COMPLETE HOW TO TREAT QUIZZES ONLINE
www.australiandoctor.com.au/cpd to earn CPD or PDP points.

Low testosterone part 2

Introduction

THIS is the second of a two-part series on the investigation and management of low testosterone in men. In part 1, we covered the approach to the clinical and biochemical assessment of the man presenting with possible hypogonadism.

Part 2 will cover the management of low testosterone, which in many cases will involve strategies other than, or complementary to, testosterone therapy.

cont'd next page

INSIDE

THE AUTHOR

DR MATHIS GROSSMANN
associate professor, department of medicine, Austin Health, University of Melbourne, Heidelberg, Victoria; and head of clinical andrology and consultant endocrinologist, endocrine unit, Austin Health, Heidelberg, Victoria.

Australian Doctor.

Management of organic hypogonadism

THERE is no question that, provided there are no contraindications, men with organic hypogonadism should be treated with testosterone replacement to establish or maintain secondary sexual characteristics, sexual function, body composition and wellbeing. In Australia, the PBS subsidises testosterone replacement for men with hypogonadism due to established testicular or pituitary disease without restrictions. Currently available testosterone formulations and their advantages and disadvantages are listed in table 1.

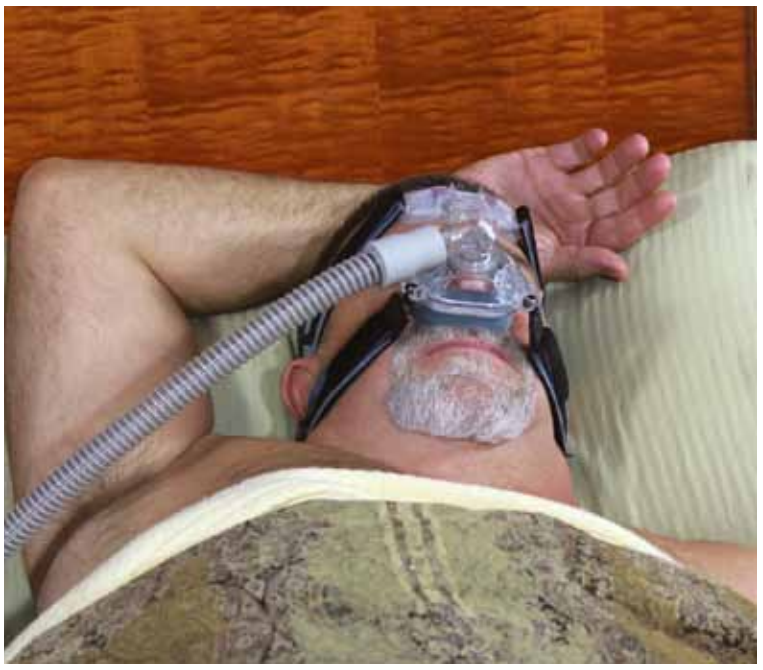
It must be noted that testosterone treatment should never be started before diagnostic workup is complete and a clear diagnosis has been made. First, failure to do so may lead to missing importtant underlying pathologies, such as a pituitary tumour. Second, exogenous testosterone treatment suppresses the hypothalamic–pituitary–thyroid axis (HPT) axis even in healthy men, and once testosterone has been commenced, accurate evaluation for an underlying aetiology is virtually impossible.

Third, testosterone treatment compromises fertility, whereas spermatogenesis in men with secondary hypogonadism can be restored with gonadotropin treatment.

Contraindications to testosterone treatment

Breast or prostate cancer
A palpable prostate nodule or induration*
PSA greater than 4ng/mL (or greater than 3ng/mL in men at high risk of prostate cancer*)
Severe lower urinary tract symptoms (international prostate symptom score over 19)
Haematocrit over 50%
Untreated severe obstructive sleep apnoea
Unstable cardiac disease (eg, poorly controlled cardiac failure, recent cardiovascular events)
When fertility is desired
*Unless urological evaluation is negative

Source: Adapted from references 9 and 10



Untreated severe obstructive sleep apnoea is a contraindication to testosterone treatment.

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 6nmol/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 be prescribed in conjunction with a specialist endocrinologist, urologist or registered member of the Australasian Chapter of Sexual Health Medicine.

Table 1: Testosterone formulations currently available in Australia

Preparation/ administration	Advantages	Disadvantages	Testosterone monitoring
Testosterone gel 1% (Testogel) Daily	Can be self-administered Short half-life*	Chance for inadvertent transfer to close contacts (spouse, children, nurses) Imprecise dose adjustment Marked variation in blood levels Skin irritation	Morning, prior to application, after use for seven days
Testosterone patch Daily	Can be self-administered Short half-life*	Skin irritation Limited scope for dose variation	Morning after evening application
Testosterone transdermal solution (Axiron) Daily	Can be self-administered Short half-life* Less risk of inadvertent transfer to others	Pump applicator required Must be administered in the axilla Skin irritation May not wash, shower or swim within two hours of application	Monitor after two weeks, trough level taken 2-8 hours after application
Testosterone undecanoate 40mg capsule (Andriol) 2-3 times a day	Can be self-administered Short half-life*	Frequent dosing required (2-3 times a day) Marked variation in blood levels GI intolerance	Monitor after two weeks
Testosterone undecanoate 1g IM injection (Reandron 1000) Three-monthly	Convenience Compliance Stable testosterone levels	Injection-site pain Contraindicated in men with coagulopathies or thrombocytopenia Cannot be self-administered Post-injection cough due to pulmonary oil microembolism	Morning, prior to fourth injection. Aim for trough level 10-15nmol/L. Allow a further 2-3 injections after dose adjustment before rechecking

*Advantages of a short half-life include faster offset in case of side effects and faster recovery of HPT axis if treatment is stopped, with less risk of iatrogenic hypogonadism.

