Male hypogonadism &
testosterone replacement therapy

Adverse events should be reported. Reporting forms and information can be found at
www.mhra.gov.uk/yellowcard  Adverse events should also be reported to Besins Healthcare (UK) Ltd,
35A High Street, Marlborough, Wilts, SN8 1LW, UK. Tel: 01672 516 885. Email: drugsafety@besins-
healthcare.com
Above are illustrative screen grabs taken from www.whatistds.com
Overview

• Understanding hypogonadism
• Diagnostic tools
• Associated guidelines
• Treatment of hypogonadism
• Safety considerations & monitoring
• Secondary clinical benefits
• Co-morbidities
• Summary
Hypogonadism: Definition

- Endocrine Society Clinical Practice Guideline:
  - "Hypogonadism in men is a clinical syndrome that results from failure of the testis to produce physiological levels of testosterone and a normal number of spermatozoa due to disruption of one or more levels of the hypothalamic-pituitary-testicular axis."
- The terms “testosterone deficiency” or “androgen deficiency” are also used.

Sex hormones and hypogonadism

The hypothalamic-pituitary-gonadal axis in men

Effect of testosterone & its metabolites

### Hypogonadism: Prevalence

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Definition of hypogonadism used</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BLSA</strong>¹</td>
<td>890 men 1961-1995</td>
<td>• Total T &lt; 325 ng/dl</td>
<td>• 12% of men in their 50s, 19% in their 60s, 28% in their 70s, <strong>49% in their 80s</strong></td>
</tr>
<tr>
<td><strong>MMAS</strong>²</td>
<td>1691 men at baseline 1987-89</td>
<td>• Total T &lt; 200 ng/dl; <strong>or</strong> • Total T 200–400 ng/dl &amp; free T &lt; 8.91 ng/dl</td>
<td>• Crude prevalence of androgen deficiency 6% at baseline; 12.3% at second assessment</td>
</tr>
<tr>
<td></td>
<td>1087 men at second assessment 1995-97</td>
<td><strong>And ≥ 3 signs/symptoms of hypogonadism</strong></td>
<td></td>
</tr>
<tr>
<td><strong>HIM Study</strong>³</td>
<td>2162 men 2003-2004</td>
<td>• Total T &lt; 300 ng/dl; <strong>or</strong> • Currently receiving T therapy</td>
<td>• Crude prevalence 38.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>And ≥ 3 signs/symptoms of hypogonadism</strong></td>
<td>• Prevalence increased with age</td>
</tr>
<tr>
<td><strong>BACH Survey</strong>⁴</td>
<td>1475 men 2002-2005</td>
<td>• Total T &lt; 300 ng/dl &amp; free T &lt; 5 ng/dl</td>
<td>• Crude prevalence of symptomatic androgen deficiency 5.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>**And presence of low libido, ED, or osteoporosis; <strong>or</strong> • ≥ 2 of: sleep disturbance, depressed mood, lethargy, diminished physical performance</td>
<td>• Prevalence significantly greater in the oldest age group (18.4%)</td>
</tr>
<tr>
<td><strong>EMAS</strong>⁵</td>
<td>3219 men 2006</td>
<td>• Total T &lt; 320 ng/dl &amp; free T &lt; 64 pg/ml</td>
<td>• Overall prevalence 2.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>And ≥ 3 sexual symptoms</strong></td>
<td>• Prevalence increased with age from 0.1% for men 40-49 yr to 5.1% for men 70-79 yr</td>
</tr>
</tbody>
</table>

The clinical picture of testosterone deficiency

<table>
<thead>
<tr>
<th>Symptoms &amp; Signs suggestive of Androgen Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of libido</td>
</tr>
<tr>
<td>Decreased muscle bulk/strength</td>
</tr>
<tr>
<td>Increased body fat</td>
</tr>
<tr>
<td>Loss of body hair</td>
</tr>
<tr>
<td>Breast discomfort</td>
</tr>
<tr>
<td>Subfertility</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
</tr>
<tr>
<td>Poor concentration/memory</td>
</tr>
<tr>
<td>Depressed mood</td>
</tr>
<tr>
<td>Mild anaemia</td>
</tr>
<tr>
<td>Decreased spontaneous erections</td>
</tr>
<tr>
<td>Low bone mineral density</td>
</tr>
<tr>
<td>Hot flushes/ sweats</td>
</tr>
<tr>
<td>Decreased energy, motivation, initiative &amp; self-confidence</td>
</tr>
</tbody>
</table>

Hypogonadism: Classification

Functionally, hypogonadal states may be classified according to the level at which the hypothalamic-pituitary-testicular axis is defective

**Primary hypogonadism**
- abnormality is in the testes
- low testosterone levels
- elevated gonadotropin levels
- impairment of spermatogenesis

**Secondary hypogonadism**
- abnormality lies above the level of the testes
- decreased gonadotropin stimulation of potentially normal testes
- low testosterone levels
- low or low-normal gonadotropin levels
- impairment of spermatogenesis

