Joint Trust Guideline for the Adult Testosterone Replacement and Monitoring

A clinical guideline recommended for use

<table>
<thead>
<tr>
<th>For Use in:</th>
<th>All Clinical Areas</th>
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<tbody>
<tr>
<td>By:</td>
<td>All Health Care Professionals</td>
</tr>
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<td>If Yes - does the strategy/policy deviate from the recommendations of NICE? If so why?:</td>
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This guideline has been approved by the Trust's Clinical Guidelines Assessment Panel as an aid to the diagnosis and management of relevant patients and clinical circumstances. Not every patient or situation fits neatly into a standard guideline scenario and the guideline must be interpreted and applied in practice in the light of prevailing clinical circumstances, the diagnostic and treatment options available and the professional judgement, knowledge and expertise of relevant clinicians. It is advised that the rationale for any departure from relevant guidance should be documented in the patient's case notes.

The Trust's guidelines are made publicly available as part of the collective endeavour to continuously improve the quality of healthcare through sharing medical experience and knowledge. The Trust accepts no responsibility for any misunderstanding or misapplication of this document.
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Version Information

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<thead>
<tr>
<th>Version No</th>
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<tr>
<td>JCG0043 v1</td>
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<tr>
<td>JCG0043 v2.1</td>
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<td>Dr Brooks removed as an author</td>
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Does the patient fulfil criteria (one or more) for testosterone testing?
(poor sexual development; persistent loss of libido and/or erectile dysfunction;
azoospermia; osteoporosis or flushes)

Yes – check 9am testosterone.

No, no test required.

Testosterone <12 nmol/L, Repeat test plus LH/FSH/LFT/SHBG.

Total testosterone >12 nmol/L, reassure, no further test indicated.

Testosterone 8-12 nmol/L on 2 occasions before 9.30am, but free testosterone* >220 pmol/L This confirms physiologically normal levels. Reassure no further test indicated.

Testosterone 8-12 nmol/L on 2 occasions before 9.30am – calculate free testosterone. Free testosterone <220 pmol/L confirms hypogonadism – refer to endocrinology to investigate cause and consider treatment.

Testosterone <8 nmol/L on 2 occasions before 9.30am – confirms hypogonadism – refer to endocrinology for investigation of cause and to consider treatment.
Formulary status of testosterone products

NB – testosterone replacement is a long term and non urgent therapy usually managed in primary care under secondary care guidance. As such, many testosterone products (such as the depot preparation Nebido®, and topical preparations Testogel®, Tostran® and Testim® are not included within the hospital formulary and so prescriptions should be issued by primary care.

Objectives

- To produce a trust guideline for appropriate assessment and management of testosterone deficiency in men.

Rationale

- Testosterone deficiency (Trust reference range 9.9 – 27.8 nmol/L taken at 9am) has increasing incidence with increasing age (0.1% in 40-49 year old men to 5.1% in the 70-79 year old men) but only symptomatic patients require and benefit from treatment.
- Testosterone replacement therapy may improve the physical and emotional wellbeing for the features in table 1 in symptomatic patients with confirmed biochemical testosterone deficiency.
- Widespread use of testosterone supplementation e.g. for patients presenting with erectile dysfunction or non-specific symptoms but without confirmed abnormal biochemistry is inappropriate, ineffective and carries with it significant risks e.g. of stroke.
- Recent evidence shows no increase in risk of cardiovascular disease with testosterone replacement therapy (Tan et al 2014)

Broad recommendations

- Replacement is recommended in men describing at least 2 sexual symptoms (loss of libido, loss of early morning erections or erectile dysfunction) with confirmed low early morning testosterone on repeat testing, and in the absence of acute intercurrent illness.
- Patients should only be initiated on replacement by those with the experience and availability to monitor testosterone therapy.
- Testosterone replacement is contraindicated in active testicular or prostate cancer, breast cancer, elevated haematocrit (>52%), poorly controlled heart failure, untreated obstructive sleep apnoea or patients seeking fertility.