Testosterone treatment compromises fertility, whereas spermatogenesis in men with secondary hypogonadism can be restored with gonadotropin treatment.

cont'd page 24

Management of the older man with functional hypogonadism

Lifestyle measures and optimisation of comorbidities

IN contrast to organic hypogonadism, the risk–benefit ratio of testosterone treatment in men with so-called late-onset hypogonadism (LOH) is not known (see table 2). This is because there are no large, long-term randomised controlled clinical trials to inform about patient-important benefits (eg, fracture reduction, improved functional mobility or mortality) or therapy-associated risks. Priority should lie in the implementation of lifestyle measures (especially weight loss), optimisation of comorbidities (eg, depression, sleep apnoea or glycaemic control in diabetes) and, where possible, removal of offending medications (eg, opioids, glucocorticoids). This strategy may safely raise testosterone levels and has other health benefits.

Obesity is the strongest risk factor for low testosterone, even overriding the effects of age. This is in part because obesity blunts the age-related LH rise that can compensate for testicular dysfunction occurring in some older men. Consistent with this, successful weight loss, whether by diet or surgery, can lead to substantial increases in testosterone in obese men. The increase in testosterone is proportional to the amount of weight lost: 10% weight loss increases testosterone by 2-3nmol/L, whereas profound weight loss after bariatric surgery can raise testosterone by more than 10nmol/L in morbidly obese men.[4]

It should be noted that, in certain scenarios, even functional hypogonadism may be associated with profound androgen deficiency that could require testosterone replacement therapy. One example is patients requiring narcotic analgesics. 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 LOH.

Testosterone therapy in older men without organic hypogonadism

In a proportion of older men, measures to reverse functional hypogonadism may be unsuccessful — either because their implementation is not feasible (eg, cessation of opioids) or they are not achieved or maintained (eg, weight loss). In some men, features of LOH may persist despite successful implementation of these measures. For example, not all obese men will normalise testosterone levels, even after successful weight loss; therefore, testosterone levels should be repeated if symptoms persist. If testosterone remains low, it should be ensured that underlying organic HPT axis pathology has not been missed.

If first-line measures fail, the question arises as to whether a trial of testosterone treatment is justified to determine whether there is benefit. In general, the response to testosterone therapy is inversely correlated to the pre-treatment testosterone levels, age, BMI and number of chronic comorbidities. If considered, testosterone treatment should target men with more severe and specific signs and symptoms, and an unequivocally and repeatedly low testosterone level. The risk–benefit ratio will be better in the younger, leaner man with fewer comorbidities who has specific symptoms and consistently low testosterone.

Testosterone threshold levels that predict a response to testosterone treatment are not well defined and are likely to be different not only among individuals but also for different clinical endpoints. A panel of US experts was divided on the total testosterone level below which to consider testosterone treatment, with opinions ranging from 6.9nmol/L to 10.4nmol/L.[9] Population-based studies in healthy Australian men using gold-standard LCMS/MS assay technology have reported lower limits for total testosterone of 9.8nmol/L for healthy young men and 6.4nmol/L for older men reporting excellent health.[11,14]

Testosterone treatment in older men should only be commenced after appropriate counselling, informing the patient about the absence of high-level evidence regarding long-term risks and benefits. It is advisable to document this discussion in the medical records. Clear patient-specific goals should be identified, and the patient should be informed at the outset that testosterone therapy will be stopped should there be no benefit, according to defined treatment goals agreed between the patient and practitioner.

If testosterone treatment is considered in older men, contraindications must be excluded. Since symptoms of androgen deficiency should improve within 1-3 months, a therapy trial of 3-6 months is usually of sufficient duration. Although somatic effects of testosterone treatment, such as BMD gains, require longer treatment, testosterone should generally not be used for such indications in asymptomatic men, given more effective therapeutic alternatives are available (see table 3).

The initial use of short-acting testosterone formulations minimises the risk of iatrogenic hypogonadism if testosterone treatment is stopped because of lack of benefit. In men suitable for long-term testosterone therapy, different options are available (see table 1). Choice depends on patient and physician preference.

