A practical guide on the assessment and management of testosterone deficiency in adult men

Based on the 2017 British Society for Sexual Medicine (BSSM) guidelines on adult testosterone deficiency, with statements for UK practice

Why does it occur?
Testosterone deficiency (TD), also known as hypogonadism, may result from:
- Problems with the testes [primary (hypergonadotropic) TD]
- Problems with the hypothalamus and pituitary gland [secondary (hypogonadotropic) TD]
- Problems with the hypothalamus/pituitary and testes (combined primary and secondary TD)
- Impaired action/suppression of testosterone

How is it diagnosed?
- The diagnosis of symptomatic TD requires the presence of characteristic signs and symptoms, PLUS reduced serum concentrations of total testosterone (TT) or free testosterone (FT)

**Psychological**
- Changes in mood (e.g. anger, irritability, sadness, depression)
- Decreased well-being/poor self-rated health
- Diminished cognitive function (including impaired concentration, verbal memory and spatial performance)

**Cardiometabolic**
- Increased body mass index (BMI)/obesity
- Visceral obesity
- Metabolic syndrome
- Insulin resistance and type 2 diabetes

**Physical**
- Decreased body hair
- Gynaecomastia
- Decreased muscle mass and strength
- Hot flushes/sweats
- Sleep disturbances
- Fatigue
- Osteoporosis/height loss/low trauma fractures

**Sexual**
- Delayed puberty
- Small testes
- Infertility
- Decreased sexual desire and activity
- Decreased frequency of sexual thoughts
- Erectile dysfunction (ED)
- Delayed ejaculation
- Decreased volume of ejaculate
- Decreased or absent morning/night-time erections

- The 3 most common symptoms of TD are ED, loss of early morning erections and low sexual desire – men often present with sexual dysfunction and a desire for treatment
Who should be screened for TD?

- Adult men with consistent and multiple signs of TD
- All men presenting with ED, loss of spontaneous erections or low sexual desire
- All men with type 2 diabetes mellitus, BMI >30 kg/m² or waist circumference >102 cm (40.2 inches)
- All men on long-term opiate, antipsychotic or anticonvulsant medication

History taking

<table>
<thead>
<tr>
<th>Enquire about previous and current prescription and non-prescription drug use</th>
<th>Assess and exclude systemic illness, ongoing acute disease, malabsorption and malnutrition</th>
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<tbody>
<tr>
<td>Consider the use of validated questionnaires, such as the Androgen Deficiency in the Ageing Male (ADAM) questionnaire (included in the Sexual Advice Association SMART SAA app, available at: <a href="http://sexualadviceassociation.co.uk/">http://sexualadviceassociation.co.uk/</a>), or the Ageing Males’ Symptoms (AMS) Scale (available at: <a href="http://www.issam.ch/AMS_English.pdf">http://www.issam.ch/AMS_English.pdf</a>) – information on interpreting the scores can be found at: <a href="http://zeg-berlin.de/wp-content/uploads/2017/01/norm.pdf">http://zeg-berlin.de/wp-content/uploads/2017/01/norm.pdf</a></td>
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</table>

Physical examination

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<tr>
<th>Measure height, weight, BMI and waist circumference</th>
<th>Assess the degree of body hair (including facial and pubic)</th>
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<tbody>
<tr>
<td>Examine for the presence and degree of breast enlargement, and abnormalities of the penis, testicles and scrotum</td>
<td>Check the prostate via digital rectal examination (DRE)</td>
</tr>
<tr>
<td>Arrange blood investigations, including prostate-specific antigen (PSA), haematocrit, and appropriate tests according to physical findings and to determine cardiovascular (CV) risk</td>
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Laboratory diagnosis

Serum testosterone – measure between 7–11 am, with a reliable method, on at least 2 occasions, preferably 4 weeks apart. Fasting levels should be obtained where possible, as recommended by the European Association of Urology (EAU). If low/borderline, measure LH and FSH, plus SHBG to calculate FT.

