIONS
Complete this quiz online and fill in the GP evaluation form to earn 2 CPD or PDP points.
We no longer accept quizzes by post or fax.

The mark required to obtain points is 80%. Please note that some questions have more than one correct answer.

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1. Which TWO statements regarding the background of low testosterone are correct?
a) Male hypogonadism results from failure of the testes to produce physiological levels of testosterone and a normal number of spermatozoa.
b) The diagnosis of male hypogonadism is clinical, based on the signs and symptoms of androgen deficiency.
c) The diagnosis of male hypogonadism is serological, based on a low serum testosterone level.
d) Male hypogonadism is caused by organic pathology that disrupts one or more levels of the hypothalamic–pituitary–testicular (HPT) axis.

2. Which THREE statements regarding organic hypogonadism are correct?
a) In organic hypogonadism, low testosterone levels cause clinical features.
b) Testosterone treatment in organic hypogonadism may worsen fertility.
c) The prevalence of organic hypogonadism in Australia is estimated to be one in 2000 men.
d) The cardinal physical sign of Klinefelter's syndrome is small, firm testes.

3. Which THREE features relate to organic hypogonadism?
a) Proven HPT axis pathology
b) Erectile dysfunction
c) Low libido
d) Gynaecomastia

4. Which THREE features relate to functional hypogonadism?
a) Small testes
b) No recognisable structural HPT axis pathology
c) Low energy and mood
d) Symptomatic and somatic response to testosterone therapy less likely

5. Which TWO statements regarding late-onset hypogonadism (LOH) are correct?
a) LOH remains a less well-defined and controversial concept.
b) Older men, especially when obese and suffering from comorbidities, not uncommonly present with non-specific features reminiscent of androgen deficiency.
c) These older men have large reductions in testosterone levels relative to reference ranges based on healthy young men.
d) Structural HPT axis pathology is usually demonstrated.

6. Which THREE statements regarding LOH are correct?
a) Symptoms may include fatigue, low energy and sexual dysfunction.
b) Glucocorticoids or opioids can increase testosterone levels.
c) Loss of muscle mass, gain of fat mass and loss of bone density in men with LOH may also be seen in hypogonadal young men.
d) The age-related drop in testosterone in men is gradual, with the majority of older men having testosterone levels in the normal range.

7. Which TWO statements regarding eligibility criteria for PBS-subsidised testosterone treatment are correct?
a) Men over 40 who do not have an established pituitary or testicular disorder must have a circulating testosterone level of less than 6.0nmol/L, confirmed by at least two morning testosterone measurements.
b) There are restrictions for testosterone replacement in men with organic hypogonadism due to an established pituitary or testicular disorder.
c) Treatment is also subsidised for total testosterone levels between 6.0nmol/L and 15.0nmol/L, provided the LH level is greater than 1.5 times the upper limit of the eugonadal reference range or greater than 14 IU/L.
d) The GP is able to prescribe testosterone therapy provided the serum testosterone levels meet the PBS criteria.

8. Which THREE statements regarding the physiology of testosterone are correct?
a) Testosterone production is regulated by the HPT axis.
b) Circulating testosterone is largely plasma protein–bound.
c) Oestrogen, the main circulating androgen, plays critical roles in virilisation and maintenance of the male phenotype.
d) There is increasing evidence that oestradiol has important biological actions in men, such as regulation of bone mass, fat distribution and insulin resistance.

9. Which TWO statements regarding the biochemical diagnosis of low testosterone are correct?
a) Testosterone levels should only be measured if androgen deficiency is suspected clinically.
b) Testosterone measurement in asymptomatic older men contributes to the management of chronic conditions like diabetes and CVD.
c) As a result of circadian rhythmicity, testosterone levels are the highest in the early morning.
d) Food intake can increase testosterone levels abruptly, by up to 25%.

10. Which TWO statements regarding elucidating the cause of hypogonadism are correct?
a) After establishing a low testosterone value on repeat testing, FSH and LH should be measured to distinguish between primary or secondary hypogonadism.
b) Elevated gonadotropin values denote secondary hypogonadism.
c) If testes are small, karyotype is indicated to evaluate for Klinefelter's syndrome.
d) The majority of obese older men with lowered testosterone will have high gonadotropin levels due to hypothalamic–pituitary stimulation.

CPD QUIZ UPDATE
The RACGP requires that a brief GP evaluation form be completed with every quiz to obtain category 2 CPD or PDP points for the 2014-16 triennium. You can complete this online along with the quiz at **www.australiandoctor.com.au.** Because this is a requirement, we are no longer able to accept the quiz by post or fax. However, we have included the quiz questions here for those who like to prepare the answers before completing the quiz online.

Australian Doctor Education

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NEXT WEEK

Next week's How to Treat is part 2 in the series on testosterone. Part 2 will discuss the management of low testosterone in men, which will often include strategies other than, or complementary to, testosterone therapy. The author is **Associate Professor Mathis Grossmann**, department of medicine, Austin Health, University of Melbourne; and head of clinical andrology and consultant endocrinologist at the endocrine unit, Austin Health, Heidelberg, Victoria.