The therapeutic target should be to raise serum testosterone levels to the low- to mid-normal range of healthy young men. On treatment, testosterone levels that are higher than mid-normal should be avoided, based on early evidence that this may be harmful in older men. A recent Australian observational study of older men reported that men with mid-normal testosterone levels between 9.8nmol/L and 15.8nmol/L had the lowest mortality, while older men either below or above this range were more likely to die.[15] Similarly, in a randomised controlled trial, the increased risk of cardiovascular events during testosterone therapy was correlated with higher on-treatment serum testosterone levels.[16]

Possible benefits of testosterone therapy in older men

The most consistent effects of testosterone treatment in older men are modest improvements in body composition (around a 2kg gain in muscle mass and a 2kg loss of fat mass) and an improvement in lumbar spine bone density (about a 4% increase) (see table 3). Some

Table 2: 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

Treatment in older men should only be commenced after appropriate counselling, informing the patient about the absence of high-level evidence regarding long-term risks and benefits.

Table 3: Possible benefits of testosterone therapy in older men

Domain	Testosterone effect	First-line therapy
Sexual	Modest increase in overall function if total testosterone is less than 12 (some studies), libido improves more than erectile function	PDE-5 inhibitor, no added benefit of testosterone treatment
Muscle	Increase in mass (1.6-2.7 kg) and strength, no evidence for improved physical function	Exercise
Fat	1.6-2.0kg decrease	Weight loss
Glucose metabolism	Modest improvement in insulin resistance in some randomised controlled trials, no effect on HbA_{1c}	Lifestyle, antidiabetic medications
Bone	3.7% increase in lumbar spine BMD, no fracture data	Antiresorptives
Mood/ cognition	No consistent effects	Counselling, antidepressants

studies have shown improvements in muscle strength and insulin resistance, but diabetes does not improve.[17,18] There is no high-level evidence for benefits in physical performance, falls, glycaemic control, fractures or mood. No data exist on mortality or quality of life. For many conditions associated with low testosterone, more specific first-line therapies targeting these domains individually — such as exercise; and antiglycaemic, antiresorptive, or antidepressant pharmacotherapy — are available (see table 3).

Management of sexual dysfunction in older men

Sexual symptoms are most closely clustered with low testosterone and one of the most common reasons why older men seek testosterone treatment.[3] Weight loss and increased physical activity have been shown to improve erectile dysfunction in several controlled trials and should be implemented first. In addition, such lifestyle modifications can improve the success rate of phosphodiesterase-5 (PDE-5) inhibitor treatment.

In contrast, the evidence that testosterone improves sexual function in older men with low testosterone levels is not consistent. Decreased libido, although non-specific, is more strongly related to low testosterone than erectile dysfunction. In young men, erectile function is maintained at very low levels of testosterone, and the correlation of low testosterone with erectile dysfunction is weak. In contrast, predominant erectile dysfunction with preserved libido, the typical presentation in older men with comorbidities, often has a strong neurovascular pathogenesis. Indeed, the association between low testosterone and erectile dysfunction probably reflects their shared association with vascular disease.

The most recent meta-analysis of randomised controlled trials of men presenting with erectile dysfunction concluded that, while PDE-5 inhibitors were more effective than placebo in improving sexual intercourse success and erectile function, the effects of testosterone treatment were inconclusive.[19] Moreover, in a recent randomised placebo-controlled trial, men whose sexual function had been optimised with a PDE-5 inhibitor did not derive further benefit with the addition of testosterone. Interestingly, PDE-5 inhibitor use alone led to significant increases in testosterone levels in these men.[20] Therefore in older men, testosterone treatment should be primarily considered in men who fail lifestyle measures and PDE-5 inhibitors and have persistently low testosterone levels after the PDE-5 inhibitor dose has been optimised.

Testosterone treatment: potential risks and monitoring for adverse events

YOUNG men with organic hypogonadism generally have a favourable risk–benefit ratio with testosterone therapy, provided contraindications have been excluded and men are monitored for side effects (see table 4). While no randomised controlled clinical trials are available, the safety of testosterone replacement therapy (ie, the restoration of physiological circulating testosterone levels in men with organic androgen deficiency) is well established, based on open-label trials and more than 70 years of clinical experience.

Compared with otherwise healthy young men with organic androgen deficiency receiving testosterone replacement for pathological androgen deficiency, older men with significant comorbidities — such as prostate disease, cardiovascular disease or undiagnosed obstructive sleep apnoea — may be at higher risk of adverse outcomes. Prostate and cardiovascular events are of particular concern. Trials to date have been underpowered to provide definitive outcome data regarding prostate and cardiovascular events in older men, and long-term risks are unknown.

To date, experimental and clinical studies have not demonstrated that testosterone increases the risk of prostate cancer. The true risk, however, is not known because of the absence of adequately powered long-term randomised controlled trials. It has been estimated that a randomised controlled trial of 6000 men would be necessary to detect a 30% increase in prostate cancer risk with testosterone therapy, yet the largest completed trials have included fewer than 500 men.[21] A large-scale testosterone trial similar in magnitude to HRT studies in women is unlikely to eventuate in the near future.

Although PSA testing in the general population is controversial, Australian and international guidelines recommend regular prostate monitoring in older men receiving testosterone.[9,10] While the exact age cut-off is not known, most practitioners commence prostate monitoring in testosterone-treated men once they reach the age of 50-55. It is important to note that, given the prostate is an androgen-responsive organ, testosterone treatment will usually lead to a modest increase in the PSA level. While the amount of such a physiological PSA increase is not well defined, the best evidence suggests that PSA increases of more than 1.4nm/mL a year are uncommon and should trigger prostate evaluation.[9] Nevertheless, one practical concern is that as a result of prostate monitoring during testosterone therapy, overdiagnosis of clinically insignificant prostate cancer may occur.

