TESTOSTERONE REPLACEMENT IN MEN WITH THE METABOLIC SYNDROME AND TYPE 2 DIABETES MELLITUS

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TESTOSTERONE REPLACEMENT IN AGEING MEN WITH TYPE 2 DIABETES MELLITUS

Diabetes Mellitus

Testosterone treatment:
- Indications?
- Benefits?
- Risks?
- Alternatives?

Low Testosterone (T) Hypogonadism

Obesity & Metabolic Syndrome

Erectile (Sexual) Dysfunction
TESTOSTERONE REPLACEMENT IN AGEING MEN WITH TYPE 2 DIABETES MELLITUS

- Obesity-related metabolic dysregulation and low testosterone (T)
- Sexual dysfunction and low T
- T replacement therapy in diabetic men
  - Diagnosis
  - Potential benefits & risks
  - Management algorithm
  - Role of PDE5-Is
  - Monitoring
Obesity and Low T in the Metabolic Syndrome and Diabetics
European Male Ageing Study (EMAS) Age (n=3210)
Baseline Reproductive Hormone Levels and Age

Testosterone (nmol/L)

Free Testosterone (pmol/L)

LH (U.L)

SHBG (nmol/L)

Wu et al. JCEM 2008
European Male Ageing Study (EMAS) Age (n=3210)
Baseline Reproductive Hormone Levels and BMI by Age

- **Testosterone (nmol/L)**
  - Graph showing the trend of testosterone levels across different BMI categories and age groups.

- **Free Testosterone (pmol/L)**
  - Graph showing the trend of free testosterone levels across different BMI categories and age groups.

- **LH (U/L)**
  - Graph showing the trend of LH levels across different age groups.

- **SHBG (nmol/L)**
  - Graph showing the trend of SHBG levels across different age groups.

Wu et al. JCEM 2008
Secondary Hypogonadism

Risk factors

- Morbidity (≥1)
- Alcohol (frequent)
- Smoking (current)
- BMI ≥30 kg/m²
- BMI ≥25 - <30 kg/m²
- Age (years)

Adjusted Relative Risk Ratio

Symptoms

- Slow walking speed
- Unable to bend
- Low vigorous activity
- Erectile dysfunction
- Sexual thoughts
- Poor morning erection

Adjusted Odds Ratio

*p < 0.05  **p < 0.01  ***p < 0.001

Tajar et al. JCEM 2011
Hormone Changes (Rise/Fall) are Related to % Weight Loss/Gain
(Data adjusted for age, centre, changes in smoking status, alcohol consumption co-morbidities & physical activity)

% Weight loss ← 0 → Weight gain %
n = 2395, *p<0.05, **p<0.01

Secondary Hypogonadism is REVERSIBLE with WEIGHT LOSS
Secondary Hypogonadism DEVELOPS with WEIGHT GAIN
Effect of Supervised Interventional Weight Loss on Testosterone Levels in Eight Studies

(Grossmann 2011)
Low Testosterone is associated with T2DM

Meta-analysis of over 28 cross-sectional studies

- Confirms previous meta-analysis by Ding 2006: 30-40% have low TT
- Dhindsa et al 2010: 50% of obese diabetic men have low FT

(Corona et al 2010)
Prospective cohort studies show that low T predicts incident MetS and each of its components

- **Complete MetS** (Guay & Traish 2011, confirmed by by Corona 2011 in a meta-analysis of 3 studies). but Bhasin 2011: SHBG and not T)
- **Visceral obesity** (Allan 2010, McDonalds 2010, Brand 2010)
- **Type II diabetes** (Wu 2010, Corona 2011)
- **Adverse lipid profile** (Haring 2011)
- **High blood pressure** (Torkler 2011)
- **Insulin resistance (IR)** (Kim 2010)
- T2DM and MetS at baseline also predict the occurrence of low T (Rodriguez 2007, Guay 2011, Corona 2011), **suggesting a bi-directional relationship in a viscous circle**
# Studies of Testosterone Treatment in Patients with Metabolic Syndrome and/or Type 2 Diabetes Mellitus