## Hypogonadism: Classification

<table>
<thead>
<tr>
<th>Mixed hypogonadism</th>
<th>Late-onset hypogonadism</th>
</tr>
</thead>
<tbody>
<tr>
<td>– combined defects in the testes and the hypothalamic-pituitary axis</td>
<td>– defined as “hypogonadism in a male who has had normal pubertal development and as a result developed normal male secondary sex characteristics”</td>
</tr>
<tr>
<td>– low testosterone levels</td>
<td>– often either secondary or mixed hypogonadism</td>
</tr>
<tr>
<td>– variable gonadotropin levels</td>
<td></td>
</tr>
<tr>
<td>– impairment of spermatogenesis</td>
<td></td>
</tr>
</tbody>
</table>

Hypogonadism: Signs and symptoms

<table>
<thead>
<tr>
<th>Suggesting prepubertal-onset hypogonadism:</th>
<th>Associated with late-onset hypogonadism:</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Small testes</td>
<td>– Loss of libido</td>
</tr>
<tr>
<td>– Cryptorchidism</td>
<td>– Erectile dysfunction</td>
</tr>
<tr>
<td>– Gynaeecomastia</td>
<td>– Sarcopenia</td>
</tr>
<tr>
<td>– High voice</td>
<td>– Low bone mass</td>
</tr>
<tr>
<td>– Unclosed epiphyses</td>
<td>– Depressive thoughts</td>
</tr>
<tr>
<td>– Linear growth into adulthood</td>
<td>– Fatigue</td>
</tr>
<tr>
<td>– Eunuchoid habitus</td>
<td>– Loss of body hair</td>
</tr>
<tr>
<td>– Sparse body hair/facial hair</td>
<td>– Hot flushes</td>
</tr>
<tr>
<td>– Infertility</td>
<td>– Loss of vigour</td>
</tr>
<tr>
<td>– Low bone mass</td>
<td></td>
</tr>
<tr>
<td>– Sarcopenia</td>
<td></td>
</tr>
<tr>
<td>– Reduced sexual desire/activity</td>
<td></td>
</tr>
</tbody>
</table>

Hypogonadism: Symptoms

- Cross-sectional cohort study of 434 men aged 50-86 yrs
- Loss of libido or vigor increase significantly at TT levels <15 nmol/l (432 ng/dl)
- Depression, disturbed sleep, and lack of concentration were significantly more common at TT<10 nmol/l (288 ng/dl)
- ED was significantly more common at levels <8 nmol/l (230 ng/dl).

### Causes of primary hypogonadism

<table>
<thead>
<tr>
<th>Disease</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klinefelter’s syndrome</td>
<td>Typically caused by a 47,XXY karyotype; affects 1 in 500 males</td>
</tr>
<tr>
<td>Testicular tumours</td>
<td>Affects 12 per 100,000 males</td>
</tr>
<tr>
<td>Maldescended or ectopic testes</td>
<td>Failure of testicular descent; 85% idiopathic</td>
</tr>
<tr>
<td>Orchitis</td>
<td>Viral or unspecified orchitis</td>
</tr>
<tr>
<td>Acquired anorchia</td>
<td>Traumatic, tumour, torsion, inflammation, iatrogenic, surgical removal</td>
</tr>
<tr>
<td>Secondary testicular dysfunction</td>
<td>Medication, drugs, toxins, systemic diseases</td>
</tr>
<tr>
<td>Testicular atrophy</td>
<td>Idiopathic or specific causes</td>
</tr>
<tr>
<td>Congenital anorchia</td>
<td>Can be caused by mutations in different genes</td>
</tr>
<tr>
<td>Gonadal dysgenesis (‘streak gonads’)</td>
<td>Can be caused by mutations in different genes</td>
</tr>
<tr>
<td>46,XX male syndrome</td>
<td>Prevalence of 1 in 10,000-20,000</td>
</tr>
<tr>
<td>47,XYY syndrome</td>
<td>Prevalence of 1 in 2,000</td>
</tr>
<tr>
<td>Noonan syndrome</td>
<td>Prevalence of 1 in 1,000 to 1 in 5,000; genetic origin</td>
</tr>
<tr>
<td>Inactivating LH receptor mutations, Leydig cell hypoplasia</td>
<td>Prevalence of 1 in 1,000,000 to 1 in 20,000</td>
</tr>
</tbody>
</table>

Causes of secondary hypogonadism

<table>
<thead>
<tr>
<th>Disease</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kallmann syndrome</td>
<td>Associated with GnRH deficiency and anosmia, genetically determined; prevalence 1 in 10,000</td>
</tr>
<tr>
<td>Prader-Willi syndrome</td>
<td>Congenital disturbance of GnRH secretion; prevalence 1 in 10,000</td>
</tr>
<tr>
<td>GnRH receptor mutation/deficiency</td>
<td>Congenital</td>
</tr>
<tr>
<td>Congenital adrenal hypoplasia with hypogonadotropic hypogonadism</td>
<td>X-chromosomal recessive disease; prevalence 1 in 12,500</td>
</tr>
<tr>
<td>Hypopituitarism</td>
<td>Possible causes include radiotherapy, trauma, infections, haemochromatosis, vascular insufficiency, congenital</td>
</tr>
<tr>
<td>Pituitary adenomas</td>
<td>Include hormone-secreting adenomas; hormone-inactive pituitary adenomas; metastases from the pituitary or pituitary stalk</td>
</tr>
<tr>
<td>Hyperprolactinaemia</td>
<td>May be drug-induced or due to prolactin-secreting pituitary adenomas, chronic renal failure, or hypothyroidism</td>
</tr>
<tr>
<td>Secondary GnRH deficiency</td>
<td>Possible causes include medications, drugs, toxins, systemic diseases, alcohol abuse, obesity, type 2 diabetes</td>
</tr>
</tbody>
</table>

