TESTOSTERONE DEFICIENCY

Testosterone deficiency is associated with a wide range of adverse health risks, including type 2 diabetes,1,2 metabolic syndrome,3 cardiovascular disease,1,2 erectile dysfunction (ED)2,4 and increased mortality5 in men, but recent research shows it is currently underdiagnosed and undertreated. “There’s more to testosterone than just sex,” Dr David Edwards, GP with a special interest in sexual dysfunction, Chipping Norton, told the recent UK National Congress of Men’s Health 2016, sponsored by Besins Healthcare UK, at which GPs and specialists shared latest research and guidelines on how to improve the management of testosterone deficiency.

Testosterone deficiency can be defined as a clinical and biochemical syndrome characterised by a deficiency of testosterone, or testosterone action, and relevant symptoms and signs.6 The prevalence of symptomatic testosterone deficiency is 2–6 per cent in adult men,6 increasing with age. “The prevalence is higher in some groups of patients, particularly in those with type 2 diabetes,” said Dr Jonny Coxon, GP in Brighton and fellow of the European Committee of Sexual Medicine. Figures from NHS Diabetes show that 16 per cent of men with type 2 diabetes have lower than normal testosterone levels and a further 24 per cent have borderline low levels.7

UNDERDIAGNOSIS

Lack of awareness and embarrassment among men contribute to the lack of diagnosis of testosterone deficiency. A recent UK survey of 90 men with hypogonadism found that more than half (55 per cent) waited 3–24 months before seeking advice for symptoms and 35 per cent waited for more than two years.8 Common reasons for delay included: not thinking it was a serious problem (49 per cent), assuming it was to do with age (44 per cent), and being embarrassed (41 per cent).8 Even when hypogonadism was clinically diagnosed, many men were not treated. The survey showed 38 per cent of men diagnosed did not receive testosterone replacement therapy (TRT), and of these 31 per...
Diagnosing testosterone deficiency

“There is considerable uncertainty among health professionals on when to suspect testosterone deficiency, how to test for testosterone, how to treat low testosterone and how to monitor treatment,” explained Dr Anand Patel, GP in Lewes and fellow of the European Committee of Sexual Medicine. He explained that guidelines11,12 recommend the diagnosis of testosterone deficiency should be based on:

- Signs and symptoms
- Low testosterone levels measured on two or more separate occasions.

Testosterone deficiency is associated with a wide range of signs and symptoms (see Table 1) some of which increase in prevalence with decreasing testosterone levels.13 Simple questionnaires, such as the Androgen Deficiency in the Aging Male (ADAM) questionnaire14 (see Table 2), can be helpful in identifying features of testosterone deficiency in older men.

Measuring and interpreting testosterone levels

Testosterone levels follow a circadian rhythm so should be measured between 8 and 10am, after abstaining from sex and alcohol for three days. Guidelines15 recommend that patients with serum total testosterone below 8nmol/L will usually benefit from testosterone treatment. A short therapeutic trial (up to six months) may be justified in patients with borderline serum total testosterone levels (8–12 nmol/L) and a clinical picture of testosterone deficiency, while it is not usually required in patients with levels above 12nmol/L.

Laboratories vary in the cut-off level that they give for low total testosterone. It is often 8 or 10nmol/L but is currently only 6.7nmol/L in Wales. “This means many symptomatic patients are being left untreated,” warned Dr Patel. “Don’t just treat the lab value. Consider the symptoms and treat the patient accordingly,” he advised.

Treating testosterone deficiency

Treatment options include:
- Nonpharmacological treatment – including addressing sleep apnoea, weight reduction and lifestyle modification, which can all improve testosterone synthesis
- Management of co-morbid conditions, including review of medication (such as glucocorticoids and statins) that may be contributing to testosterone deficiency
- Testosterone replacement therapy.

TRT is available in a range of preparations, with different routes of delivery, ease of use, pharmacokinetics and cost. “Achieving good compliance is crucial,” Dr Patel told the meeting, recommending that all options should be discussed with patients.

Oral testosterone preparations

Oral preparations would normally be inactivated by the liver but testosterone undecanoate in castor oil is absorbed into the lymphatic system. Dr Patel suggested that the advantages are the convenience of taking an oral preparation and modifiable dosage. He also suggested that disadvantages include having to take it twice a day with meals, and variable serum testosterone levels and clinical response.