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th># patients (ID/C)</th>
<th>Hypogonadism cut off</th>
<th>Trial duration (weeks)</th>
<th>Drugs</th>
<th>Dose</th>
<th>Comparator</th>
<th>Metabolic status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boyanov 2003</td>
<td>Sofia, Bulgaria</td>
<td>24/24</td>
<td>TT &lt;15 nM</td>
<td>12</td>
<td>O-TU</td>
<td>120 mg daily</td>
<td>No TRT</td>
<td>T2DM</td>
</tr>
<tr>
<td>Kapoor 2006</td>
<td>Barnsley, UK</td>
<td>12/12</td>
<td>TT &lt;12 nM</td>
<td>12</td>
<td>i.m T</td>
<td>200 mg/2weeks</td>
<td>Placebo</td>
<td>T2DM</td>
</tr>
<tr>
<td>La Vignera 2008</td>
<td>Catania, Italy</td>
<td>7/5</td>
<td>TT &lt;8 nM</td>
<td>52</td>
<td>T gel 1%</td>
<td>50 mg/daily</td>
<td>No TRT</td>
<td>T2DM</td>
</tr>
<tr>
<td>Heufelder 2009</td>
<td>Munich, Germany</td>
<td>16/16</td>
<td>TT &lt;12 nM</td>
<td>52</td>
<td>T gel 1%</td>
<td>50 mg/daily</td>
<td>No TRT</td>
<td>T2DM with IDF-MetS</td>
</tr>
<tr>
<td>Aversa 2010</td>
<td>Rome, Italy</td>
<td>32/10</td>
<td>TT &lt;11 nM</td>
<td>52</td>
<td>TU</td>
<td>1000 mg/12 weeks</td>
<td>Placebo</td>
<td>NCEP-ATPIII-MetS</td>
</tr>
<tr>
<td>Gopal 2010</td>
<td>Mumbai, India</td>
<td>11/11</td>
<td>cFT &lt;225 pM</td>
<td>12</td>
<td>i.m T</td>
<td>200 mg/2weeks</td>
<td>Placebo</td>
<td>IDF-MetS</td>
</tr>
<tr>
<td>Jones 2011</td>
<td>Multi-center</td>
<td>103/102</td>
<td>TT &lt;11 nM</td>
<td>104</td>
<td>T gel 2%</td>
<td>60 mg/Daily</td>
<td>Placebo</td>
<td>T2DM</td>
</tr>
<tr>
<td>Aversa 2011</td>
<td>Rome, Italy</td>
<td>40/10</td>
<td>TT &lt;12 nM</td>
<td>30</td>
<td>TU</td>
<td>1000 mg/12 weeks</td>
<td>Placebo</td>
<td>IDFT2DM</td>
</tr>
<tr>
<td>Tishova 2011</td>
<td>Moscow, Russia</td>
<td>105/65</td>
<td>TT &lt;12 nM</td>
<td>30</td>
<td>TU</td>
<td>1000 mg/12 weeks</td>
<td>Placebo</td>
<td>T2DM</td>
</tr>
<tr>
<td>Hackett 2013</td>
<td>BLAST, U.K.</td>
<td>97/102</td>
<td>TT 8 –12 nM</td>
<td>40</td>
<td>TU</td>
<td>1000 mg/12 weeks</td>
<td>Placebo</td>
<td>T2DM</td>
</tr>
<tr>
<td>Giannati 2014</td>
<td>Melbourne, Australia</td>
<td>45/43</td>
<td>TT &lt;12.0 nM</td>
<td></td>
<td>TU</td>
<td>1000 mg/12 weeks</td>
<td>Placebo</td>
<td>T2DM</td>
</tr>
</tbody>
</table>