Medications that can cause hypogonadism

- **Highly active antiretroviral therapy**
  There is a high prevalence of low testosterone levels in HIV-infected men. 21% of HIV-infected men on highly active antiretroviral therapy have low free testosterone levels\(^1\). These low levels are associated with weight loss, progression to AIDS, wasting, depression and loss of muscle mass and exercise capacity\(^2\)

- **Opioids**
  In male patients suffering from chronic pain, opioid administration induces severe hypogonadism, leading to impaired physical and psychological conditions such as fatigue, anaemia and depression\(^3\)

- Results suggest that a constant, long-term supply of testosterone can induce a general improvement of the male chronic pain patient’s quality of life, an important clinical aspect of pain management\(^3\)

3. Aloisi AM et al. Reproductive Biology & Endocrinology 2011, 9:26
Medications that can cause hypogonadism

- **Glucocorticoids**
  - Testosterone levels are lower in glucocorticoid-treated men than in age-matched controls. There is a high prevalence of low T levels in glucocorticoid-treated men due to glucocorticoid-induced suppression of all components of the hypothalamic-pituitary-testicular axis.
  - The endocrine clinical guidelines suggest that clinicians offer T therapy to men receiving high doses of glucocorticoids who have low T levels to promote preservation of lean body mass and bone mineral density.
  - In a study, the effect of chronic glucocorticoid therapy on serum testosterone levels was studied in men aged 67 +/- 4 years with chronic pulmonary disease. The serum testosterone level was significantly reduced in 14 of 16 patients, compared with age and disease-matched controls (p < 0.001). The corticosteroid dosage and the serum testosterone level were inversely related (r = -0.78).

Diagnosis
Hypogonadism: Diagnosis

• According to the 2010 Endocrine Society Guideline and the 2012 EAU Guidelines, the diagnosis of hypogonadism is based on:
  – the identification of signs and symptoms suggestive of testosterone deficiency, and
  – the presence of low testosterone levels measured by a reliable assay on two or more occasions

ADAM Questionnaire

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 noted 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 you answered “Yes” to question 1 or 7, or if you answered “Yes” to any 3 questions in total, you may wish to talk to your doctor about having a blood test to determine your testosterone level. Take this questionnaire to your doctor to help start the discussion.

Aging Males' Symptoms (AMS) scale

- Self-administered scale designed to:
  - assess symptoms of aging (independent from those which are disease-related) in males
  - evaluate the severity of symptoms over time
  - measure changes pre- and post-androgen replacement therapy

- Well validated and widely used tool used to detect symptoms of testosterone deficiency syndrome and monitor its treatment

- Translated into over 20 languages

## Aging Males' Symptoms (AMS) scale

### AMS Questionnaire

Which of the following symptoms apply to you at this time? Please, mark the appropriate box for each symptom. For symptoms that do not apply, please mark "none".

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>none</th>
<th>mild</th>
<th>moderate</th>
<th>severe</th>
<th>extremely severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Decline in your feeling of general well-being (general state of health, subjective feeling)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>2. Joint pain and muscular ache (lower back pain, joint pain, pain in a limb, general back ache)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>3. Excessive sweating (unexpected/sudden episodes of sweating, hot flushes independent of strain)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>4. Sleep problems (difficulty in falling asleep, difficulty in sleeping through, waking up early and feeling tired, poor sleep, sleeplessness)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>5. Increased need for sleep, often feeling tired</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>6. Irritability (feeling aggressive, easily upset about little things, moody)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>7. Nervousness (inner tension, restlessness, feeling fidgety)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>8. Anxiety (feeling panicky)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>9. Physical exhaustion / lacking vitality (general decrease in performance, reduced activity, lacking interest in leisure activities, feeling of getting less done, of achieving less, of having to force oneself to undertake activities)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>10. Decrease in muscular strength (feeling of weakness)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>11. Depressive mood (feeling down, sad, on the verge of tears, lack of drive, mood swings, feeling nothing is of any use)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>12. Feeling that you have passed your peak</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>13. Feeling burnt out, having hit rock-bottom</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>14. Decrease in beard growth</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>15. Decrease in ability/frequency to perform sexually</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>16. Decrease in the number of morning erections</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>17. Decrease in sexual desire/libido (lacking pleasure in sex, lacking desire for sexual intercourse)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

Have you got any other major symptoms? Yes ☐ No ☐
If Yes, please describe: ____________________________

THANK YOU VERY MUCH FOR YOUR COOPERATION

Hypogonadism: Laboratory Evaluation

• Low testosterone levels are usually associated with:\textsuperscript{1}
  – elevated LH and FSH concentrations (primary hypogonadism), or
  – low or normal LH and FSH concentrations (secondary hypogonadism)

• Measurement of serum testosterone concentration requires consideration:\textsuperscript{2}
  – types/forms of testosterone to be measured (total, free/unbound, bioavailable)
  – time of measurement
  – frequency of measurement

\textsuperscript{1} Bhasin S, et al. \textit{J Clin Endocrinol Metab} 2010;95:2536-2559.
Hypogonadism: Laboratory Evaluation

- Measurements of testosterone available from clinical laboratories:¹
  - total testosterone
  - If the serum total testosterone level is between 8-12nmol/l, repeating the measurement of total testosterone with SHBG to calculate free testosterone may be helpful²

* An online free testosterone calculator can be found at [http://www.issam.ch/freetesto.htm](http://www.issam.ch/freetesto.htm)

---
In the presence of a clinical picture of testosterone deficiency and borderline serum testosterone levels, a short therapeutic trial (up to 6 months) of testosterone may still be justified.

