Testosterone and Sexual Dysfunction

19th October 2017

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Past President of the British Society for Sexual Medicine (BSSM)

Chairman: Primary Care Testosterone Advisory Group
Learning Objectives

1) To be able to appreciate the importance of Testosterone Deficiency (TD)

2) To be aware of comorbidities that have a close association with TD and also medications that can reduce testosterone levels.

3) To be aware of treatment options both medical and lifestyle.

4) To have a basic understanding of the management of TD and testosterone replacement.
Testosterone Deficiency (TD)

- TD also known as hypogonadism, testosterone deficiency syndrome but is *not* the ‘male menopause’.
- Describes patients with a clinical syndrome of symptoms, with or without clinical signs, in conjunction with biochemical evidence of testosterone deficiency. Dhatariya K, Nagi D & Jones TH *Pract Diab Int* Nov/Dec 2010 27 9 408-412
So why is Low Testosterone an Issue?

• 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
  – depression

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

We ignore Men’s Health at our peril....

Erectile Dysfunction (ED) and Testosterone Deficiency Syndrome (TDS) can be.......
We ignore Men’s Health at our peril....

Erectile Dysfunction (ED) and Testosterone Deficiency Syndrome (TDS) can be.......

‘Harbingers of Doom’
Harbingers of doom......

• ED is a marker for CVD, Diabetes, LUTS.
• ED is an early marker for Endothelial Dysfunction.
• ED if ignored can lead to an Early Death.

• TD is associated with increased mortality and comorbidity
HYPOGONADISM IS AN UNDERDIAGNOSED CONDITION

- Patient Embarrassment
- Perception as symptoms of ageing
- Lack of clinical awareness
Treatment seeking is often delayed

- In total, 55% of all respondents waited between 3 and 24 months, with 35% waiting for more than 2 years before seeking advice.

<table>
<thead>
<tr>
<th>Reason</th>
<th>Respondents (n=90), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>I didn't think it was a serious problem</td>
<td>49</td>
</tr>
<tr>
<td>I thought it was just a part of life</td>
<td>46</td>
</tr>
<tr>
<td>I assumed it was to do with my age</td>
<td>44</td>
</tr>
<tr>
<td><strong>I was embarrassed</strong></td>
<td>41</td>
</tr>
<tr>
<td>I thought it would just go away</td>
<td>29</td>
</tr>
<tr>
<td>I didn't want to waste the doctor's time</td>
<td>28</td>
</tr>
<tr>
<td>I didn't think it could be treated</td>
<td>26</td>
</tr>
<tr>
<td>I didn't know what it was</td>
<td>24</td>
</tr>
<tr>
<td>I didn't think it was a medical issue</td>
<td>20</td>
</tr>
<tr>
<td>I was too busy/didn't have time</td>
<td>11</td>
</tr>
</tbody>
</table>

D Edwards & J David et al: The Journal of Sexual Medicine, Volume 13, Number 5, Supplement 2, May 2016
Testosterone Physiology

Anabolic steroid hormone

- >95% from testes
- Also from adrenal cortex

- LH from anterior pituitary
- GnRH (in PULSES) from hypothalamus
Sex hormones and hypogonadism

The hypothalamic-pituitary-gonadal axis in men

BSSM guidelines for testosterone testing to diagnose hypogonadism: TT and FT cut-offs

• There are no broadly accepted lower limits for normal TT or FT levels, but in the presence of symptoms, guidelines recommend:

- **TT >12 nmol/L or FT >0.225 nmol/L**
  - TRT not normally required

- **TT 8–12 nmol/L**
  - Consider 3-6mo Trial of TRT

- **TT <8 nmol/L or FT <0.225 nmol/L**
  - Consider TRT

BSSM, British Society for Sexual Medicine;
FT, free testosterone; TRT, testosterone replacement therapy; TT, total testosterone
Clinicians should actively look for TD in patients with:-

- Type 2 Diabetes
- Metabolic syndrome
- Abdominal obesity
- ED particularly in those responded poorly to PDE5i therapy
- Unexplained tiredness
- Older patients with unexplained fractures, osteoporosis or anaemia.
- Patients with chronic disease.
- Don’t forget chronic opioid use....
Drugs affecting testosterone

• Opioids
  – Regular use → suppressed levels in up to 70% of men

• Glucocorticoids
  – may suppress hypothalamic-pituitary-testicular axis
Drugs affecting testosterone

- Antidepressants / anxiolytics / antipsychotics
  - with/without hyperprolactinaemia

- Finasteride / dutasteride
  - (including for hair loss) – can persist for years

Drugs affecting testosterone

- **Carbamazepine** & some other anti-epileptics
  - ↑ SHBG, ↓ bioavailability

- Previous **anabolic steroid** abuse
- Anti-retrovirals
- Statins
Hypogonadism: Diagnosis