Total n=770 patients; mean study duration 38 weeks  
Adapted from Corona et al., 2013
<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Age (yr)</th>
<th>T  Rx</th>
<th>Duration (Weeks)</th>
<th>∆Waist (cm)</th>
<th>∆HbA1C (%)</th>
<th>∆HOMA-IR</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kapoor 2006</td>
<td>24</td>
<td>64</td>
<td>TE 200mg/2w</td>
<td>12</td>
<td>-1.6*</td>
<td>-0.37*</td>
<td>-1.7* (-39%)</td>
<td>↓ total Chol (-0.4 mmol/L), no change in other lipids</td>
</tr>
<tr>
<td>Heufelder 2009</td>
<td>32</td>
<td>57</td>
<td>TTS T 50mg/d</td>
<td>52</td>
<td>-6.0</td>
<td>-0.8</td>
<td>-0.9* (-59%)</td>
<td>↓ CRP</td>
</tr>
<tr>
<td>Kalichenko 2010</td>
<td>184</td>
<td>52</td>
<td>TU 1000mg/12w</td>
<td>30</td>
<td>-4.6</td>
<td>Not reported</td>
<td>-1.7* (-31%)</td>
<td>↓ body weight 3.9 Kg, No change fasting sugar</td>
</tr>
<tr>
<td>Aversa 2010</td>
<td>50</td>
<td>58</td>
<td>TU 1000mg/12w</td>
<td>52</td>
<td>-5.0</td>
<td>-1.1</td>
<td>-2.6* (-60%)</td>
<td>No change lipids Hct (+3.8%)</td>
</tr>
<tr>
<td>Jones 2011</td>
<td>220</td>
<td>60</td>
<td>TTS T 60mg/d</td>
<td>26</td>
<td>N.S</td>
<td>-0.7*</td>
<td>-0.05</td>
<td>No change % body fat</td>
</tr>
<tr>
<td>Solvay (Unpub)</td>
<td>180</td>
<td>NR</td>
<td>TTS T 50mg/d</td>
<td>26</td>
<td>NR</td>
<td>N.S.</td>
<td>N.S.</td>
<td>2.0 Kg ↑ lean mass</td>
</tr>
<tr>
<td>Hackett 2013</td>
<td>190</td>
<td>62</td>
<td>TU 1000mg/12w</td>
<td>30</td>
<td>-1.7*</td>
<td>-0.11</td>
<td>0.15.</td>
<td>↓ total Chol (-0.2 mmol/L),</td>
</tr>
<tr>
<td>Gianatti 2014</td>
<td>88</td>
<td>62</td>
<td>TU 1000mg/12w</td>
<td>40</td>
<td>-1.2</td>
<td>-0.36</td>
<td>-0.08</td>
<td>↓ fat mass ↑ lean mass</td>
</tr>
</tbody>
</table>
Effects of Testosterone Treatment in T2DM and Metabolic Syndrome

- Evidence from RPCTs is weak
  - Only 8 placebo-controlled studies of variable quality
  - Number of patients evaluated are limited
  - Duration of the studies is short
- Some but not all studies show improvements in
  - Glycaemic control (↓ HbA1c, fasting glycaemia)
  - Insulin resistance (HOMA-IR 1 but not HOMA-IR2)
  - Waist circumference
- Real benefits, in terms of hard clinical outcomes, will require further study by large-scale and longer RPCTs
RECOMMENDATION 8. Testosterone and Obesity, Metabolic Syndrome & Type 2 Diabetes Mellitus (DM)

8.1. Metabolic syndrome features (obesity, HT, dyslipidemia, impaired glucose regulation, insulin resistance) are present in hypogonadal men

- Epidemiological studies show a close relationship between obesity and low serum T levels in healthy men
- 20%-64% of obese men have low serum total or free T level
- Metabolic syndrome and type 2 DM are associated with low serum T
- Serum testosterone should be measured in men with type 2 DM and symptoms suggestive of T deficiency (Level 2b, Grade A)
RECOMMENDATION 8. Testosterone and Obesity, Metabolic Syndrome and Type 2 Diabetes

8.2. The effects of testosterone treatment on glycemic control of men with diabetes mellitus are uncertain

- It is premature to recommend testosterone treatment for the metabolic syndrome or DM in the absence of laboratory and other clinical evidence of hypogonadism
- In men with hypogonadism and metabolic syndrome or DM, testosterone treatment for traditional hypogonadal symptoms may have other unproven benefits on their metabolic status

