

# Low testosterone levels

## Focus on the man not the number

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**Men concerned about low testosterone levels in the setting of older age or illness should be offered a holistic assessment and encouraged to engage in healthy lifestyle behaviours. Only men who are androgen deficient due to underlying hypothalamic, pituitary or testicular disorders warrant testosterone therapy.**

**A**s men grow older, their testosterone levels gradually decline.<sup>1</sup> This is closely associated with increased central adiposity and the accumulation of medical comorbidities.<sup>2,3</sup> These changes have prompted speculation that falling sex hormone levels are an inevitable part of reproductive ageing in men. It is important to identify men with androgen deficiency due to underlying hypothalamic, pituitary or testicular disorders, as these men benefit from testosterone therapy.<sup>4</sup> However, most men have an intact hypothalamic–pituitary–testicular (HPT) axis, and are best served by a holistic assessment and support to engage in healthy lifestyle behaviours, facilitating loss of excess weight.<sup>5</sup>

This article explores factors contributing to lower testosterone levels in ageing men, outlines the pathway for diagnosis of androgen deficiency and discusses options for men to improve their general health.

### Testosterone and ageing

Older men have lower testosterone levels compared with younger men.<sup>1</sup> However, there is no abrupt decline beyond a certain age, rather the differences are small and incremental over many years.<sup>1</sup>

MedicineToday 2021; 22(1-2): 63-67

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Healthy older men can have testosterone levels comparable to those of younger men.<sup>6</sup> When a large group of men in their mid-70s was followed into their 80s, a decline in testosterone levels accompanied by an increase in luteinising hormone (LH) was seen, suggestive of Leydig cell impairment.<sup>7</sup> However, in many men in their 40s and 50s, lower testosterone levels are not due to an inevitable decline in testicular function, but are contributed to by the increasing presence of obesity and other medical comorbidities that reduce activity of the HPT axis.<sup>2,3</sup> Other factors known to affect testosterone levels include disrupted sleep, depression and use of medications such as opioids.<sup>8-10</sup>

### Androgen deficiency: a clinical diagnosis

Although obesity and other comorbidities that reduce HPT-axis activity may be accompanied by symptoms such as tiredness, lethargy, sleepiness, low mood and loss of libido, they are not accepted indications for testosterone therapy.<sup>4</sup> Men presenting with such symptoms do merit a careful clinical evaluation, looking for other symptoms and signs of androgen deficiency such as infertility, reduced muscle mass, increased fat, gynaecomastia and osteopenia or osteoporosis.<sup>4</sup> Small testes on examination may be an indicator of Klinefelter's syndrome, or some other testicular disorder. In men in whom the diagnosis of androgen deficiency is suspected, ideally an early morning (waking) fasting blood sample should be collected for measurement of testosterone using a reliable assay to confirm the clinical diagnosis.<sup>4</sup>

Reference ranges for testosterone in older men are lower than those for younger men.<sup>4,11</sup> Published reference ranges are 10.4 to 30.1 nmol/L for men aged 21 to 35 years with normal reproductive function,<sup>12</sup> and 6.4 to 25.7 nmol/L for healthy men aged 70 to 89 years.<sup>11</sup> If testosterone is low, the level of sex hormone-binding globulin (SHBG) should be measured, as men with low SHBG levels (e.g. in those with obesity or insulin resistance) may have lower than expected testosterone without being androgen deficient. Interpretation of testosterone concentrations in conjunction with

SHBG is recommended, as the utility of calculating 'free' testosterone remains under debate.<sup>4,13</sup>

Low testosterone and elevated LH levels indicate a primary (testicular) cause of androgen deficiency. An elevated follicle-stimulating hormone level indicates impairment of spermatogenesis. Low testosterone and normal LH (and follicle-stimulating hormone) levels may be seen in men with hypothalamic or pituitary disease (i.e. secondary hypogonadism), but are also found in men with reduced activity of the HPT axis due to the presence of systemic illness or medical comorbidities.<sup>13</sup>

### Physiological testosterone therapy for hypogonadism

Men who are androgen deficient due to underlying hypothalamic, pituitary or testicular disorders should be considered for testosterone therapy.<sup>4,14</sup> In some cases, treating the underlying cause would restore normal testosterone levels without the need for testosterone treatment (e.g. cabergoline therapy for prolactinoma). In most cases, where there is permanent damage to the pituitary or testes, long-term testosterone therapy is needed.