• According to the 2010 Endocrine Society Guideline and the 2012 EAU Guidelines, the diagnosis of hypogonadism is based on:

✓ Signs & Symptoms

✓ Low Testosterone levels measured on two or more separate occasions

Clinical signs and symptoms\textsuperscript{1}

- Diminished sexual desire and erectile quality
- Diminished energy and low drive
- Reduced sense of vitality or well-being, low self-esteem
- Increased fatigue
- Depressed mood and emotional
- Loss of pubic and body hair
- Diminished bone density
- Anaemia
- Impaired cognition, concentration
- Diminished muscle mass and strength
- Hot flushes/palpitations
- Abdominal obesity/gynaecomastia
- Subfertility/decreased genital size \textsuperscript{25%}

\textsuperscript{1} Lazarou S, Morgentaler A. Curr Urol Rep 2005; 6: 476–481.
Testosterone levels decrease with increasing waist circumference

Men aged 25–84 years (n=1584)

<table>
<thead>
<tr>
<th>Waist circumference (cm)</th>
<th>Total testosterone (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;94</td>
<td>536</td>
</tr>
<tr>
<td>94–101.9</td>
<td>346</td>
</tr>
</tbody>
</table>

Limit of lower normal

p<0.001 for trend

Measuring Serum Testosterone¹

![Graph showing circadian rhythm of testosterone](image)

* 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
Treatment of T deficiency

Non-pharmacological treatment:

• Address:
  – sleep apnoea
  – weight reduction
  – lifestyle modification

• Improving any can ↑ T synthesis

Changes Testosterone related to weight change – longitudinal results
European Male Ageing Study (n=2395)

Treatment of T deficiency

- Treatment of Co-morbid conditions
- Medication – Swap or stop if contributing
Testosterone Replacement Therapy (TRT)

- Preparations differ:
  - Route of delivery
  - Ease of use
  - Pharmacokinetics
  - Cost

- **Compliance** is crucial

- Must **advise** re all options, including not treating
Oral Testosterone

• Would normally be inactivated by the liver
• Testosterone undecanate in castor oil
  – Absorbed into lymphatic system
• Advantages:
  – Oral convenience, modifiable dosage
• Disadvantages:
  – Taken 2-4x/day with meals
  – Variable serum T levels & clinical response
Transdermal Testosterone

- Transdermal = **gels** only in UK:
- **Advantages:**
  - Flexible dose modifications
  - No needles, rapid steady state
  - Ease of Withdrawal
- **Disadvantages:**
  - Variable absorption
  - Possible transfer during intimate contact

1. Short-acting:
   - Usually 3-weekly

• **Advantages:**
  - Low cost

• **Disadvantages:**
  - More injections
  - Considerable fluctuation in T levels between injections
2. Long-acting:
   – Every 10-14 weeks

• *Advantages*:
  – Fewer injections
  – Maintains better steady state of T levels

• *Disadvantages*:
  – Can get painful injection site (4ml, needs to be SLOW)
  – Cannot withdraw quickly
Testosterone Replacement Therapy (TRT)

Goal:

– Restore T levels to mid-normal range
– Alleviate signs of symptoms of TD
– Without significant side effects or safety concerns
– *Sustained supraphysiological levels should be avoided*
Testosterone Therapy: Monitoring

- Aim to achieve testosterone of at least 15nmol/l
- Monitor PSA at 3, 6 and 12 mths and annually thereafter
- Monitor FBC
Stop if no symptom improvement after 6 months
Testosterone Therapy – 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

\(^1\) Chakrabarty A. Androl Gynecol: Curr Res 2013, 1:3
Who should be initiating & monitoring patients with Testosterone Replacement Therapy?

** guidance:**

“The great majority of men with TD can be effectively assessed and managed by the generalist”

**Exceptions:**

- Fertility issues
- Polycythaemia
- Prostate Ca diagnosis
- Other endocrinopathies

Time-dependent and symptom-specific onset of effects of testosterone substitution

Libido
Vigor
Depression
Red blood count
Obesity
Insulin sensitivity
Erectile function
Bone density

Saad, Zitzmann et al. EJE 2011
Weight (kg) in 411 Obese Hypogonadal Men on Long-Term Treatment with Testosterone Undecanoate According to Obesity Class

Baseline
Year 1
Year 2
Year 3
Year 4
Year 5
Year 6
Year 7
Year 8
Class I
Class II
Class III

* p<0.0001 vs baseline
# p<0.0001 vs previous year

Waist Circumference (cm) in 411 Obese Hypogonadal Men on Long-Term Treatment with Testosterone Undecanoate According to Obesity Class