(Level 2a, Grade B)

(Wang et al ISA, EAA, ISSAM & EAU 2008)
Erectile Dysfunction in Diabetes

- Prevalence of ED among diabetic men - 35 to 90% (Malvige & Levy 2009)
- Neurogenic or vasculogenic aetiologies (Malvige & Levy 2009)
- ED prevalence 3x, incidence 2x that of non-diabetics (Feldman 1994; Johannes 2000)
- Earlier onset, more severe & poorer QoL (Penson 2003)
- More debilitating and more likely to seek professional help (Eardley 2007)
Serum testosterone is low in a small & variable (1% to 48%) proportion of patients presenting with ED > 8000 men from 10 large series with routine testosterone measurement (Buvat et al 2012)

<table>
<thead>
<tr>
<th></th>
<th>Number of series</th>
<th>Number of ED patients</th>
<th>Men with T 10.4 nmol/L (&lt;3 ng/ml)</th>
<th>Percent of hypogonadal subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages together</td>
<td>9</td>
<td>6099</td>
<td>674</td>
<td>11%</td>
</tr>
<tr>
<td>Less than 50 years old</td>
<td>3</td>
<td>1249</td>
<td>89</td>
<td>7.1%</td>
</tr>
<tr>
<td>50 years old and over</td>
<td>4</td>
<td>6831</td>
<td>1242</td>
<td>18.2%</td>
</tr>
</tbody>
</table>

Intra-penile mechanisms of erection, and of PDE5 Inhibitor action is dependent on adequate testosterone levels

- T modulates PDE5 expression and activity \( (\text{Traish 1999, Morelli 2004}) \)
- Castration prevents the enhancing effect of PDE5-I on erection, and testosterone restores it \( (\text{Traish 1999, Morelli 2004, Zhang 2005}) \)
- In animal models, a minimal testosterone level seems a prerequisite for adequate functioning of PDE5-I
Phosphodiesterase-5 (PDE-5) inhibitors and hormonal treatments for erectile dysfunction: A systematic review and meta-analysis


Short-term trials (12 weeks) indicate that PDE-5 inhibitors were more effective than placebo in improving sexual intercourse success (69% vs. 35%). The proportion of men with improved erections was significantly greater among those treated with PDE-5 inhibitors (range, 67-89%) than with placebo (range, 27-35%).