The current evidence regarding testosterone treatment and cardiovascular outcomes is contradictory and inconclusive.[22] Some observational studies in older men have shown increased, and some decreased, risk of cardiovascular events with testosterone treatment. However, no firm conclusion can be drawn from these mostly retrospective studies because of the non-randomised design with the potential for multiple sources of

cont'd next page

Table 4: Testosterone therapy: adverse events

More common	Erythrocytosis* Acne and oily skin Detection of subclinical prostate cancer Growth of metastatic prostate cancer Reduced sperm production and fertility
Uncommon	Gynaecomastia Male pattern balding (familial) Growth of breast cancer Induction or worsening of obstructive sleep apnoea
FORMULATION-SPECIFIC ADVERSE EFFECTS	
Injectable testosterone	Fluctuation in mood or libido (short-acting esters) Pain at injection site Excessive erythrocytosis (especially in older patients) Post-injection cough due to pulmonary oil microembolism
Transdermal patches	Frequent skin reactions at application site
Transdermal gel	Potential risk for testosterone transfer to partner or another person who is in close contact Skin irritation
Testosterone pellets	Infection, fibrosis or pellet extrusion

*Most common adverse effect, more frequent with injectable testosterone

Source: Adapted from references 9 and 10

Monitoring testosterone therapy

1. Evaluate the patient 3-6 months after treatment initiation and then annually to assess whether symptoms have responded to treatment and whether the patient is suffering from any adverse effects
2. Monitor the testosterone level 3-6 months after initiation of testosterone therapy; therapy should aim to raise the serum testosterone level into the mid-normal (young men) to low- to mid-normal range (older men)
3. Check haematocrit at baseline, at 3-6 months and then annually; if haematocrit is greater than 54%, stop therapy until haematocrit decreases to a safe level, evaluate the patient for hypoxia and sleep apnoea, and reinitiate therapy with a reduced dose
4. Measure BMD of lumbar spine and/or femoral neck after 1-2 years of testosterone therapy in hypogonadal men with osteoporosis or low-trauma fracture, consistent with regional standard of care
5. In men 40 or older with a baseline PSA greater than 0.6ng/mL, perform a digital rectal examination and check PSA level before initiating treatment at 3-6 months and then in accordance with guidelines for prostate cancer screening
6. Obtain urological consultation if the following occur:
   - I. An increase in serum PSA concentration of more than 1.4ng/mL within any 12-month period of testosterone treatment; a PSA velocity of more than 0.4ng/mL a year, using the PSA level after six months of testosterone administration as the reference (only applicable if PSA data are available for a period exceeding two years)
   - II. Detection of a prostatic abnormality on digital rectal examination
   - III. Severe obstructive symptoms (International Prostate Severity Score of over 19)
7. Evaluate formulation-specific adverse events

Source: Adapted from reference 9

Principles in the approach to men with lowered testosterone levels without recognisable hypothalamic-pituitary-testicular axis pathology

The first-line approach should focus on assessment for and treatment of associated comorbidities and emphasis on lifestyle measures, especially weight loss in overweight and obese men.

Testosterone treatment should only be considered in carefully selected symptomatic men, where first-line measures fail, after explicit discussion regarding the experimental nature of this treatment and the uncertainty regarding the risk–benefit ratio of testosterone therapy.

In general, less obese younger men with lower testosterone levels and fewer comorbidities are more likely to derive a benefit from testosterone treatment, and they may be at lower risk of adverse events.

A 3-6-month trial is usually of sufficient duration since symptoms, if caused by androgen deficiency, should improve within 1-3 months. At the outset, the patient should be informed that treatment will be stopped should there be no improvement in predefined treatment goals.

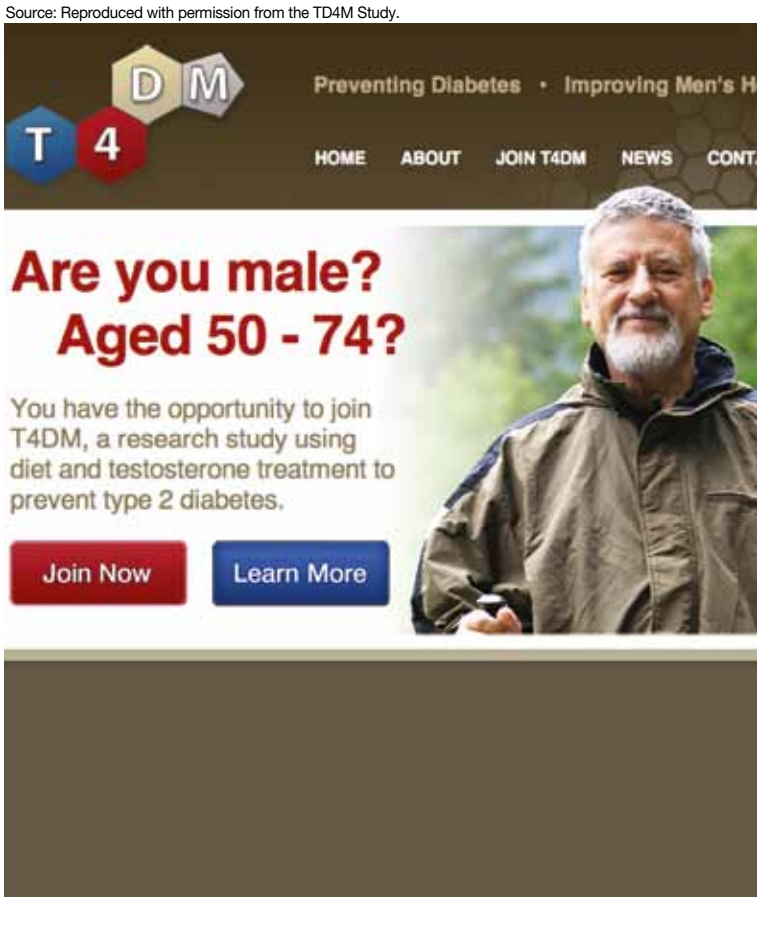
Long-acting testosterone should initially be avoided to enable rapid cessation of therapy in case of adverse events and to reduce the risk of iatrogenic suppression of the endogenous HPT axis, although this risk is relatively low with a short course of testosterone therapy.