- Baseline
- Year 1
- Year 2
- Year 3
- Year 4
- Year 5
- Year 6
- Year 7
- Year 8

Class I
Class II
Class III

NI=
NII=
NIII=

*p<0.0001 vs baseline # p<0.0001 vs previous year

-10.62±0.32 -13.87±0.35 -14.34±0.36

BMI (kg/m²) in 411 Obese Hypogonadal Men on Long-Term Treatment with Testosterone Undecanoate According to Obesity Class

- Baseline
- Year 1
- Year 2
- Year 3
- Year 4
- Year 5
- Year 6
- Year 7
- Year 8

Class I
Class II
Class III

BMI (kg/m²) values:
- Baseline
- Year 1
- Year 2
- Year 3
- Year 4
- Year 5
- Year 6
- Year 7
- Year 8

* p<0.0001 vs baseline
# p<0.0001 vs previous year

Fasting Glucose (mg/dl) in 411 Obese Hypogonadal Men on Long-Term Treatment with Testosterone Undecanoate According to Obesity Class

- Baseline: -15.43±1.78
- Year 1: -20.69±2.09
- Year 2: -21.45±2.91

* p<0.0001 vs baseline
# p<0.0001 vs previous year

HbA$_1c$ (%) in 411 Obese Hypogonadal Men on Long-Term Treatment with Testosterone Undecanoate According to Obesity Class

- Baseline
- Year 1
- Year 2
- Year 3
- Year 4
- Year 5
- Year 6
- Year 7
- Year 8

Class I
Class II
Class III

1.15 ± 0.06
1.79 ± 0.08
1.87 ± 0.13

*p<0.0001 vs baseline
# p<0.0001 vs previous year

Total Cholesterol (mg/dl) in 411 Obese Hypogonadal Men on Long-Term Treatment with Testosterone Undecanoate According to Obesity Class

**Systolic Blood Pressure (mmHg) in 411 Obese Hypogonadal Men on Long-Term Treatment with Testosterone Undecanoate According to Obesity Class**

- **Baseline Year 1 Year 2 Year 3 Year 4 Year 5 Year 6 Year 7 Year 8**
  - **Class I**
  - **Class II**
  - **Class III**

<table>
<thead>
<tr>
<th>Year</th>
<th>Class I</th>
<th>Class II</th>
<th>Class III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>-21.57±0.83</td>
<td>-31.11±1.01</td>
<td>-33.15±1.44</td>
</tr>
<tr>
<td>Year 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 2</td>
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<td>Year 8</td>
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</tr>
</tbody>
</table>

* p<0.0001 vs baseline # p<0.0001 vs previous year

Men with testosterone deficiency and a history of cardiovascular diseases benefit from long-term testosterone therapy: observational, real-life data from a registry study

Ahmad Haider¹
Aksam Yassin²⁻⁴
Karim Sultan Haider¹
Gheorghe Doros⁵
Farid Saad⁴,⁶
Giuseppe MC Rosano⁷

Many patients (59.7%) had diabetes but were not well controlled by standard treatment.
HbA$_1c$ (%) in 77 hypogonadal men with a CVD history receiving continuous treatment with testosterone undecanoate injections

Recent history shows that doctors especially GPs can adapt to change....

• Cholesterol....initially patients were referred to specialist ‘lipid clinics’ for something called ‘statins’.

• Hypertension....initially patients were admitted into hospital overnight for initiating treatment with a group of drugs called ‘ACE inhibitors’.
UK Policy Statements on Testosterone Deficiency written by the BSSM

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³. GP with a Special Interest in Sexual Dysfunction, Chipping Norton, Oxfordshire & Past Chairman of the British Society for Sexual Medicine (BSSM)
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⁵. GP, with Specialist Interest in Men’s Health and Urology, Backwell & Nailsea Medical Group, North Somerset and Chair of Primary Care Urology Society
BSSM Policy Statements on Testosterone Deficiency

• Testosterone deficiency is a well-established, significant medical condition.
• Testosterone deficiency has well-established symptoms.
• Testosterone therapy for men with testosterone deficiency is effective, rational, and evidence-based.
• There is no scientific basis for withholding testosterone therapy from men on the basis of age.
Continued......

• Testosterone Deficiency is associated with increased Cardiovascular and all-cause mortality.

• The evidence does not support an increased cardiovascular risk associated with testosterone therapy.

• There is no evidence that supports any increase in the risk of cancer of the prostate with testosterone replacement therapy *

• A major research initiative to explore the benefits of testosterone therapy in cardio-metabolic disease is overdue.

* Testosterone is contraindicated in cases of known or suspected cancer of the prostate
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
• Patients should be monitored in accordance with a standardised monitoring plan to ensure that any potential side effects are detected early