Assessment

Signs and symptoms

Consider testosterone deficiency in patients presenting with signs and symptoms in table 1, but...
not during acute illness.

<table>
<thead>
<tr>
<th>Testing indicated</th>
<th>Testing not routinely indicated</th>
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<tr>
<td>Height loss, low trauma fracture (a fracture sustained in a fall from standing height or less), or confirmed low bone mineral density (osteoporosis)</td>
<td>Increased body fat/BMI</td>
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<tr>
<td>Hot flushes/sweats</td>
<td>Diminished physical or work performance</td>
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<tr>
<td>Gynaecomastia</td>
<td></td>
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<tr>
<td>Incomplete or delayed sexual development</td>
<td>Decreased energy, motivation, self confidence</td>
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<tr>
<td>Reduced libido</td>
<td>Depression, dysthymia</td>
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<td>Decreased spontaneous erections</td>
<td>Poor concentration and memory</td>
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<tr>
<td>Loss of body hair, reduced shaving</td>
<td>Sleep disturbance</td>
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<tr>
<td>&lt; 5mL or shrinking testes</td>
<td>Mild normocytic, normochromic anaemia</td>
</tr>
<tr>
<td>Low or zero sperm count</td>
<td>Reduced muscle bulk and strength</td>
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- Testosterone therapy should be temporarily discontinued if there is a significant rise in PSA or change in urological symptoms until urological evaluation has been performed.

Confirming the diagnosis of hypogonadism

NB testosterone should only be prescribed in men with 2 or more sexual features of hypogonadism as well as confirmed unequivocally abnormal biochemistry as below.

Testosterone therapy should only be instituted in patients with either two confirmed total testosterone levels <8 nmol/L taken at an appropriate time, or in patients with highly suggestive symptoms plus a risk factor plus low free or bioavailable testosterone.

Either: Total testosterone <8 nmol/L at 9am (no later than 9.30am) on 2 occasions

Or: Total testosterone 8.1 -12 nmol/L, but free testosterone calculated from total testosterone, SHBG and albumin below 220 pmol/L. Free testosterone calculator is available via http://www.issam.ch/freetesto.htm

AND known pituitary disease OR confirmed low bone mineral density OR presence of at least 2/3 specific sexual symptoms below:

- Poor sexual desire = 3 or less sexual thoughts in the last month
- Loss of early morning erections = less than one full strength erection in last month
- Erectile dysfunction = never or rarely sufficient for intercourse

Investigations

Initial screen

- Perform a non-fasting 9am (no later than 9.30am) serum testosterone, whilst physiologically well for the purpose of establishing potential testosterone deficiency (<12 nmol/L).

Confiratory test

- Repeat a non-fasting 9am serum testosterone, with SHBG, liver function test, LH and FSH whilst physiologically well, to confirm testosterone deficiency (<8 nmol/L), or to allow calculation of free testosterone for borderline cases (8.1 -12 nmol/L). This will also indicate whether this represents primary or secondary testicular failure.

Further investigations

- On confirmation of hypogonadism, it is recommended that patients are referred to endocrinology for further assessment into the cause of their hypogonadism and ongoing management.

- High FSH and LH are consistent with primary testicular failure. Most commonly, this is
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due to childhood mumps or maldescent of the testes. Patients with Klinefelters also present with this biochemistry. Endocrine evaluation is important to determine the most likely cause, arrange counselling, karyotype analysis and treatment, and to consider abdominal imaging in the first instance for patients with undescended testes.

- Low (or inappropriately normal) FSH and LH are consistent with secondary testicular failure. Refer to endocrinology, who will arrange baseline pituitary function including prolactin. MRI imaging of the pituitary should be performed if there is severe hypogonadism (serum testosterone levels < 5.2 nmol/L), any other abnormalities of pituitary function (e.g. elevated prolactin), or symptoms of a space occupying lesion e.g. visual field defect.