Testosterone for the prevention of diabetes mellitus (T4DM), an Australian multicentre study

Large, well-conducted clinical trials to provide more evidence to guide clinicians and patients regarding the risks and benefits of testosterone therapy are lacking. One important such trial, the largest trial worldwide, is Testosterone for the prevention of diabetes mellitus (T4DM), an Australian multicentre, NHMRC-funded study testing the hypothesis that testosterone therapy, in addition to a lifestyle program (administered by Weight Watchers), can prevent the development of type 2 diabetes mellitus in high-risk men.

The study is recruiting men aged 50-74 who have a waist circumference of 95cm or more but who do not have diabetes. This trial is currently open for recruitment at all Australian capital cities. Men interested in participating in this study can find more information and join the study online by visiting www.t4dm.org.au

Source: Reproduced with permission from the TD4M Study.



from previous page

bias and confounding.

One randomised controlled trial has shown an increase in cardiovascular events with testosterone treatment in relatively frail older men; however, numbers were small and may well have been due to chance. Another randomised controlled trial in a similar population of men has not confirmed this finding.[6,23] One recent meta-analysis including almost 3000 mainly older men did show an increased risk of a broad range of cardiovascular-related events with testosterone therapy, but because of limitations, these data are not definitive.[24] A US Federal Drug Administration–commissioned review of the existing data found no numeric increase of major adverse cardiac events in testosterone-treated men. Nevertheless, the Federal Drug Administration now mandates labelling of US testosterone products to warn about a possible increased risk of heart attack and stroke.

Overall, until better evidence is available, it seems prudent to use testosterone treatment with great caution, if at all, in older men — especially in those with known cardiovascular disease. Unstable cardiac disease or recent cardiovascular events (within 6-12 months) constitute contraindications. Negative effects of testosterone on fertility should be considered in men who have not completed their families.

References

Available on request from howtotreat@cirrusmedia.com.au

Case studies

Case study one

MIKE, aged 64, presents with low libido, erectile dysfunction and low energy levels. He has gradually gained weight over the past 10 years. Mike has type 2 diabetes mellitus of six years' duration. A recent HbA_{1c} was 8.2%. Other comorbidities include well-controlled hypertension, asymptomatic stable ischemic heart disease with one previous coronary stent and no other known macrovascular complications.

He reports poor dietary habits and does not exercise. Mike denies symptoms of sleep apnoea. He is an ex-smoker of 20 pack years and consumes 1-2 standard drinks of alcohol a week. He fathered two children in his 30s without difficulties, and he recalls normal pubertal development. Current medications include metformin, a sulfonylurea, an angiotensin II inhibitor, a statin and a low-dose aspirin.

Physical examination shows central obesity (BMI 31kg/m^2), normal male-pattern body hair, mild loss of muscle bulk, 18mL testes, lipomastia but no gynaecomastia, full visual fields and no clinical evidence of Cushing's syndrome.

Morning fasting total testosterone is modestly reduced at 7.4nmol/L, with an assay-specific reference range (RR) of 10-27.6nmol/L. Repeat total testosterone is 7.8nmol/L. Sex hormone–binding globulin is low/normal at 24nmol/L (RR 13-71nmol/L), consistent with insulin resistance. Free testosterone level is modestly reduced at 167pmol/L and 179pmol/L on repeat, relative to the reference range in young men (RR 230-610pmol/L), consistent with older age. LH is 4.3 IU/L (RR 1-10) and FSH 3.7 IU/L (RR 1-10). Prolactin, iron studies and thyroid function are normal. Pituitary imaging is not performed.

This patient presents with sexual symptoms and a repeatedly low testosterone level and therefore fulfils the diagnostic criteria proposed for LOH. A trial of lifestyle measures is recommended, with emphasis on weight loss. Over the next year, Mike loses 11kg of body weight, and his LOH resolves: repeat total testosterone levels are 11.1nmol/L and 12.0nmol/L. Energy levels improve, and he reports adequate sexual function with the use of a PDE-5 inhibitor. His HbA_{1c} has decreased to 6.8%, and his sulfonylurea dose is reduced.