**Testosterone levels requiring substitution**

1. Wylie et al. BSSM guidelines on the management of sexual problems in men: the role of androgens 2010
Measuring Serum Testosterone

Circadian rhythm of testosterone *

* Above levels of testosterone are taken from young healthy males

1. Adapted from Diver M et al. Clin Endocrinol 2003;58:710-717
Hypogonadism: Diagnostic Algorithm

Testosterone Therapy

• Major goal
  – to alleviate the symptoms of hypogonadism by restoring serum testosterone levels to normal physiological levels, with a minimum of adverse effects

Testosterone Therapy

• Optimally, testosterone therapy should:
  – raise circulating testosterone levels to normal physiological ranges
  – provide a daily testosterone release similar to normal endogenous production
  – reproduce fluctuations that match the circadian rhythm
  – deliver serum testosterone that can be converted at tissue level to its metabolites at the desired concentrations
  – have little or no negative effects on the prostate, liver, lipid profile, or cardiovascular system
  – be convenient
  – enable flexible dosing and, if required, be possible to easily/rapidly discontinue

Gooren LJ, Bunck MC. Drugs. 2004;64:1861-1891.
Testosterone Replacement Therapy (TRT): For whom?

• TRT is indicated in men diagnosed as hypogonadal and in whom no contraindications exist
  – Diagnosis should be based on the presence of signs/symptoms of T deficiency and unequivocally low serum T levels on 2 separate morning tests.

• TRT is contraindicated in men with:
  – Known or suspected prostate or breast cancer
  – PSA > 4 ng/ml (>3ng/ml in individuals at high risk for prostate cancer, such as African Americans or men with first degree relatives who have prostate cancer)
  – severe sleep apnoea
  – haematocrit > 50%
  – severe lower urinary tract symptoms due to BPH (relative contraindication)
  – As TRT may suppress sperm production, it is not recommended in men who wish to retain fertility

TRT: For how long?

• It is important to realize that testosterone treatment is considered lifelong therapy\(^1\)
• In patients who have a positive response to TRT, i.e. alleviation of symptoms and restoration of physiological testosterone levels, treatment may continue in accordance with a standardised monitoring plan\(^2\)
  – to ensure that testosterone levels are optimal
  – to ensure that any potential adverse effects are detected early

Associated Guidelines
BSSM guidelines on the management of sexual problems in men: the role of androgens

• The initial assessment of all men with ED and/or diminished libido should include determination of serum testosterone.

• There is general agreement that a total testosterone level above 12nmol/l does not require replacement. Patients with total T level below 8nmol/l will usually benefit from treatment. If the total T level is between 8 and 12nmol/l, repeating the measurement of total T with SHBG and albumin to calculate free testosterone may be helpful.

• In the presence of a clinical picture of testosterone deficiency and borderline serum T levels, a short therapeutic trial (e.g. up to 6 months) of testosterone may still be justified.

• The aim of therapy should be a total T level of at least 15nmol/l

• The combination of testosterone and PDE5i treatment should be considered in hypogonadal men with ED who fail to respond to either treatment alone.

1. Wylie K et al. 2010. BSSM guidelines on the management of sexual problems in men: the role of androgens
The diagnosis of testosterone deficiency should be restricted to men with persistent symptoms suggesting hypogonadism.

Total testosterone assessment should be repeated at least on two occasions with a reliable method in men with:

- Total testosterone levels close to the lower normal range (8-12 nmol/l), the free testosterone level should be measured to strengthen the laboratory assessment.
- Suspected or known abnormal sex hormone-binding globulin (SHBG) levels, free testosterone should also be included.

LH serum levels should be analysed to differentiate between primary, secondary, and late-onset hypogonadism.

ISA, ISSAM, EAA, EAU, ASA recommendations

- The initial assessment of all men with ED and/or diminished libido should include determination of serum testosterone.
- There is general agreement that a total testosterone level above 12nmol/l does not require substitution. Similarly there is a consensus that patients with total T level below 8nmol/l will usually benefit from treatment. If the total T level is between 8 and 12nmol/l, repeating the measurement of total T with SHBG to calculate free testosterone may be helpful.
- In the presence of a clinical picture of testosterone deficiency and borderline serum T levels, a short therapeutic trial (e.g. 3 months) of testosterone may still be justified.
- The combination of testosterone and PDE5i treatment should be considered in hypogonadal men with ED who fail to respond to either treatment alone.

1.14.4 Erectile dysfunction

1.14.4.1 Review the issue of erectile dysfunction with men annually.

1.14.4.2 Provide assessment and education for men with erectile dysfunction to address contributory factors and treatment options.

