

**UPDATED PRIMARY CARE MANAGEMENT PATHWAY: LOW
TESTOSTERONE. V14. MAR 2014 Dr Webster & Endocrine Team,
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This updated protocol describes how men who have been found to have symptomatic low testosterone levels may be followed up in Primary Care after they have had investigation and treatment decisions made under the specialist clinic.

Low testosterone may cause no symptoms and be discovered incidentally on blood testing; otherwise, the main symptoms are erectile dysfunction (ED), and low libido.

Low testosterone levels indicate hypogonadism, which can be primary or secondary. Primary is a failure of the testes to produce testosterone, and this can be caused by many factors (see below), and secondary is related to a lack of pituitary signal. The LH (luteinising hormone) assay will be high in the former and low in the latter.

Background:

Testosterone is important for general as well as sexual health in men. Testosterone levels in men peak in their mid 20s then slowly decline throughout life. Symptoms of testosterone deficiency commonly include decreased libido, loss of morning erections and erectile dysfunction, but may also involve tiredness (fatigue), reduced physical strength and endurance, loss of motivation and concentration, irritability, and low mood. As these symptoms may be caused by conditions other than testosterone deficiency, it is important that any diagnosis of hypogonadism is supported by biochemical evidence of low circulating testosterone levels.

Hypogonadism is defined as a clinical syndrome complex that comprises symptoms and signs as well as biochemical evidence of testosterone deficiency.

Testosterone levels have a diurnal variation and should be measured early in the morning (before 11am, not fasting). Readings below the reference range, on at least two occasions 6-8 weeks apart, support a diagnosis of hypogonadism.

Chronically low testosterone levels can be found in

Primary hypogonadism

- Older age
- Chemo- and radiotherapy to pelvis
- Undescended testicles
- Mumps orchitis
- Testicular trauma
- Klinefelter syndrome

Secondary hypogonadism

- Drugs (opiates, glucocorticoids)
- Pituitary disease (adenomas, hyperprolactinaemia)
- Kallmann's syndrome
- Haemochromatosis
- Hypothalamic disorders (strictly, 'tertiary' hypogonadism) eg sarcoidosis, histiocytosis

Common Association with Other Conditions:

It is becoming increasingly recognised that older men with common medical conditions are more likely to have borderline low serum testosterone levels ("late onset hypogonadism"). These conditions include

- obesity, metabolic syndrome
- type 2 diabetes
- Osteoporosis
- COPD
- Coronary heart disease and cardiac failure
- HIV
- Inflammatory conditions (e.g. arthritis)
- Renal and liver failure.

While treatment with testosterone may have some short-term benefits in these conditions, the long-term efficacy and safety of testosterone replacement in these conditions has yet to be established.

Investigation:

- Six to eight weeks after the initial reading, repeat testosterone (morning before 11am), LH, FSH, oestradiol and prolactin, and PSA if over 40 years old, FBC (see below), and TSH. Note that the labs no longer perform Free Androgen Index.
- Screen for diabetes, hypertension, raised cholesterol and other cardiovascular risk factors, including u&e's and LFTs.
- Assess weight and offer support for weight loss if appropriate
- Consider DEXA scan in longstanding hypogonadism

Referral Pointers:

- Refer if any suggestion of pituitary disease (low testosterone with low or normal gonadotrophins, or hyperprolactinaemia). Refer to the Endocrine Consultants.
- Refer if any sexual problems (low sexual desire or interest, erectile / sexual dysfunction). Refer to the Andrology team.

Diagnosis:

- Symptoms likely to be related to low testosterone levels
- A 9am Testosterone level over 12 nmol/l does not need replacement
- Patients with levels under 8 nmol/l usually derive benefit.
- Between 8 and 12 nmol/l offer treatment if the calculated free testosterone level is 0.225nmol/l or below, AND there are clinical symptoms

Treatment & Monitoring:

- Testosterone treatment in patients with classical hypogonadism (ie with symptoms) is effective and safe and usually longterm. For men with a low testosterone but no or very few symptoms, treatment may not be required but a 6 month trial could be commenced, stopping if there is no symptomatic benefit.
- In most cases, testosterone replacement therapy should be initiated following review in secondary care.
- **Before starting treatment in men over 40 a history should be taken for prostatic symptoms and PSA should be measured. In addition, it is recommended that a DRE is performed by either the Urology clinic or GP before testosterone replacement therapy is started. (Endocrinology clinic will ask the GP to do this before starting the treatment recommended by the clinic but prescribed by the GP).**
- As testosterone can cause secondary polycythaemia, a FBC should be checked before starting treatment. A Haematocrit of 53% and above requires prompt haematological referral (48% if the patient also has cardiovascular morbidity)
- Once stable, patients may be referred back to primary care for further treatment and monitoring.
- Optimal testosterone level of between 15 and 18 nmol/l should be the target
- **Monitoring should include a FBC, PSA, and testosterone level at 3-6 months, then at 12 months; thereafter an annual FBC, PSA (in men over the age of 40), testosterone level and blood lipids. A DRE should be done annually in men over 40, or more frequently if PSA rises >1.4nmol/l within the year or worsening of prostatic symptoms.**
- A raised PSA or suspicious finding on DRE should prompt a urological referral, even if it has risen but still remains in the normal range. A rise of more than 1.4nmol/l in the first year of treatment, or by 0.4nmol/l per year in the first 2 years, should be referred
- DEXA scanning may be indicated to monitor response to treatment if bone density is low.

