Low testosterone and the metabolic syndrome: a high-risk combination

MIKE KIRBY

Hypogonadism and the metabolic syndrome commonly coexist, and when combined, pose a high cardiovascular risk and can have a profound effect on a man’s health and wellbeing. Mike Kirby describes the features of both conditions and provides advice on management.

Box 1. The new International Diabetes Federation definition of the metabolic syndrome

Central obesity (measured by waist circumference*)
- ≥94cm in men, ≥80cm in women (Europids, Ethnic South/Central Americans, Sub-Saharan Africans, Eastern Mediterranean and Middle East [Arab] populations)
- ≥90cm in men, ≥80cm in women (South Asians, Chinese, Japanese)

Plus any two of the following:
- Raised blood pressure: systolic ≥130mmHg or diastolic ≥85mmHg or taking medication for this
- Raised triglycerides: ≥1.7mmol/l or taking medication for this
- Reduced HDL: <1.03mmol/l in men, <1.29mmol/l in women or taking medication for this
- Raised fasting plasma glucose: ≥5.6mmol/l or previously diagnosed type 2 diabetes. If >5.6mmol/l an oral glucose tolerance test is strongly recommended, but this is not necessary to define presence of the syndrome

*If body mass index >30kg/m², central obesity can be assumed

The concept of ‘men’s health’ has traditionally focused on urological problems and prostatic disease. Although these conditions are obviously important to health and quality of life in men, it is cardiovascular disease (CVD), type 2 diabetes and the portfolio of risk factors associated with the metabolic syndrome that pose the greatest threats in terms of morbidity and premature death. Evidence now suggests that hypogonadism is an additional feature of the metabolic syndrome, and men presenting with symptoms of either can provide us with an opportunity to improve their wider health.

THE METABOLIC SYNDROME

The metabolic syndrome refers to the ‘clustering’ of a number of metabolic abnormalities that increase the risk of type 2 diabetes and CVD. These include obesity, insulin resistance, dyslipidaemia and hypertension. The more components of the metabolic syndrome that are present, the greater the cardiovascular risk. People with the metabolic syndrome have a fivefold greater risk of developing diabetes than those without the syndrome. They are also three times as likely to have a heart attack or stroke and twice as likely to die from these.

The metabolic syndrome is a significant problem. Around 25% of European adults are estimated to have it and the prevalence appears to be increasing worldwide.

How is it diagnosed?

In 2006, the International Diabetes Federation set out to overcome the shortcomings of previous definitions and produce one universally accepted, easy-to-use diagnostic tool that addresses both clinical and research needs (Box 1).

Why does it occur?

The metabolic syndrome appears to be precipitated by multiple underlying risk factors. These include:
- abdominal obesity
- insulin resistance
- physical inactivity
- ageing
**HYPOGONADISM**

Hypogonadism is a term used for testosterone deficiency. Testosterone is essential for the development and maintenance of male characteristics, but it also has effects on most major organs including the brain, skin, muscle, bone and kidney. Hypogonadism can significantly reduce a man’s quality of life and it also increases his risk of death.6,7

Although we know the prevalence of hypogonadism increases with age, estimates of prevalence vary. The European Male Ageing Study reported an overall prevalence of 2.1% in men aged 40–79 years and rates of 0.1% in 40–49 year-olds, 0.6% in 50–59 year-olds, 3.2% in 60–69 year-olds and 5.1% in 70–79 year-olds.8 However, the British Society for Sexual Medicine says that over 8% of men aged 50–79 years are hypogonadal.9

How is it diagnosed?

A diagnosis of treatable hypogonadism is based on clinical signs and symptoms suggestive of testosterone deficiency combined with biochemical evidence.9 The probability of symptoms increases with decreased levels of testosterone.8 The symptoms most strongly associated with hypogonadism are low libido, loss of morning erections and erectile dysfunction. Other signs and symptoms can be seen in Box 3.

For the measurement of total testosterone, blood should be taken in the morning between 7am and 11am (preferably at 9am), using a reliable method, on more than one occasion.9 The advice on when to treat is summarised in Table 1.