1.14.4.3 Offer a phosphodiesterase-5 inhibitor (choosing the drug with the lowest acquisition cost), in the absence of contraindications, if erectile dysfunction is a problem.

1.14.4.4 Following discussion, refer to a service offering other medical, surgical, or psychological management of erectile dysfunction if phosphodiesterase-5 inhibitors have been unsuccessful.

1. NICE Clinical Guideline 87, May 2009
Treatment Options
Testosterone therapy

- Number of testosterone preparations available in the UK\(^1\)
- Differ by route of application
- Preparations of natural testosterone should be used for substitution therapy\(^2\).
- Transdermal, intramuscular and oral preparations have a proven safety profile and are effective\(^2\).
- The selection of the preparation should be a joint decision of an informed patient and physician\(^2\).

1. MIMS Online Feb 2015
2. Wylie K et al. 2010. BSSM guidelines on the management of sexual problems in men: the role of androgens
Benefits of Testosterone Therapy

• Improved body composition¹
• Improvement in bone mineral density¹
• Improved sexual function¹
• Improved mood, sense of well-being¹
• Improvement in MetS parameters²
• Improved Quality of Life³,⁴

Testosterone preparations – UK

• Oral
  – Capsules

• Transdermal
  – Gels

• Intramuscular injections
  – Short-acting
  – Long-acting

1. MIMS Online Feb 2015
Pharmacokinetics of testosterone preparations

Note: X-axes are different time scales according to duration of action of the particular therapy

1. Adapted from Gooren LJJG et al. *Drugs* 2004.64(17):1861-1891.
Testogel® (Testosterone)

- Clear, colourless hydroalcoholic gel<sup>1</sup>
- 5 g sachet contains 50 mg of testosterone<sup>1</sup>
- Indicated for male hypogonadism, where testosterone deficiency has been clinically and biochemically confirmed<sup>1</sup>

Testogel® efficacy

- Continuous 24-hour delivery from a single daily application\(^1\)
- Improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men\(^2\)

\(^1\) Testogel. Summary of Product Characteristics; 2006.
Testogel® tolerability

• Incidence of skin reactions in clinical studies with Testogel® was 10%\(^1\)

Testogel® : precautions for use

- Avoidance of potential testosterone transfer
  - Wash hands with soap and water after applying Testogel
  - Cover the area of application with clothing once the gel has dried
  - Shower before anticipated skin-to-skin contact with partner
  - Always keep the area of application covered with clothing when in contact with children or a pregnant woman

Safety & Monitoring
Potential adverse effects linked to TRT

- Erythrocytosis
- Growth of metastatic prostate cancer
- Detection of subclinical prostate cancer
- Leg oedema and worsening of heart failure
- Reduced sperm production and infertility
- Acne, oiliness of skin
- Breast tenderness
- Induction/worsening of obstructive sleep apnoea
- Gynaecomastia
- Growth of breast cancer
- Male pattern balding
- Formulation-specific effects

Weak evidence of association with TRT

## Testosterone Therapy: Monitoring

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Schedule</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone level</td>
<td>After 3-6 months, then annually</td>
<td>Serum testosterone ideally in mid-normal range</td>
</tr>
<tr>
<td>Haematocrit</td>
<td>Baseline, after 3-6 months, then annually</td>
<td>If haematocrit &gt;54% discontinue TRT until decreases to a safe level, exclude hypoxia/sleep apnoea, resume TRT at reduced dose</td>
</tr>
<tr>
<td>Bone mineral density</td>
<td>After 1-2 years</td>
<td>Measure in hypogonadal men with osteoporosis or low trauma fracture</td>
</tr>
<tr>
<td>Prostate health</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Serum PSA</td>
<td>Baseline, after 3-6 months, then according to prostate cancer screening guidelines</td>
<td>Measure in men aged ≥40 years with baseline PSA &gt;0.6 ng/ml</td>
</tr>
<tr>
<td>- Digital rectal examination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>Every office visit</td>
<td>Also monitor for formulation-specific adverse events</td>
</tr>
</tbody>
</table>

Testosterone & Prostate Safety

- TRT is contraindicated in men with:
  - Known or suspected prostate or breast cancer
  - PSA > 4 ng/ml (>3 ng/ml in individuals at high risk for prostate cancer, such as African Americans or men with first degree relatives who have prostate cancer)  

- Currently there is no conclusive evidence that testosterone therapy increases the risk of prostate cancer. There is also no evidence that testosterone treatment will convert subclinical prostate cancer to clinically detectable prostate cancer

- There has been a revolutionary change in concept and practice with regard to the use of T therapy in men with prostate cancer (PCa) over the last 10–15 years. The long-taught idea that raising serum T necessarily causes rapid and universal growth of existing PCa has been found to be untenable

Testosterone & Prostate Safety

- The saturation model impels a change in the traditional teaching that T is “like food for a hungry tumour.” Rather, it suggests that T is “like water for a thirsty tumour.” The critical distinction is that once thirst is quenched, additional water serves only as excess\(^1\).

- Proposed saturation model for the relationship of prostate cancer (PCa) growth and serum T concentration. The traditional belief has been that higher T concentration caused increasing rates of PCa growth, as represented by curves a and b. All available evidence demonstrates a powerful effect of T on PCa growth at low T concentration, yet little or no effect above the near-castrate range. The proposed model for the relationship between T and PCa is thus shown as curve c and is consistent with a saturation model, as seen in many other biologic systems\(^2\).