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Sildenafil, m/n</th>
<th>Placebo, m/n</th>
<th>RR (95% CI)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Becker et al. 2003 (65)</td>
<td>5/166</td>
<td>22/485</td>
<td>2.28 (1.60-3.20)</td>
<td>2.26 (1.50-3.40)</td>
</tr>
<tr>
<td>Choi et al. 2001 (52)</td>
<td>59/110</td>
<td>43/111</td>
<td>2.28 (1.50-3.40)</td>
<td>2.26 (1.50-3.40)</td>
</tr>
<tr>
<td>Choi et al. 2003 (38)</td>
<td>58/66</td>
<td>25/465</td>
<td>2.28 (1.50-3.40)</td>
<td>2.26 (1.50-3.40)</td>
</tr>
<tr>
<td>Christiansen et al. 2000 (56)</td>
<td>29/568</td>
<td>27/506</td>
<td>2.30 (1.24-4.39)</td>
<td>2.30 (1.24-4.39)</td>
</tr>
<tr>
<td>Diambro et al. 1995 (73)</td>
<td>43/57</td>
<td>10/54</td>
<td>3.64 (2.47-5.37)</td>
<td>3.64 (2.47-5.37)</td>
</tr>
<tr>
<td>Glas et al. 2001 (17)</td>
<td>100/124</td>
<td>43/121</td>
<td>3.71 (1.76-6.98)</td>
<td>3.71 (1.76-6.98)</td>
</tr>
<tr>
<td>Goldstein et al. 1996 (42)</td>
<td>21/500</td>
<td>50/200</td>
<td>2.67 (2.24-3.69)</td>
<td>2.67 (2.24-3.69)</td>
</tr>
<tr>
<td>Gomez et al. 2002 (64)</td>
<td>58/76</td>
<td>39/82</td>
<td>1.65 (1.26-2.16)</td>
<td>1.65 (1.26-2.16)</td>
</tr>
<tr>
<td>Heiman et al. 2009 (70)</td>
<td>59/80</td>
<td>23/81</td>
<td>2.25 (1.50-3.40)</td>
<td>2.25 (1.50-3.40)</td>
</tr>
<tr>
<td>Jones et al. 2006 (93)</td>
<td>7/8103</td>
<td>36/899</td>
<td>2.08 (1.57-2.66)</td>
<td>2.08 (1.57-2.66)</td>
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<tr>
<td>Kadioglu et al. 2008 (94)</td>
<td>19/147</td>
<td>63/147</td>
<td>2.08 (1.72-2.43)</td>
<td>2.08 (1.72-2.43)</td>
</tr>
<tr>
<td>Longinio et al. 2008 (36)</td>
<td>52/483</td>
<td>22/482</td>
<td>2.33 (1.63-3.52)</td>
<td>2.33 (1.63-3.52)</td>
</tr>
<tr>
<td>Levinson et al. 2008 (39)</td>
<td>56/128</td>
<td>34/126</td>
<td>2.75 (2.03-3.73)</td>
<td>2.75 (2.03-3.73)</td>
</tr>
<tr>
<td>Meade et al. 2001 (44)</td>
<td>126/459</td>
<td>30/456</td>
<td>3.25 (2.44-4.34)</td>
<td>3.25 (2.44-4.34)</td>
</tr>
<tr>
<td>Montorsi et al. 1999 (22)</td>
<td>290/381</td>
<td>30/127</td>
<td>3.26 (2.37-4.48)</td>
<td>3.26 (2.37-4.48)</td>
</tr>
<tr>
<td>Olsson et al. 2002 (51)</td>
<td>106/266</td>
<td>36/266</td>
<td>2.00 (1.55-2.62)</td>
<td>2.00 (1.55-2.62)</td>
</tr>
<tr>
<td>Padro et al. 1998 (74)</td>
<td>101/136</td>
<td>23/125</td>
<td>3.01 (2.61-3.57)</td>
<td>3.01 (2.61-3.57)</td>
</tr>
<tr>
<td>Tan et al. 2000 (43)</td>
<td>109/125</td>
<td>40/121</td>
<td>2.64 (2.03-3.45)</td>
<td>2.64 (2.03-3.45)</td>
</tr>
<tr>
<td>Yang et al. 2002 (46)</td>
<td>106/200</td>
<td>70/200</td>
<td>2.23 (1.90-2.64)</td>
<td>2.23 (1.90-2.64)</td>
</tr>
<tr>
<td>Summary</td>
<td>211/2698</td>
<td>673/2168</td>
<td>2.50 (2.27-2.76)</td>
<td>2.50 (2.27-2.76)</td>
</tr>
</tbody>
</table>

**Men with type 2 diabetes**

Boulton et al. 2001 (53) | 66/100 | 11/108 | 6.06 (3.40-10.78) |
Benedetti et al. 1999 (49) | 17/120 | 25/97  | 5.92 (2.29-15.44) |
Safranieid, 2004 (55) | 7/144 | 17/198 | 4.17 (2.50-6.89) |
Summary | 244/287 | 41/368 | 5.06 (3.78-6.89) |

**Men with type 1 diabetes**

Stuckey et al. 2003 (37) | 63/856 | 27/790 | 2.26 (1.64-3.04) |

**Men with stable CAD or CVD**

DeMuro et al. 2004 (40) | 41/170 | 20/122 | 2.11 (1.38-3.12) |
Koetz et al. 2006 (59) | 44/89 | 19/70 | 4.02 (2.40-6.70) |
Olsson et al. 2001 (60) | 94/123 | 21/87 | 2.99 (1.96-4.32) |
Summary | 179/262 | 54/229 | 2.68 (2.02-3.62) |