Measuring serum luteinising hormone (LH) helps differentiate between primary and secondary hypogonadism. Serum prolactin should be measured when secondary hypogonadism is suspected or the total testosterone level is less than 5.2nmol/l, to avoid missing a prolactinoma.9

In clinical practice, testosterone deficiency in adult men is often missed, even in the presence of associated symptoms, because these men often ignore their symptoms or attribute them to other causes such as ageing.

**Why does it occur?**

In contrast to the dramatic fall in oestrogen levels at the time of the menopause in women, testosterone levels in men decline gradually after the age of about 30, at a rate of around 1.5% per year. However, androgen secretion in men does not generally cease altogether and testosterone levels remain highly variable in older men.2,11

Testosterone deficiency is more common in men with certain diseases such as diabetes, asthma, chronic obstructive pulmonary disease, renal and HIV-related diseases, prostate disease and alcoholism. It is also more common in men with the metabolic syndrome or its individual components (Box 4).3,12–14

**THE LINK BEWEEN THE METABOLIC SYNDROME AND HYPOGONADISM**

Further evidence of the link between testosterone deficiency and the metabolic syndrome is provided by a study that found that men with prostate cancer who underwent long-term androgen deprivation therapy had significantly higher rates of the metabolic syndrome than those who did not.15

The nature of the link between these conditions is likely to be multifactorial and differ between individuals. Hypogonadism associated with the metabolic syndrome includes:

- Depressed mood
- Insomnia
- Impaired cognitive function
- Reduced vitality
- Fatigue
- Low libido
- Erectile dysfunction
- Absence of morning erections
- Delayed ejaculation
- Hot flushes
- Anaemia
- Weakness
- Reduced muscle mass
- Increased body fat
- Testicular atrophy
- Osteopenia/osteoporosis
- Loss of facial, axillary and pubic hair
metabolic syndrome may be related to a low-grade inflammatory state, which leads to diminished testosterone synthesis.\textsuperscript{16,17} Increased visceral fat, another feature of the metabolic syndrome, may contribute to hypogonadism through activity of an enzyme called aromatase, which converts testosterone to oestrogen.\textsuperscript{18} Fat cells also synthesise the protein leptin and inflammatory cytokines, which have been inversely associated with testosterone levels, due to their detrimental effect on the production of LH.\textsuperscript{19,20}

Androgen deficiency promotes the production of fat cells, which contributes to obesity and the metabolic syndrome.\textsuperscript{21} It also results in impaired glucose metabolism, higher levels of triglycerides and cholesterol, and lower levels of high-density lipoprotein (HDL) cholesterol, which are all features of the metabolic syndrome.\textsuperscript{22–26}

TREATMENT

The metabolic syndrome

Once the metabolic syndrome is diagnosed, it should be carefully managed to reduce the risk of type 2 diabetes and CVD. Many features of the metabolic syndrome can be improved with changes in lifestyle – by increasing physical activity and eating a healthy, Mediterranean-style, calorie-controlled diet. If lifestyle changes are not effective, or the person is considered to be at high risk for CVD, drug therapy tailored to the individual components will be required.\textsuperscript{4}

Hypogonadism

Treatment of proven testosterone deficiency is with testosterone replacement (Table 1), either with daily testosterone gel or long-acting testosterone undecanoate injections every three months. Testosterone replacement therapy (TRT) may produce a wide range of benefits in men with hypogonadism,\textsuperscript{27} including improvements in:

- bone density
- muscle mass and body composition
- erythropoiesis

In men with sexual dysfunction, TRT may also improve the response to phosphodiesterase-5 (PDE-5) inhibitors. This is of particular relevance to men with type 2 diabetes in whom the response to PDE-5 inhibitors alone may be little more than 50%.\textsuperscript{9}

The metabolic syndrome with coexisting hypogonadism

In hypogonadal men, long-term TRT has been shown to ameliorate the components of the metabolic syndrome, with reductions in waist circumference, total and low-density lipoprotein cholesterol, blood pressure, blood glucose, HbA\textsubscript{1c}, and C-reactive protein, and increases in HDL cholesterol. This widespread effect was attributed to common mechanisms of action linking the pathophysiology of both conditions.\textsuperscript{21}

A small study analysed the effects of supervised diet and exercise with or without transdermal testosterone on components of the metabolic syndrome in hypogonadal men with this syndrome and newly diagnosed type 2 diabetes. After 52 weeks of treatment, 81% of men receiving testosterone no longer met the criteria of the metabolic syndrome versus 31% of those who did not receive testosterone.\textsuperscript{28} The presence of diabetes and the metabolic syndrome should be a trigger to measure testosterone.