- Endocrinology will consider baseline bone densitometry scanning in men with profound hypogonadism and subsequently if indicated.

- Do not start testosterone replacement therapy in individuals seeking fertility.

Management

- For confirmed hypogonadism, refer to endocrinology to complete investigation and supervise treatment.

- Initiation of testosterone replacement may restore secondary sexual characteristics, improve sexual function, well being, muscle mass and bone mineral density. Patients must be counselled that testosterone therapy does not improve fertility.

- Investigate and treat the underlying cause where possible e.g. medical control of hyperprolactinaemia may restore testosterone levels and fertility as well as restoring normal vision; opioid withdrawal or weight loss may also lead to restoration of normal testosterone levels.

- Arrange digital rectal examination (may be performed by GP) and PSA prior to therapy. Refer to urology prior to treatment if either test is abnormal.

- Treatment is currently available as daily gels, 2-4 weekly injections, or 12 weekly depot injections. Suitable adult replacement doses are 1 sachet of Testogel®, 1 tube of Testim® or 3-6 pumps of Tostran® via a metered dose applicator daily, 250mg testosterone esters 3 weekly, or 1g Nebido® every 12 weeks (with an additional dose 6 weeks after initiation of treatment). However, prepubertal patients, older patients, those with mild hypogonadism, and those with very severe long standing hypogonadism should be started on significantly lower doses and titrated up by an experienced endocrinologist.

Follow up and monitoring

- Safety monitoring (PSA, FBC and LFT testing) should be performed at 3 months, with clinical and biochemical review of treatment efficacy at 6 months then annually thereafter. If there is no significant improvement in symptoms at 6 months, consider withdrawal of testosterone replacement.

- PSA followed by digital rectal examination should be performed prior to treatment and repeated annually thereafter.

- If testosterone therapy is successful patients should be reviewed on a yearly basis. If a clear cause has been identified and a management plan agreed, this follow up may be
provided by the patient’s GP with their agreement. Aim to maintain:

- Haematocrit < 52 -54%. Higher levels may need temporary drug cessation, and then reintroduction of testosterone at a lower dose.
- PSA <1.4 ug/L increase annually. Rapid or sustained rises require urological evaluation (Cause for concern would be a PSA increase 1ng/ml over baseline or a PSA velocity greater than 0.35 ng/ml per year)
- No adverse effects on liver function tests.

- Testosterone dose should be adjusted to achieve a mid normal range 4-6 hours post gel (following treatment for at least a month) application, or between Nebido® doses, or the bottom of the normal range pre (trough) and the top of the normal range one week post(peak)intramuscular dose.
- Digital rectal examination of the prostate should be performed prior to commencing therapy in men over 40 years or with a PSA >0.6 ug/L, and annually unless increased background risk Perform an earlier interim DRE if clinically indicated (change in urinary symptoms, rising PSA).

Clinical audit standards

Appropriate investigation to confirm diagnosis prior to treatment initiation: 2x early morning testosterone levels <8 nmol/L or if 8.1 -12 nmol/L, with appropriate calculation of free testosterone.

Appropriate clinical indications documented prior to treatment.

Adequate annual monitoring in place.

Summary of development and consultation process undertaken before registration and dissemination

The authors listed above drafted this guideline on behalf of the Directorate of Endocrinology which has agreed the final content. During its development it was has been circulated for comment to urology and chemical pathology.

This version has been endorsed by the Clinical Guidelines Assessment Panel.

Distribution list/ dissemination method

All Nursing Policies and Guideline folders
Trust Intranet

References

Bhasin s et al. Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes: An Endocrine Society Clinical Practice Guideline. 2010 J Clin Endocrinol Metab 95:2536-2559


Testosterone: is it really time to treat his oomph? DTB 2016;54:5 50-53