**Men with hypertension**

Albuquerque et al. 2006 (76) | 40/46 | 16/41 | 2.98 (1.56-5.41) |
Poccard et al. 2004 (77) | 196/279 | 51/283 | 3.94 (3.04-6.11) |
Summary | 238/325 | 66/524 | 3.14 (1.94-5.18) |

**Men with depression**

Fava et al. 2006 (86) | 50/71 | 20/71 | 2.50 (1.67-3.73) |
Seifman et al. 2001 (55) | 60/66 | 60/20 | 7.96 (4.13-16.34) |
Tigges et al. 2004 (61) | 64/77 | 28/81 | 2.40 (1.73-3.30) |
Summary | 124/214 | 56/222 | 3.41 (1.89-6.24) |

**Men with multiple sclerosis**

Fowler et al. 2005 (57) | 52/108 | 27/112 | 3.21 (2.65-5.15) |
Safranieid, 2009 (101) | 33/102 | 18/101 | 1.62 (1.03-2.51) |
Summary | 125/206 | 45/213 | 2.66 (1.32-5.35) |

**Men who had neural or vascular disorders**

Lindsay et al. 2002 (58) | 11/14 | 3/18 | 43.71 (1.62-15.22) |

CAD = coronary artery disease; CVD = cardiovascular disease; RR = relative risk.
1) Results from 15 RCTs evaluating hormonal treatment of ED were inconsistent & inconclusive on whether treatment improved outcomes.

2) Evidence was also insufficient regarding whether men with ED had a higher prevalence (variable 1 – 48%) of hypogonadism than men without ED.
Effects of Testosterone Treatment on Erection in ED patients unresponsive to PDE5-I (Shabsigh et al 2004)

- 76 ED patients, mean age 58.5 yr
- Non-responders to 100 mg Sildenafil
- Low to low normal T (≤14 nmol/L)
- T gel (50 mg/d) or placebo gel (double blind) for 12 weeks, + Sildenafil on demand
- IIEF erectile function domain

At week 4, significant improvement in response to Sildenafil in the T gel group compared with the placebo gel group

At weeks 8 and 12, statistical significance of difference was not maintained
<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Baseline testosterone (nmol/l)</th>
<th>Treatment</th>
<th>Overall efficacy rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aversa et al. 98*</td>
<td>20</td>
<td>&lt;13.9 (&lt;400 ng/dl)</td>
<td>T-patch, sildenafil 100mg</td>
<td>80%</td>
</tr>
<tr>
<td>Kalichenko et al. 99§</td>
<td>120</td>
<td>&lt;11.8 (&lt;340 ng/dl)</td>
<td>Oral TU, sildenafil 100mg</td>
<td>70%</td>
</tr>
<tr>
<td>Shabsigh et al. 99*§</td>
<td>75</td>
<td>&lt;13.9 (&lt;400 ng/dl)</td>
<td>T-gel, sildenafil 100mg</td>
<td>70%</td>
</tr>
<tr>
<td>Chatterjee et al. 90</td>
<td>12</td>
<td>9 patients &lt;13.9 (&lt;400 ng/dl)</td>
<td>T-im, sildenafil 50–100mg</td>
<td>100%</td>
</tr>
<tr>
<td>Foresta et al. 91</td>
<td>15</td>
<td>&lt;6.94 (&lt;200 ng/dl)</td>
<td>T-patch, sildenafil 50mg</td>
<td>Normalized NPT</td>
</tr>
<tr>
<td>Shamloul et al. 92§</td>
<td>40</td>
<td>&lt;11.8 (&lt;340 ng/dl)</td>
<td>Oral TU, sildenafil 50–100mg</td>
<td>Improvement</td>
</tr>
<tr>
<td>Greenstein et al. 93</td>
<td>31</td>
<td>&lt;13.9 (&lt;400 ng/dl)</td>
<td>T-gel, sildenafil 100mg</td>
<td>63%</td>
</tr>
<tr>
<td>Tas et al. 94</td>
<td>23</td>
<td>&lt;13.9 (&lt;400 ng/dl)</td>
<td>T-im, sildenafil 50–100mg</td>
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<tr>
<td>Rochira et al. 100*</td>
<td>24</td>
<td>&lt;6.94 (&lt;200 ng/dl)</td>
<td>T-im, sildenafil 50mg</td>
<td>Improvement in NPT</td>
</tr>
<tr>
<td>Hwang et al. 95§</td>
<td>32</td>
<td>&lt;10.4 (&lt;300 ng/dl)</td>
<td>Oral TU, sildenafil 100mg</td>
<td>57%</td>
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<tr>
<td>Rosenthal et al. 96§</td>
<td>90</td>
<td>&lt;12.1 (&lt;350 ng/dl)</td>
<td>T-gel, sildenafil 100mg</td>
<td>92%</td>
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<tr>
<td>Yassin et al. 97§</td>
<td>69</td>
<td>&lt;11.8 (&lt;340 ng/dl)</td>
<td>T-gel, tadalafil 20mg</td>
<td>65%</td>
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<tr>
<td>Buvat et al. 101*</td>
<td>73</td>
<td>&lt;10.4 (&lt;300 ng/dl)</td>
<td>T-gel, tadalafil 10mg/day</td>
<td>51%</td>
</tr>
</tbody>
</table>