Transdermal testosterone

Transdermal preparations are available as gels in the UK. Dr Patel highlighted that the advantages include flexible dose modifications, not requiring injections, achieving a rapid steady state and ease

<table>
<thead>
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<th>Metabolic disorders</th>
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<td>Hyperlipidaemia</td>
<td>Abdominal obesity</td>
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<td>Hypertension</td>
<td>Poor insulin regulation</td>
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<td>Poor glycaemic control</td>
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Sexual dysfunction

- Reduced sexual desire and activity
- Erectile dysfunction including loss of morning erections

Physical decline

- Loss of bone mineral density
- Fatigue
- Sarcopenia (loss of skeletal muscle mass and strength)

Brain function disorders

- Depression
- Loss of concentration

Table 1. Signs and symptoms of testosterone deficiency

1. Do you have a decrease in libido (sex drive)?
2. Do you have a lack of energy?
3. Do you have a decrease in strength and/or endurance?
4. Have you lost height?
5. Have you noticed a decreased ‘enjoyment of life’?
6. Are you sad and/or grumpy?
7. Are your erections less strong?
8. Have you noticed a recent deterioration in your ability to play sports?
9. Are you falling asleep after dinner?
10. Has there been a recent deterioration in your work performance?

If the answer is “Yes” to question 1 or 7, or at least three of the other questions: further evaluate for symptoms of testosterone deficiency and consider testing
of withdrawal. Potential disadvantages include variable absorption and the risk of possible transfer during intimate contact, Dr Patel suggested, although he added that patients should be advised on where to apply gels in order to minimise this risk.

**Intramuscular testosterone**

Intramuscular preparations are usually given three-weekly. Dr Patel explained that this option is low in cost but considerable fluctuations in testosterone levels occur between injections. He noted that long-acting intramuscular testosterone is given every 10–14 weeks, requiring fewer injections and maintaining better steady state testosterone levels than shorter acting preparations. However, Dr Patel also highlighted that the injection site may be painful and the treatment cannot be withdrawn quickly.

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### Testosterone deficiency

<table>
<thead>
<tr>
<th>History, physical examination and TT</th>
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<tr>
<td>Low or borderline low testosterone; TT&lt;12nmol/L (&lt;346ng/dL)</td>
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<tr>
<td>Repeat TT + LH, SHBG, PRL</td>
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<tr>
<td>Testosterone deficiency if TT&lt;8nmol/L (&lt;231ng/dL)</td>
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<tr>
<td>Normal testosterone; TT&gt;12nmol/L (&gt;346ng/dL)</td>
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<tr>
<td>No testosterone deficiency – seek other causes</td>
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<tr>
<td>TT 8–12nmol/L (231–346ng/dL) ± ↑ SHBG, bother ++</td>
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<tr>
<td>High LH</td>
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<tr>
<td>Exclude contraindications</td>
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<tr>
<td>Reassess, consider referral or trial of TRT</td>
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<tr>
<td>Successful Monitor TT, FBC</td>
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<tr>
<td>Failure Review diagnosis</td>
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<tr>
<td>Low/normal LH</td>
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<tr>
<td>Investigate pituitary + other causes</td>
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<tr>
<td>No identifiable cause</td>
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<tr>
<td>Identified cause</td>
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<tr>
<td>Manage cause</td>
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**Key:** TT = morning total testosterone; LH = luteinising hormone; SHBG = sex hormone-binding globulin; PRL = prolactin; TRT = testosterone replacement therapy; FBC = full blood count

**Figure 1.** Process of care for the assessment and management of testosterone deficiency in adult men.6–16
Monitoring treatment
The goal of TRT is to restore testosterone levels to the mid-normal range and alleviate signs and symptoms of testosterone deficiency without significant side-effects or safety concerns. Patients should be monitored to achieve testosterone levels of at least 15nmol/L. Prostate-specific antigen (PSA) should be measured at three, six and 12 months and then annually, in addition to monitoring full blood count (FBC). TRT should be stopped if there is no symptom improvement after six months.

Follow-up of patients on TRT should include measuring testosterone, haematocrit, PSA and lipid levels, as follows:
- Gel formulations – in the morning after application
- Short-acting injection – midpoint of cycle
- Long-acting injection – trough level.

Clinically, patients should be assessed for beneficial effects, including sexual desire, erections, motivation and energy, and for adverse effects, such as acne, gynaecomastia/breast tenderness, oedema, increased packed cell volume (PCV), and varying mood and libido, which may occur with high testosterone levels. They should also be examined for hair growth and muscle development and have their BMI checked.

Testosterone treatment is considered lifelong therapy. Patients who respond positively may continue treatment with a standardised monitoring plan, checking that testosterone levels are optimal and ensuring any potential adverse effects are detected early.