Testosterone Therapy – Contraindications:

- Prostate cancer
- Severe lower urinary tract symptoms

- Significant erythrocytosis with haematocrit over 50%
 - Untreated severe obstructive sleep apnoea
 - Untreated severe cardiac failure
 - Liver cancer
 - Serious liver or kidney disease
 - Breast cancer
 - Fertility considerations (relative contra-indication)
- NB obese men are more likely to get side effects of testosterone therapy

Testosterone Preparations – Sheffield Formulary (July 2012):

6.4.2 - Male sex hormones and antagonists

Testosterone esters oily injection (Sustanon 250®) 250mg/ml 1ml amp (£2.45 every 3 weeks)

Testosterone undecanoate oily injection (Nebido®) 250mg/ml 4ml amp (£80.00 every 10-14 weeks)

Testosterone 50mg/5g gel (Testogel®) 30 x 5g sachets (£31.11)

Testosterone 2% gel (Tostran®) 10mg/metered application 60g (20 doses £26.67)

Androgens should not be a treatment for impotence or impaired spermatogenesis unless there is associated hypogonadism, which should be properly investigated.

Tostran® may be preferred to Testogel® for those patients who require doses different from the standard Testogel® sachet size or who prefer smaller gel volumes.

1. Testogel (local application 1% gel). The recommended dose is 5 g of gel (i.e. 50 mg of testosterone) applied once daily at about the same time, preferably in the morning to the shoulders, upper arms and abdomen. The daily dose should be adjusted by the doctor depending on the clinical or laboratory response in individual patients, not exceeding 10 g of gel per day. The adjustment of posology should be achieved by 2.5 g of gel steps.

2. Tostran (2% gel) - The daily dose should not exceed 4 g of gel (80 mg testosterone). The dose can be applied to the abdomen (entire dose over an area of at least 10 by 30 cm), or to **both** inner thighs (one half of the dose over an area of at least 10 by 15 cm for each inner thigh). Daily rotation between the abdomen and inner thighs is recommended to minimise application site reactions.

The gel should be applied to clean, dry, intact skin. It should be rubbed in gently with one finger until dry, then the application site should be covered, preferably with loose clothing. Hands should then be washed with soap and water.

Each full depression of the canister piston delivers one half gram of gel (10 mg testosterone).

3. Nebido – IM injection - One ampoule / vial of Nebido (corresponding to 1000 mg testosterone undecanoate) is injected every 10 to 14 weeks. Injections with this frequency are capable of maintaining sufficient testosterone levels and do not lead to accumulation. Levels are achieved more quickly if the second dose is given 6 weeks after the first, thereafter being every 10 to 14 weeks. Cannot be self administered, though in Urology, Sustanon sometimes is.

Nebido should be given by deep IM route with the patient laid down, over 1-2 minutes, observing for signs of Pulmonary Oil Microembolism –

- **A serious lung problem.** pulmonary oil microembolism (POME) reaction. POME is caused by tiny droplets of oil that have traveled to the lungs. Symptoms of a POME reaction may include:
 - cough or urge to cough
 - difficulty breathing
 - sweating
 - feeling of throat tightening
 - chest pain
 - dizziness
 - fainting

NB Testosterone monitoring levels should be taken 6-12 hours post application (gels) or 2 weeks in advance of the next anticipated depot Nebido

Length of Time on Treatment

- Testosterone replacement could be longterm if the patient finds it beneficial and well tolerated, and annual monitoring is satisfactory
- Testosterone may no longer be needed if the patient loses sufficient weight to allow the testosterone level to increase again
- On discharge from the clinic, the letter should state the anticipated length of time on treatment, this having been discussed with the patient.

Reference:

British Society for Sexual Medicine (BSSM) 2010 – Guidelines on the management of sexual problems in men: the role of androgens. Developed by Prof Kevan Wylie (Chair)

<http://www.bssm.org.uk/downloads/default.asp>

And discussion with GPs, Urology and Endocrine Departments