--

Testosterone & Prostate Safety

• The relationship between total testosterone and prostate cancer has been an area of interest among physicians for decades.
• Conflicting results have been reported on the relationship between total testosterone and subsequent prostate cancer. Much of this controversy appears to be based on conflicting study designs, definitions and methodologies.
• To date no prospective study with sufficient power has been published to unequivocally resolve the issue.
• The preponderance of studies of the safety of exogenous testosterone in men with a prostate cancer history suggests that there is little if any risk.
• However, because the risk has not proved to be zero, the most prudent course is to follow such men with regular prostate specific antigen measurements and digital rectal examinations.

Testosterone & Cardiovascular Safety

Food & Drug Administration (FDA)

• On Sept 17\textsuperscript{th} 2014, the FDA scheduled an Advisory Committee to “discuss the appropriate indicated population for testosterone therapies and the potential for cardiovascular risk associated with this use”

• It was unanimously held that existing, recently published research data on increased CV risk with testosterone therapy was too weak to draw any conclusions

• The advisory panel voted to include some new information on potential cardiovascular risk, but expressed the opinion that whatever language is chosen, it should reflect the weakness of the evidence

• The advisory panel voted to require industry to further study the CV safety of testosterone treatments.
In October 2014, the pharmacovigilance & risk assessment committee (PRAC) of the EMA released the following recommendations.

Overall the PRAC concluded that findings in the literature do not consistently show an increased risk of cardiovascular events and do not corroborate the signal of an increased risk of cardiovascular events associated with testosterone therapy.

Taking the totality of data into account it is judged that the signal for an increased CV risk associated with the use of testosterone remains weak and inconclusive.

The committee recognised the limited available information on testosterone therapy for age-related hypogonadism and also the lack of reference. Further studies will be needed to provide relevant safety and efficacy data in this patient population.

Pharmacovigilance Risk Assessment Committee EMEA/H/A-31/1396 EMA/PRAC/599233/2014
Secondary Clinical Benefits
Secondary Clinical Benefits of Testosterone Replacement Therapy (Testogel®) in Symptomatic Hypogonadal Men

TDS is commonly associated with a number of other clinical conditions.

Although the primary aim of testosterone replacement therapy is to return testosterone levels to within the normal range and alleviate the symptoms of TDS, a number of potential secondary benefits have been shown.
Testogel® (testosterone), in combination with a PDE5 inhibitor, improves erectile function in hypogonadal men with erectile dysfunction after 6 months testosterone replacement therapy\(^1\)

1. Adapted from Greenstein A et al. J Urol 2005;173: 530-532
Addition of Testogel® (testosterone) therapy to hypogonadal men with ED who are non-responders to sildenafil

![Graph showing mean change from baseline IIEF erectile function domain across weeks.]

- **Week 4**: p=0.029
- **Week 8**: p=ns
- **Week 12**: p=ns
- **Endpoint**: p=ns

Mean change from baseline IIEF erectile function domain

- **Placebo + Sildenafil 100mg**
- **Testosterone + Sildenafil 100mg**

n=75 hypogonadal men with ED

1. Adapted from Shabsigh R et al. J Urol 2004; 172: 658-663
Increased percentage of hypogonadal men with newly diagnosed type 2 diabetes reaching HbA$_1c$ target after Testogel® (testosterone) therapy in addition to lifestyle modifications compared to lifestyle modifications alone (52 weeks)$^1$

$n = 32$ hypogonadal men newly diagnosed with type 2 diabetes

* $p<0.001$ vs diet & exercise alone

Testogel® (testosterone) therapy alongside lifestyle modifications in hypogonadal men with type 2 diabetes & metabolic syndrome can help improve glycaemic control\(^1\)

\(^1\) Heufelder A et al. *J Androl* 2009;30:726-733
Testogel® (testosterone) therapy in addition to lifestyle modifications in hypogonadal men with type 2 diabetes can have an effect on waist circumference.

$n = 32$ hypogonadal men newly diagnosed with type 2 diabetes

*Compared to baseline.

Testosterone therapy with short-acting i.m. testosterone in hypogonadal men with type 2 diabetes can have an effect on diabetic parameters such as the HOMA Index and HbA1c\(^1\)

Mean (±SEM) change in HOMA index

Mean (±SEM) change in HbA1c

n = 24 hypogonadal men with type 2 diabetes

Co-morbidities
Hypogonadism: Co-morbidities

• Low serum testosterone is associated with:¹-⁴
  – increased risk of developing metabolic syndrome¹
  – obesity²,⁴
  – type 2 diabetes²,⁴
  – increased cardiovascular disease risk²,⁴
  – erectile dysfunction³,⁴

• Low testosterone levels reported in up to 20% of men with symptomatic vertebral fractures and 50% of elderly men with hip fractures.⁵

Co-morbidities: The HIM Study

- Odds ratios for hypogonadism were significantly higher in men with
  - hypertension (1.84)
  - hyperlipidaemia (1.47)
  - diabetes (2.09)
  - obesity (2.38)
  - asthma or chronic obstructive pulmonary disease (1.40)