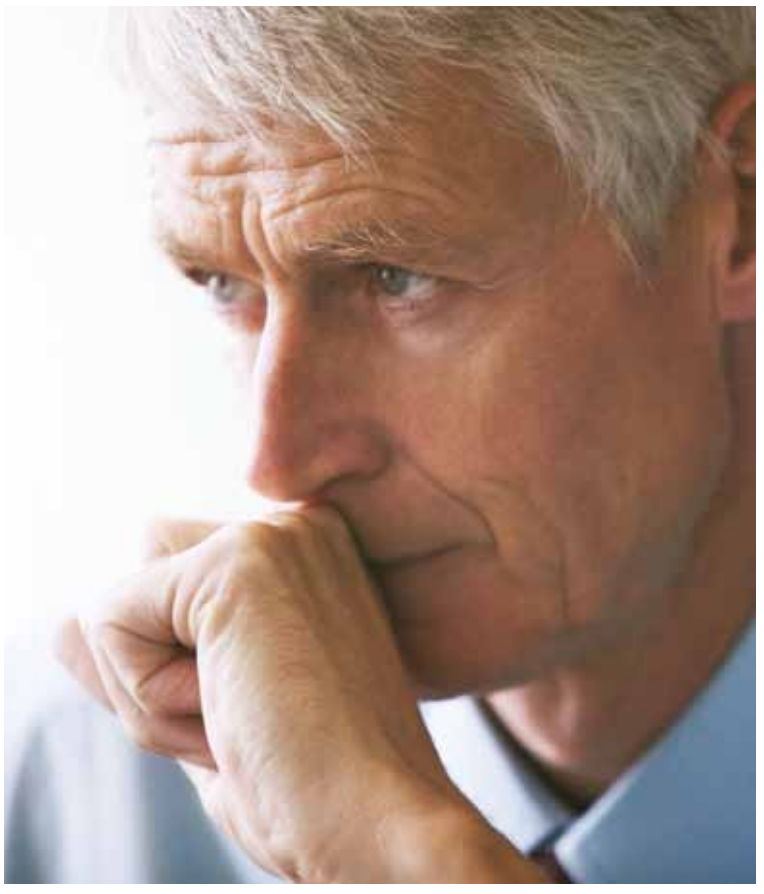
Case study two

George, aged 61, presents with fatigue, low libido, reduced erectile function and mild irritability. While he experiences modest improvement in sexual function with the use of PDE-5 inhibitors, he is still bothered by suboptimal sexual performance. George denies symptoms suggestive of sleep apnoea. His medical history is notable for type 2 diabetes mellitus and hypertension. He had a normal stress echocardiogram six months prior to presentation. Current medications include metformin, a statin and an angiotensin blocker. George's metabolic risk profile is satisfactory, with an HbA_{1c} of 6.8% and an LDL cholesterol of 2.2nmol/L.

Importantly, multiple lifestyle and weight-loss measures have failed, and he is now keen to commence testosterone treatment to find out whether this will improve his symptoms.

Physical exam shows a BMI of 31kg/m^2. There is no gynaecomastia, and body hair and muscle bulk do not appear reduced. Genital examination is normal, with a testicular size of 18mL bilaterally (normal greater than 15mL). Rectal exam reveals a smooth, non-enlarged prostate. There are no clinical signs of a pituitary mass lesion. He has a BP of 130/72mmHg.

Importantly, multiple lifestyle and weight-loss measures have failed, and he is now keen to commence testosterone treatment to find out whether this will improve his symptoms.



Fasting total testosterone levels are modestly low at 7.1 and 7.9nmol/L on repeat (RR 10-27.6), as are his calculated free testosterone levels: 155pmol/L and 170pmol/L (RR 230-610pmol/L). His LH is 2.5 IU/L (RR 1-10), and prolactin levels and iron studies are normal. Pituitary imaging is not performed because of an absence of clinical suspicion and the fact that his testosterone levels are only modestly reduced. George's PSA level of 2.9mcg/L (RR less than 6.5) and his haematocrit of 46 (RR 40-52) are both in the normal range.

Given the failure of first-line weight loss and lifestyle measures, you discuss the limited evidence regarding the risks and benefits of testosterone therapy in his situation and inform George about the absence of long-term, large clinical trials.

He is keen to proceed with testosterone treatment. You agree on a six-month trial of testosterone therapy with appropriate monitoring. You advise that testosterone treatment will be stopped should his symptoms not improve or adverse effects occur. You provide him with a private script for topical testosterone and educate him regarding contact precautions to avoid gel transfer.

At review one month later, his total testosterone is adequate at 15.4nmol/L. He feels "definitely more energetic" and reports better response when using a PDE-5 inhibitor. He elects to continue with topical testosterone treatment. At three months, he feels that the benefits are perhaps less consistent. Repeat assessment shows a total testosterone of 14.6nmol/L, a mild increase in his PSA to 3.4mcg/L and a haematocrit of 48. He remains keen to continue with testosterone, and you arrange review after a further three months.