FT – an online FT calculator and downloadable app, sponsored by the Primary Care Testosterone Advisory Group (PCTAG), can be found at http://www.pctag.uk/testosterone-calculator/

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<th>FSH – follicle-stimulating hormone, LH – luteinising hormone, SHBG – sex hormone-binding globulin</th>
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<td>*LH to differentiate primary from secondary TD. **FSH is only necessary if fertility is an issue.</td>
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</table>

Main contraindications to testosterone therapy

- Prostate cancer (locally advanced or metastatic)
- Male breast cancer
- An active desire to have children
- Haematocrit >54%
- Severe chronic heart failure [New York Heart Association (NYHA) class IV]

Testosterone therapy and ED

- Testosterone therapy (T Therapy) is appropriate for treating ED, particularly at TT levels <8 nmol/L, and for salvaging ED treatment failures with oral medication, particularly at TT levels <10.4 nmol/L.
- T Therapy reduces the need for more invasive and expensive second- and third-line treatments
- A PDE5i can be prescribed for all men with ED when commencing T Therapy as long as there are no contraindications, because T Therapy can take many months to correct ED

PDE5i – phosphodiesterase type 5 inhibitor
Diagnosing and managing TD in adult men

**Signs/symptoms suggestive of TD**

- Measure TT
- TT <12 nmol/L = low or borderline
- TT >12 nmol/L = normal

**Assess/exclude/optimally manage other comorbidities**

- TT >12 nmol/L + FT >0.225 nmol/L
- TT <12 nmol/L and/or FT <0.180 nmol/L

**Confirmed TD**

- High LH
- Primary TD

**Possible TD**

- Low or normal LH
- Secondary TD

**Fertility not desired**

- Avoid T Therapy if possible, as it may reduce spermatogenesis
- Possible alternatives include HCG, SERMs (e.g. clomifene) and AIs**

**Fertility desired**

- **Evaluate** patients at 3, 6 and 12 months, then every 12 months thereafter to assess serum testosterone levels (therapeutic target mid-upper range: 15–30 nmol/L), confirm symptomatic improvement and check for any changes in haematocrit (should remain <54%) and PSA (increases >1.4 ng/mL over any 1-year period or a velocity >0.4 ng/mL/year during sequential measurement over >2 years warrants urological evaluation + more intensive surveillance for prostate cancer thereafter); 3-monthly follow-up may be necessary in some patients, including those with suboptimal treatment response or safety issues

**Lifestyle modification and management of comorbidities unsuccessful/likely to be unsuccessful + no contraindications**

- **Trial of T Therapy + lifestyle modification**

**Failure to benefit within a reasonable time frame (defined as 6 months for libido, sexual function, muscle function and improved body fat) should prompt treatment discontinuation and investigation for other causes of the symptoms**

Adapted from Minhas and Mulhall, 2017.²,¹³

**Notes:**


*For men with TT levels <5.2 nmol/L plus low LH and FSH or increased prolactin levels, refer to endocrinology or arrange a pituitary MRI scan to exclude a pituitary adenoma.²,¹³

**These drugs should not be used if pituitary function is compromised. SERMs and AIs are not currently licensed for TD.”**
**Testosterone therapy**

- The patient should be fully informed about the expected benefits and side effects of T Therapy, to facilitate a joint decision on treatment choice

**Testosterone therapy options**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Route of administration</th>
<th>Frequency of administration</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone 1%, 1.62%* and 2% gel available</td>
<td>Transdermal gel 1% (sachets/tubes) 1.62%* (pump) 2% (pump)</td>
<td>Applied daily</td>
<td>Fast onset  Provides uniform and normal serum levels for 24 hours</td>
<td>Skin irritation at application site  Potential for interpersonal transfer  Compliance may be an issue long-term</td>
</tr>
<tr>
<td>Testosterone undecanoate</td>
<td>Intramuscular injection</td>
<td>Every 10–14 weeks, adjusted to maintain trough testosterone &gt;12 nmol/L</td>
<td>Steady state levels  Reduced frequency of administration improves compliance</td>
<td>Possible injection site pain/reaction</td>
</tr>
<tr>
<td>Testosterone enantate</td>
<td>Intramuscular injection</td>
<td>Every 2–3 weeks</td>
<td>Can be administered every 3–6 weeks for maintenance, according to individual requirement</td>
<td>Levels fluctuate  Possible injection site pain/reaction</td>
</tr>
<tr>
<td>Mix of 4 testosterone esters (including propionate) as Sustanon 250</td>
<td>Intramuscular injection</td>
<td>Usually administered every 3 weeks  May cause a reaction at the injection site</td>
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Adapted from Hackett et al. (2017) and Dohle et al. (2017).

- When considering side effects and drug withdrawal times, physicians should bear in mind the pharmacodynamic and pharmacokinetic properties of the injectable versus the transdermal formulations

**References**