Percentage of both hypogonadal and eugonadal patients reporting history of co-morbidities

The Metabolic Syndrome and Men with Low Testosterone
Definition of Metabolic Syndrome

The National Cholesterol Education Programme Adult Treatment Panel III (ATP III) report identified the metabolic syndrome as a multiplex factor for cardiovascular disease that is deserving of more clinical attention¹

Any three or more of

**Obesity**  Waist circumference > 102cm (males)

**Raised TGs**  \( \text{TG} \geq 1.7\text{mmol/L (150mg/dL)} \)

**Lowered HDL-C**  \( \text{HDL-C} < 1.0\text{mmol/L (40mg/dL)} \) (males)

**Hypertension**  \( \text{BP} \geq 130/85 \text{mmHg} \)

**Fasting Glucose**  Fasting plasma glucose \( \geq 5.6\text{mmol/L (110mg/dL)} \)

Clinical Management of Metabolic Syndrome

- **Primary goal is to reduce the risk of clinical atherosclerotic disease.**
  - Manage underlying risk factors for CVD and diabetes
    - Reduce abdominal obesity
    - Increase physical activity
    - Improve unhealthy diet
  - Manage metabolic risk factors
    - Improve dyslipidaemia
    - Reduce blood pressure
    - Reduce plasma glucose levels
    - Improve pro-thrombotic state
    - Improve pro-inflammatory state

Testosterone Levels and Metabolic Syndrome (MetS) in adult men

• Results have shown that in a group of men aged 45 years and above, as long as testosterone levels decline, the prevalence of the MetS increases independent of age.¹

• The correlations found between testosterone and 4 of the 5 components of the MetS, suggest considering male hypogonadism as a determinant of developmental abnormalities typical of MetS.¹

• In a study from 2015, 1651 men without MetS at baseline were identified from the European Male Aging Study (EMAS) population. During follow-up, 289 men developed incident MetS. Men with lower baseline total T levels were at higher risk for developing MetS. Odds Ratio = 1.72, P < 0.001²

2. Antonio L et al J Clin Endocrinol Metab. 2015 Apr;100(4):1396-404
Testosterone Levels and Metabolic Syndrome

- Prospective population based study of 702 middle-aged Finnish men\(^1\)
  - 11 year follow-up
  - Low testosterone levels independently predicted the development of metabolic syndrome
- Baltimore Longitudinal Study of Aging\(^2\)
  - Mean follow-up of 5.8 years of 618 men (mean age 63 years)
  - Lower testosterone levels predicted higher incidence of metabolic syndrome
- Data from Massachusetts Male Aging Study\(^3\)
  - 950 men with no metabolic syndrome at baseline
  - Lower testosterone levels were predictive of metabolic syndrome in long term follow-up (13-15 years)

Testosterone levels decrease with increasing number of metabolic syndrome components

p<0.0001 for trend in all subgroups

n=1491 patients attending Andrology Unit for ED

Testosterone Therapy and Mortality

- Observational cohort of 1,031 males >40 years old
- Testosterone treatment was associated with longer survival time compared with no testosterone treatment
- Overall mortality in testosterone-treated men compared with untreated men was 10.3 and 20.7% ($P < 0.0001$).

Testosterone Therapy and Mortality

- A Study from 2014 by Pye et al used prospective data from the European Male Aging Study (EMAS) to look at mortality rates in aging men with late-onset hypogonadism (LOH)\(^1\)
- Data from 2599 community-dwelling men aged 40-79 years from 8 European countries were used
- Their conclusions were as follows...
  1. Severe LOH is associated with substantially higher risks of all-cause and cardiovascular mortality, to which both the level of T and the presence of sexual symptoms contribute independently.
  2. Detecting low T in men presenting with sexual symptoms offers an opportunity to identify a small subgroup of aging men at particularly high risk of dying.

Hypogonadism & CVD

• Testosterone deficiency is associated with:
  – ↑ total cholesterol and LDL
  – ↑ production of pro-inflammatory factors
  – ↑ thickness of the arterial wall
  – endothelial dysfunction

Hypogonadism & CVD

• Roles of testosterone in maintaining cardiovascular health:\(^1\)
  – Indirect: by modulating cardiac risk factors
  – Direct: e.g. low total and bioavailable testosterone levels have been associated with increased risk of aortic atherosclerosis in men\(^2\)

• In men, testosterone levels have been found to be inversely related to mortality due to cardiovascular disease\(^3-4\)

Hypogonadism & Type 2 Diabetes

• Hypogonadal men are at higher risk for type 2 diabetes\(^1\)-\(^2\)
  – Up to 57% of men with type 2 diabetes have low testosterone levels\(^2\)
  – Prospective studies suggest that men with higher testosterone levels (449.6-605.2 ng/dl) had a 42% lower risk of developing type 2 diabetes\(^3\)

• The Endocrine Society Clinical Practice Guideline recommends screening of testosterone levels in type 2 diabetic patients\(^4\)

Hypogonadism & Erectile Dysfunction

• In a survey of 1,610 men participating in the European Male Aging Study (EMAS), 30.3% reported having experienced ED
• The probability of ED increased with decreased levels of testosterone

Testosterone therapy significantly improves body composition and Bone Mineral Density (BMD)\textsuperscript{1}

Hypogonadism: Summary

• The prevalence of hypogonadism in men appears to be correlated to increasing age
• Increased risk of hypogonadism is associated with metabolic syndrome (obesity, type 2 diabetes, and hypertension)\(^1\)
• At present, symptomatic hypogonadism is frequently undiagnosed and left untreated\(^2\)
• If untreated, hypogonadism can compromise the sexual function, body composition, cardiometabolic profile, and healthy ageing of men\(^3\)
• Testosterone therapy alleviates many of the symptoms of testosterone deficiency in hypogonadal men,\(^4\) resulting in improved physical health, mental health, sexual function, and quality of life

What is TDS?