Before starting treatment, careful assessment of existing medical comorbidities, including cardiovascular and prostate disease, is advised.<sup>14</sup> Men with active cardiovascular disease should have their treatment optimised. Prostate screening for underlying malignancy should be discussed and offered when appropriate, comprising digital rectal examination and prostate-specific antigen testing.<sup>14</sup> As elevation of haematocrit is a side effect of testosterone treatment, factors such as smoking status and presence of sleep apnoea need to be considered.

Men's fertility plans need to be considered and addressed before testosterone therapy is started, as exogenous testosterone inhibits gonadotrophin secretion and spermatogenesis.<sup>4</sup> When fertility is not an issue, options for testosterone treatment include long-acting depot testosterone injections (typically given at 12-week

intervals) or daily transdermal gel or cream formulations.<sup>14</sup> Short-acting intramuscular testosterone formulations given fortnightly result in marked fluctuations in blood testosterone concentrations,<sup>14</sup> and they are no longer PBS-listed.

Improvement in symptoms and signs of androgen deficiency should be assessed (although gynaecomastia may not resolve, or may appear or become more prominent after initiating treatment). In addition to clinical monitoring of symptoms and signs, biochemical monitoring is important to check haemoglobin and haematocrit, as well as prostate-specific antigen levels.

Measurement of the patient's testosterone levels while taking treatment should ensure these are in the physiological range (e.g. in the lower part of the normal range for trough levels). Blood tests should be taken before testosterone undecanoate injections, and for daily transdermal formulations these can be done before application or two to four hours after dosing (refer to respective product information for full details on monitoring).<sup>14</sup>

### Debunking the myth that low testosterone is intrinsic to male ageing

For middle-aged and older men without hypothalamic, pituitary or testicular disease, but with nonspecific symptoms and testosterone levels that are lower than expected for young men, concern over low testosterone is an opportunity to explore their health in a holistic fashion. Such men should be discouraged from seeking testosterone prescriptions. Instead, careful assessment and optimal management of medical comorbidities can be provided; advice can be given on losing excess weight, eating healthily and exercising regularly; and use of medications such as opioids can be judiciously reviewed.<sup>5</sup> Depression and sleep apnoea, if present, should be managed appropriately. Men who lose excess weight will improve their HPT-axis function and raise endogenous testosterone levels.<sup>2</sup> Men receiving medically indicated and ongoing corticosteroid or opioid therapy who have

associated low testosterone levels may benefit from specialist review.<sup>4</sup>

### Pharmacological intervention

As noted above, testosterone therapy is indicated for physiological replacement in men who are androgen deficient due to underlying pituitary or testicular disease.<sup>4</sup> It is important to guard against inappropriate testosterone prescribing in men without a valid indication, and to strongly discourage misuse or abuse of illicitly obtained anabolic steroids as a performance or image enhancing drug, which is associated with harms.<sup>4,15</sup> For testosterone to be considered as a pharmacological intervention to improve health in men without pituitary or testicular disease, high-quality evidence – i.e. from large, randomised clinical trials (RCTs) – is necessary.

Two major placebo-controlled RCTs, the US Testosterone Trials (T-Trials) and the Australian Testosterone for the Prevention of Type 2 Diabetes Mellitus (T4DM) trial, have provided high quality evidence on the pharmacological effects of testosterone in men without pathological hypogonadism.<sup>16,17</sup>

### US Testosterone Trials

T-Trials randomised 788 men aged 65 years and above, with baseline testosterone less than 9.5 nmol/L and symptoms consistent with hypogonadism, but without recognisable HPT-axis pathology, to daily transdermal testosterone or placebo for 12 months. Testosterone treatment resulted in a modest improvement in sexual function, which appeared to wane towards the end of the 12-month trial, while other primary outcomes of vitality and physical function were not met.<sup>16</sup>

T-Trial substudies indicated a neutral effect on cognition and improvements in volumetric bone density and anaemia.<sup>18</sup> Another T-Trial substudy involving 138 of the participating men reported an increase in volume of coronary atheromatous plaque, but interpretation was complicated by the fact that in this substudy, testosterone and placebo groups were unbalanced, with

those in the placebo group having higher plaque volumes at baseline and the end of the study.<sup>19</sup>

Overall, although providing important information, T-Trials is unlikely to alter the current clinical equipoise.<sup>20</sup>

### Testosterone for Prevention of Type 2 Diabetes Mellitus trial

The Australia-wide T4DM RCT recruited men aged 50 to 74 years, with a waist circumference 95 cm or higher, testosterone level 14 nmol/L or lower, without recognised HPT-axis pathology, and either impaired glucose tolerance or newly diagnosed type 2 diabetes.<sup>17</sup> All participating men were enrolled in a Weight Watchers program and randomly allocated to receive injections of testosterone undecanoate 1000 mg or matching placebo, at baseline, six weeks and every three months thereafter for two years (nine injections in total).