Three months later, his PSA has increased significantly to 6.8mcg/L. You stop his testosterone and arrange referral to a urologist, who recommends a prostate biopsy, which shows no evidence of prostate cancer. Three months after stopping testosterone, his PSA has returned to baseline. The patient agrees with you that a repeat trial of testosterone treatment is not worthwhile.

cont'd page 28

Conclusion

ORGANIC hypogonadism can present in many ways, including psychosexual symptoms or unexplained osteoporosis, anaemia or sarcopaenia; the diagnosis can be missed. It is a clinical diagnosis consisting of suggestive signs and symptoms, confirmed by low testosterone levels. Testosterone replacement has marked benefits but may impair fertility.

Older men with chronic disease commonly present with non-specific symptoms and modestly low testosterone levels, making the diagnosis of androgen deficiency more difficult than in younger, otherwise healthy, men without comorbidities. Older men with specific features of androgen deficiency and unequivocally low testosterone levels should be evaluated for an underlying pathological cause. It should not be assumed that their presentation is a non-specific consequence of age-related comorbidities or obesity. Low testosterone is a biomarker of poor health and identifies men at risk of increased mortality, although the poor health is usually clinically obvious. Testosterone increases with weight loss, suggesting that the HPT axis suppression is functional and reversible.

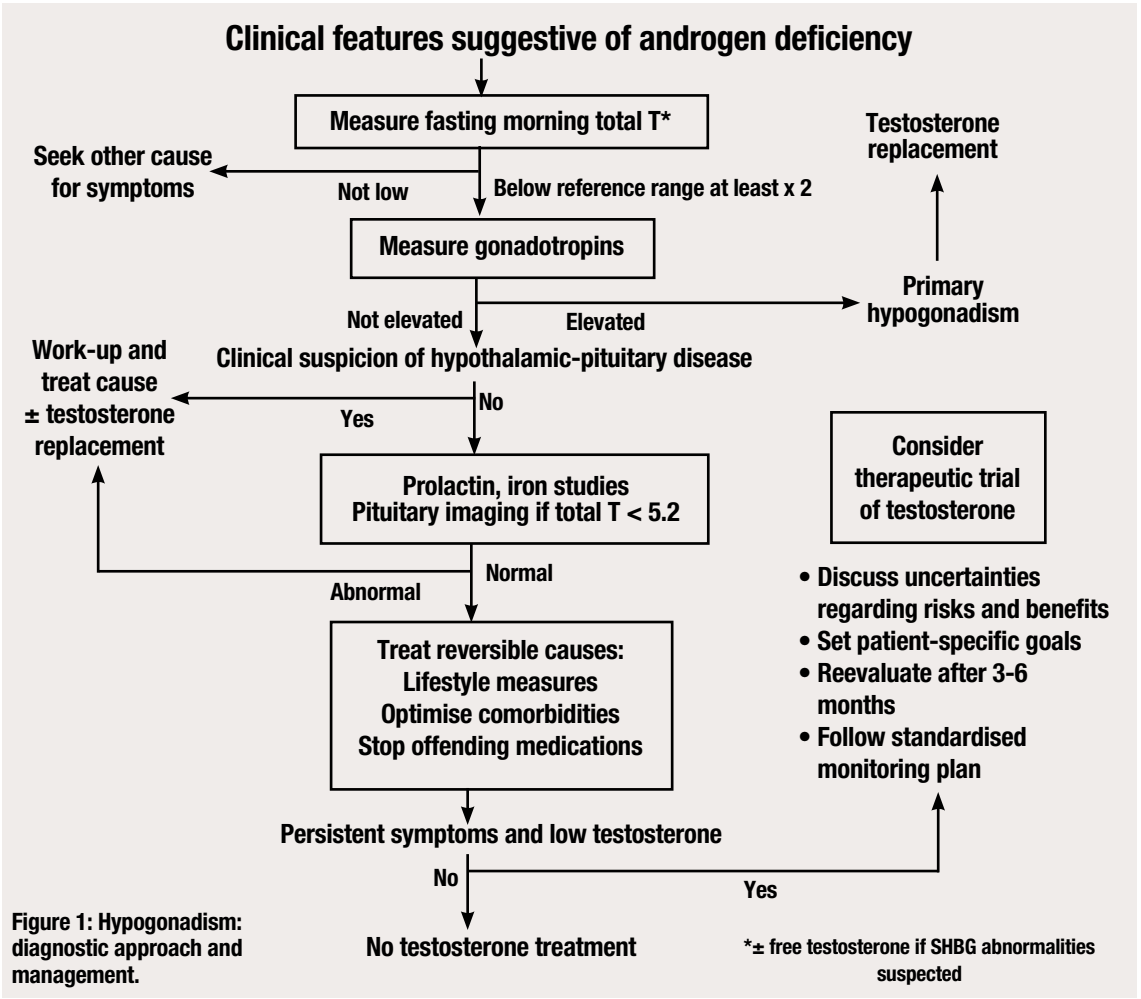


Figure 1: Hypogonadism: diagnostic approach and management.