TDS is a medical condition where the body does not produce enough of the male hormone, testosterone, and symptoms relating to low testosterone are present.

TDS: signs & symptoms

- Testosterone is produced naturally by the testicles ('balls') and is important for your physical and emotional well-being.
- It's responsible for many things in the body, including maintaining muscle and bone mass, the production of sperm, and the desire to have sex ('sex drive' or libido).
- As men get older, testosterone levels often decline naturally; however, in men with TDS the levels of testosterone drop to a point where it affects their health and enjoyment of life in a variety of different ways.
- The chances of having TDS are higher when men have certain other conditions such as obesity, diabetes, high blood pressure, heart disease, asthma, chronic obstructive pulmonary disease (COPD) and osteoporosis.

TDS: treatment options

- "I was feeling a bit low about myself -- I felt a lack of confidence."
Prescribing Information

• Abbreviated Prescribing Information Testogel® 50mg, gel in sachet
• For full prescribing information, including side effects, precautions and contraindications, please consult the Summary of Product Characteristics (SPC).

Presentation: 5 g sachets containing 50 mg of testosterone. Indication: Testosterone replacement therapy for male hypogonadism when testosterone deficiency has been confirmed by clinical features and biochemical tests. Dosage and administration: Cutaneous use. The recommended dose is 5 g of gel (i.e. 50 mg of testosterone) applied once daily. The daily dose should not exceed 10 g of gel per day. Adjustment of dosage should be in steps of 2.5 g of gel, usually based on measurements of serum testosterone concentrations. The gel should be administered by the patient himself, onto clean, dry, healthy skin over both shoulders or both arms or abdomen. Allow drying for at least 3–5 minutes before dressing.

Contraindications: Cases of known or suspected cancer of the prostate or breast, known hypersensitivity to testosterone or to any other constituent of the gel. Warnings and precautions for use: Testosterone insufficiency should be clearly demonstrated by clinical features and confirmed by 2 separate blood testosterone measurements. Risk of pre-existing prostatic cancer should be excluded and the prostate gland and breast monitored during Testogel treatment. Testogel should be used with caution in cancer patients at risk of hypercalcemia and associated hypercalciuria due to bone metastases; regular monitoring of serum calcium concentrations is recommended in these patients. Testogel may cause oedema with or without congestive cardiac failure in patients suffering from severe cardiac, hepatic or renal insufficiency. If this occurs, treatment must be stopped immediately. Testogel should be used with caution in patients with ischaemic heart disease. Testosterone may cause a rise in blood pressure and should be used with caution in patients with hypertension. In addition to measurement of serum testosterone concentrations in patients on long-term androgen treatment the following laboratory parameters should be checked periodically: haemoglobin, hematocrit (to detect polycythaemia), liver function tests, lipids profile. Testogel may affect results of laboratory tests of thyroid function.
Prescribing Information

- Irritability, nervousness, weight gain, prolonged or frequent erections may indicate excessive androgen exposure requiring dosage adjustment. Testogel should be used with caution in patients with epilepsy and migraine. Do not apply to the genital areas as the high alcohol content may cause local irritation. Testogel can be transferred to other persons by close skin to skin contact. Testogel is not indicated for use in women or in children under 18 years of age. Testogel is not a treatment for male impotence or sterility. For further details refer to the SPC. Interactions: May increase the activity of oral anticoagulants. Concomitant administration of testosterone and ACTH or corticosteroids may increase the risk of developing oedema. Pregnancy and lactation: Pregnant women must avoid any contact with Testogel application sites. This product may have adverse virilising effects on the foetus. Undesirable effects: Local skin reactions include: erythema, acne and dry skin. Systemic adverse reactions include: prostatic disorders, gynaecomastia, mastodynia, headache, dizziness, hyperaesthesia, paraesthesia, amnesia, mood disorders, hypertension, diarrhoea, alopecia, polycythaemia, increased serum lipids and urticaaria. Other known adverse drug reactions of testosterone: prostatic changes and progression of sub-clinical prostatic cancer, urinary obstruction, jaundice, changes in liver function tests, increased libido, nervousness, depression, sleep apnoea, muscle cramps, priapism and, during high dose prolonged treatment, electrolyte changes, oligospermia and priapism. In case of severe application site reactions, treatment should be reviewed and discontinued if necessary.


Adverse events should be reported. Reporting forms and information can be found at [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard) Adverse events should also be reported to Besins Healthcare (UK) Ltd, 35A High Street, Marlborough, Wilts, SN8 1LW, UK. Tel: 01672 516 885. Email: drugsafety@besins-healthcare.com