T4DM randomised 1007 men, the largest testosterone RCT completed to date.<sup>21</sup> At the end of the two-year intervention, the proportion of men with a two-hour glucose level on oral glucose tolerance testing of 11.1 mmol/L or above was 12% in the testosterone group (55/443 men) and 21% in the placebo group (87/413 men), a relative risk reduction of about 40%.<sup>21</sup> On average, men in the testosterone group gained 0.4 kg of muscle and lost 4.6 kg of fat, whereas men in the placebo group lost 1.3 kg of muscle and 1.9 kg of fat, after two years.

A safety trigger for haematocrit greater than 54% occurred in 1% of the placebo group and 22% of the testosterone group, and longer-term durability and safety remain to be further investigated.<sup>21</sup>

Of note, there was no signal for excess cardiovascular adverse events in either T-Trials or T4DM.<sup>16,20,21</sup> The effects of testosterone treatment as a pharmacological intervention on the cardiovascular system is an important question that remains unresolved.<sup>22</sup>

### Conclusions and role of GPs

GPs have important roles in addressing concerns about low testosterone in

middle-aged and older men. Firstly, they have a role to convey the truth to men that testes remain functional throughout the 50s, 60s and 70s, and beyond. A low testosterone level is not a 'disease', it is a potential indicator of an underlying health issue and/or comorbidity that must be addressed as a priority. Important steps to facilitate the function of a man's HPT axis are to identify and optimally treat obesity and other medical comorbidities, including depression and sleep apnoea, and minimise use of medications such as opioids. The 'low testosterone' enquiry offers an ideal opportunity for GPs to engage men into taking an interest in their health, provide holistic assessment and management of medical conditions, and promote healthy eating and regular exercise to help them shed excess weight.<sup>2,3,5</sup>

Secondly, GPs should be on the alert for men presenting with symptoms and signs of androgen deficiency from underlying pituitary or testicular disease.<sup>4</sup> In particular, testicular examination is important to identify men with disorders such as Klinefelter's syndrome. In men with pituitary or testicular disease causing androgen deficiency, testosterone therapy to achieve physiological levels is effective and beneficial.<sup>14</sup> Suitable evaluation before starting treatment, and clinical and biochemical monitoring during treatment, are indicated.<sup>4,14</sup> Endocrinologist referral should be considered when there is uncertainty over the diagnosis or treatment, and to meet PBS criteria for testosterone therapy for male hypogonadism.

Finally, GPs now have another opportunity to re-engage men, with the results of T4DM.<sup>21</sup> This trial has highlighted the distinction between physiological replacement therapy, where testosterone is given to men with hypothalamic, pituitary or testicular disorders who are unable to make enough testosterone of their own, as opposed to pharmacological intervention in men who do not have such HPT-axis disease. As with any pharmacological intervention, the risks and benefits need to be carefully evaluated and explained. The T4DM investigators considered it premature

### PRACTICE POINTS FOR GPs

- In men, testosterone levels decline with age in a gradual not abrupt manner.
- This change is associated with obesity and accumulation of medical comorbidities.
- Testosterone levels are also lower in men who are depressed, have interrupted sleep or are on medications such as opioids.
- Concern over lower testosterone levels is an opportunity for health professionals to engage men to improve their diet patterns and lifestyle behaviours.
- Testosterone therapy is indicated in men who are androgen deficient due to underlying pituitary or testicular disorders, providing physiological replacement.
- The results of the Australian randomised controlled trial, Testosterone for the Prevention of Type 2 Diabetes Mellitus (T4DM), provide new information on testosterone as a pharmacological intervention.

to advocate for the widespread use of testosterone for diabetes prevention in men without pathological hypogonadism.<sup>21</sup> If testosterone treatment were to be considered in this context, a concomitant lifestyle program and careful monitoring of haematocrit, cardiovascular risk factors, and prostate health would be needed. As a starting point, men should be offered a holistic assessment of, and optimised care for, factors such as weight, cardiometabolic risk, medical comorbidities and medications, and encouraged to engage in healthy dietary and lifestyle behaviours.

Practice points for GPs are listed in the Box. MT

### References

A list of references is included in the online version of this article ([www.medicinetoday.com.au](http://www.medicinetoday.com.au)).

COMPETING INTERESTS: Professor Yeap has received speaker honoraria and conference support from Bayer, Lilly and Besins Healthcare; received research support from Bayer, Lilly and Lawley Pharmaceuticals; and held advisory roles with Lilly, Besins Healthcare, Ferring and Lawley Pharmaceuticals. Professor Yeap was an investigator in T4DM.

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