In clinical practice, if TRT can be used to treat coexisting hypogonadism, it will support and enhance the pharmacological management of the metabolic syndrome and diabetes.

However, TRT is also associated with some potential risks.\textsuperscript{27} These include:

- possible stimulation of prostate cancer if already present
- equivocal effects on the symptoms of benign prostatic hyperplasia (BPH)
- gynaecomastia
- reduced testicular size
- infertility
- erythrocytosis

**Box 4. Hypogonadism: summary**

- Hypogonadism is a term used for testosterone deficiency
- It can significantly affect quality of life and increases the risk of death
- It is estimated to affect between 2% and 8% of 40–79 year-olds
- Diagnosis is based on clinical signs and symptoms combined with biochemical evidence
- Testosterone levels decline naturally with age, but hypogonadism is more common in men with certain diseases such as the metabolic syndrome

<table>
<thead>
<tr>
<th>Total testosterone level (nmol/l)</th>
<th>Advice</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;8</td>
<td>Patient is likely to benefit from replacement</td>
</tr>
<tr>
<td>&gt;12</td>
<td>No replacement required</td>
</tr>
<tr>
<td>8–12</td>
<td>Repeat measurement with sex-hormone-binding globulin and albumin to calculate free testosterone, or free testosterone by equilibrium dialysis, may be helpful</td>
</tr>
</tbody>
</table>

Table 1. When to treat testosterone deficiency\textsuperscript{9}
• increased blood viscosity
• worsening of untreated sleep apnoea, but may improve if weight loss occurs.

The relationship between testosterone and prostate cancer remains controversial and unfortunately no studies with sufficient power have been published to unequivocally resolve the issue. However, with careful monitoring, testosterone treatment is safe.

Conversely, coexistence of the metabolic syndrome and late-onset hypogonadism does appear to increase the risk of prostate cancer. TRT is currently contraindicated in men with locally advanced or metastatic prostate cancer. Hypogonadal men treated for localised prostate cancer are candidates for TRT after a period of at least two years if there is no evidence of residual cancer.

Regarding BPH, a small study investigated the effects of testosterone injections in obese hypogonadal men with the metabolic syndrome and lower urinary tract symptoms (LUTS). Five years of TRT stabilised LUTS and did not alter prostate size.

Importantly, obese men may be more likely to develop adverse effects from treatment with testosterone, but have the most to gain. This is particularly relevant when managing hypogonadism within the context of the metabolic syndrome.

When using TRT or drugs to treat individual elements of the metabolic syndrome, the benefits of treatment must always be balanced against the possible risks. To do this, the treating physician must possess adequate knowledge of the pharmacokinetics, as well as the advantages and drawbacks of the different delivery systems. Patients should be counselled on the possible benefits and risks before treatment is started and carefully monitored with regular checks on haematocrit, PSA and testosterone levels during treatment. It is important to achieve sustained therapeutic levels of testosterone.

CONCLUSION
The rising prevalence of obesity and lengthening life expectancy will be accompanied by increases in the rates of both the metabolic syndrome and hypogonadism. These conditions can have profound effects on a man’s health and wellbeing, and when combined, they are likely to pose a greater cardiovascular risk than either condition in isolation. Because they commonly coexist, men presenting with features of the metabolic syndrome or symptoms of hypogonadism should automatically be screened for both. For healthcare professionals, the key is distinguishing between the natural ageing process and ageing amplifiers such as the metabolic syndrome, and managing patients with either or both effectively.

Declaration of interests: none declared.

REFERENCES
androgens, 2010 (www.bssm.org.uk); accessed 26 August 2015).