“GPs have lacked confidence in treating testosterone deficiency but I think many are becoming more confident,” said Dr Patel. Guidance recommends that the majority of men with testosterone deficiency can be effectively assessed and managed in general practice (see Figure 1). The exceptions are men with fertility issues, a diagnosis of prostate cancer, polycythaemia and those with other endocrinopathies.

Reassuring data on the safety of testosterone therapy
“The number one concern around the use of TRT is about prostate cancer but there is no evidence that high testosterone causes prostate cancer or that low testosterone is protective,” Professor Abraham Morgentaler, associate clinical professor of surgery (urology) at Harvard Medical School, Boston, USA, told the congress.

He explained that the traditional view had been that prostate cancer is caused by androgens, with high testosterone causing rapid prostate cancer growth and low testosterone being protective.

However, in a review of the potential risks of TRT published in 2004, he found no studies demonstrating that TRT caused progression of prostate cancer.

A meta-analysis of 19 placebo-controlled testosterone therapy studies in men with low or low-normal testosterone revealed no difference in prostate cancer, PSA levels over 4.0ng/ml or urinary symptom scores in those treated with testosterone compared with placebo.

“But the dilemma is that LH/FSH [luteinising hormone-releasing hormone] agonists reduce PSA levels in prostate cancer, so clearly testosterone makes a difference,” noted Professor Morgentaler.

He explained that there are a finite number of androgen receptors so a saturation effect occurs at high levels of testosterone. He added that low free testosterone predicted prostate cancer progression in a recent study of men under active surveillance.

Two recent studies hit media headlines after suggesting a potential association between testosterone levels and cardiovascular disease, and led to the US Food and Drug Administration (FDA) launching an investigation into the risk of cardiovascular events with testosterone products.

However, Professor Morgentaler explained that these studies had flawed methodologies and more than 100 studies have shown no increased cardiovascular risk or benefits with testosterone therapy or higher endogenous testosterone levels. “Testosterone therapy improves known cardiovascular risk factors, decreasing visceral fat, reducing waist circumference and improving glycaemic control,” he noted.

Summing up
Symptomatic testosterone deficiency in older men is frequently undiagnosed and left untreated. Untreated it can compromise a man’s sexual function, body composition and cardiometabolic profile. TRT can alleviate many of the symptoms of testosterone deficiency in hypogonadal men, resulting in improved physical health, mental health, sexual function and quality of life.

“GPs can play a central role in detecting low testosterone, particularly in men at high risk, including those with type 2 diabetes, and by offering lifestyle intervention and testosterone therapy, where indicated, to improve men’s health and quality of life,” concluded Dr Patel.

References
Testosterone deficiency


Declaration of interests
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Susan Mayor is a freelance medical writer

POEMs

Self-management interventions reduce hospitalisation and improve quality of life in patients with heart failure

Clinical question:
Are self-management interventions effective for patients with heart failure?

Bottom line:
Self-management interventions can reduce hospitalisations and improve quality of life, but do not significantly reduce mortality. A subgroup analysis of patients with depression found an increase in mortality, although it is unclear why this occurred. The authors speculate that perhaps the burden of the self-management interventions was too great. (LOE = 1a)

Reference:


Synopsis:
Self-management interventions include things like monitoring signs and symptoms; improving adherence to recommendations regarding diet, exercise and medications; and smoking cessation. Previous meta-analyses have identified significant differences between studies, so these researchers performed an individual patient-level meta-analysis, assembling the datasets from 20 studies with 5624 patients. Patients were fairly evenly divided between intervention and control groups, with half aged 65 to 80 years and approximately one-third younger than 65 years. They were evenly split between New York Heart Association class I/II and III/IV in terms of severity, and 29 per cent suffered from depression. Six studies were set in the USA or Canada, and the remainder were done in Europe; all followed up patients for at least six months.

They authors found that the time to heart failure-related hospitalisation was reduced (hazard ratio [HR] 0.80; 95% CI 0.69–0.92), but mortality was not significantly reduced (HR 0.91; 0.79–1.04). They also found that heart failure-related quality of life was improved with self-management interventions (standardised mean difference 0.15; 0.0–0.30; consistent with a small effect). The reduction in hospitalisation was seen in patients aged 65 to 80 years but not in younger or older patients. They also found that mortality was increased in patients with depression who were randomised to the self-management intervention groups (HR 1.39; 1.04–1.87) but not in patients without depression (HR 0.86; 0.69–1.06). A sensitivity analysis that excluded studies at high risk of bias found generally similar results.