The first response to the ageing, obese man with a low/normal testosterone should be the optimisation of lifestyle measures and comorbidities. As a result of limited evidence, testosterone therapy in men without organic hypogonadism remains experimental, and further evidence from well-conducted clinical trials is required. The largest such trial worldwide (Testosterone for the prevention of diabetes mellitus, T4DM) is an Australian multicentre, NHMRC-funded study that is currently recruiting patients in all Australian capital cities.

Until better evidence is available, testosterone therapy in older men should be considered primarily for men who have significant clinical features and low testosterone levels that persist after a trial of lifestyle measures, a tailored diagnostic workup, exclusion of contraindications, and appropriate counselling. Clear patient-specific treatment goals should be identified, and treatment should be accompanied by a standardised monitoring plan. If treatment goals are not met, or adverse effects occur, testosterone treatment should be stopped. The suggested approach is summarised in figure 1.

How to Treat Quiz

Low testosterone part 2
— 3 July 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.

GO ONLINE TO COMPLETE THE QUIZ

www.australiandoctor.com.au/education/how-to-treat

1. Which TWO statements regarding management are correct?
a) Provided there are no contraindications, men with organic hypogonadism should be treated with testosterone replacement.
b) Testosterone treatment is always commenced as soon as possible and may be adjusted once the first testosterone level is available.
c) The PBS subsidises testosterone replacement for men with hypogonadism due to established testicular or pituitary disease without restrictions.
d) Testosterone treatment does not compromise fertility.

2. Which THREE are contraindications to the use of testosterone?
a) Breast or prostate cancer
b) Unstable cardiac disease
c) Haematocrit less than 40%
d) Untreated severe obstructive sleep apnoea

3. Which THREE are disadvantages of testosterone gel?
a) Must be administered in the axilla
b) Chance for inadvertent transfer to close contacts
c) Skin irritation
d) Variation in testosterone blood levels

4. Which THREE are disadvantages of testosterone injections?
a) Injection-site pain
b) Contraindicated in men with coagulopathies or thrombocytopenia
c) Frequent dosing required
d) Post-injection cough due to pulmonary oil microembolism

5. Which TWO testosterone products are administered once daily?
a) Testosterone gel
b) Testosterone oral capsule
c) Testosterone undecanoate IM injection
d) Testosterone patch

6. Which THREE statements regarding the management of the older man with functional hypogonadism are correct?
a) The risk–benefit ratio of testosterone treatment in men with so-called late-onset hypogonadism (LOH) is not known.
b) Treatment priorities include the implementation of lifestyle measures and the optimisation of comorbidities.
c) Diabetes is the strongest risk factor for low testosterone.
d) Removal of offending medications is advised.

7. Which TWO statements regarding the management of the older man with functional hypogonadism are correct?
a) In some men, features of LOH may persist despite successful implementation of lifestyle and other measures.
b) All obese men will normalise testosterone levels, even after successful weight loss.
c) If considered, testosterone treatment should target men with less severe signs and symptoms and a low/normal testosterone level.
d) If testosterone remains low even after successful weight loss and optimisation of comorbidities, it should be ensured that underlying organic hypothalamic–pituitary–thyroid axis pathology has not been missed.

8. Which THREE statements regarding the management of the older man with functional hypogonadism are correct?
a) The risk–benefit ratio will be better in the younger, leaner man with fewer comorbidities who has specific symptoms and consistently low testosterone.
b) Clear patient-specific goals should be identified prior to commencing testosterone therapy.
c) Testosterone treatment in older men should only be commenced after appropriate counselling, informing the patient about the absence of high-level evidence regarding long-term risks and benefits.
d) Testosterone threshold levels that predict a response to testosterone treatment are well defined.

9. Which TWO statements regarding the management of the older man with functional hypogonadism are correct?
a) A trial of 6-12 months is usually of sufficient duration to assess the improvement of symptoms of androgen deficiency.
b) The initial use of short-acting testosterone formulations minimises the risk of iatrogenic hypogonadism if testosterone treatment is stopped because of lack of benefit.
c) The therapeutic target should be to raise serum testosterone levels to the low- to mid-normal range of healthy young men.
d) Testosterone is an effective and safe option for the management of low BMD in asymptomatic men.

10. Which TWO statements regarding sexual symptoms in older men are correct?
a) There is consistent evidence that testosterone improves sexual function in older men with low testosterone.
b) Sexual symptoms are one of the most common reasons why older men seek testosterone treatment.
c) The addition of testosterone to a PDE-5 inhibitor will enhance sexual function.
d) Weight loss and increased physical activity have been shown to improve erectile dysfunction.

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

HOW TO TREAT Editor: **Dr Claire Berman**
Email: **claire.berman@cirrusmedia.com.au**

NEXT WEEK

NEXT week's How to Treat explores the management of osteoporosis. Osteoporosis has a significant patient burden of increased morbidity and mortality. However, the majority of patients presenting with a fragility fracture are neither assessed for osteoporosis, nor appropriately managed to prevent further fractures. The authors are **Dr Kirtan Ganda**, endocrinologist, Concord Repatriation General Hospital and University of Sydney, NSW; and **Professor Markus J Seibel**, professor of endocrinology, University of Sydney, NSW, and head of the department of endocrinology and metabolism, Concord Repatriation General Hospital, Sydney, NSW.