*Indicates placebo-controlled studies. §Indicates phosphodiesterase 5 inhibitor treatment had previously failed. Abbreviations: NPT, nocturnal penile test; T-gel, testosterone gel; T-im, intramuscular testosterone; T-patch, testosterone patch; TRT, testosterone replacement therapy; TU, testosterone undecanoate.
Improvement in erectile function on tadalafil 10 mg/day after addition of testosterone or placebo gel for 24 weeks

(Buvat et al 2011)
NICE Guidelines on T2DM (2008)
Recommendations for Erectile Dysfunction

• Review the issue of erectile dysfunction annually.
• Provide *assessment* and education for men with erectile dysfunction to address *contributory factors* and treatment options.
• Offer a phosphodiesterase-5 in the absence of contraindications, if erectile dysfunction is a problem.
• Following discussion, refer to a service offering other medical, surgical, or psychological management of erectile dysfunction if phosphodiesterase-5 inhibitors have been unsuccessful.

Not include measurement of testosterone
Diagnosis of Late-onset Hypogonadism (LOH)
Indications for T Treatment

• ASA, ISSAM, EAU, EAA 2008
  – Symptoms
  – T <8 nmol/L OR
  – T 8 – 12 nmol/L AND free T <220 pmol/L

• Endocrine Society 2010
  – Symptoms
  – T below lower limit (<5th centile for young men)
  – Usually <9-10 nmol/L

• European Male Ageing Study (EMAS) 2010
  – 3 sexual symptoms
  – Total T <11 nmol/L and free T <220 pmol/L
Identification of Late-Onset Hypogonadism in Middle-Aged and Elderly Men

Frederick C.W. Wu, M.D., Abdelouahid Tajar, Ph.D., Jennifer M. Beynon, M.B.,
Stephen R. Pye, M.Phil., Alan J. Silman, M.D., Joseph D. Finn, B.Sc.,
Terence W. O’Neill, M.D., Gyorgy Bartfai, M.D., Felipe F. Casanueva, M.D., Ph.D.,
Gianni Forti, M.D., Aleksander Giwercman, M.D., Ph.D.,
Thang S. Han, M.D., Ph.D., Krzysztof Kula, M.D., Ph.D., Michael E.J. Lean, M.D.,
Neil Pendleton, M.D., Margus Punab, M.D., Ph.D., Steven Boonen, M.D., Ph.D.,
Dirk Vanderschueren, M.D., Ph.D., Fernand Labrie, M.D., Ph.D.,
and Ilpo T. Huhtaniemi, M.D., Ph.D., for the EMAS Group*


Late–onset hypogonadism (LOH) can be identified by the presence of 3 sexual symptoms associated with total testosterone <11.0 nmol/L and free testosterone of <220 pmol/L, or total T <8.0 nmol/L
TESTOSTERONE THRESHOLDS FOR INCREASED SYMPTOMS IN 3369 MEN FROM GENERAL POPULATION IN THE EUROPEAN MALE AGEING STUDY (EMAS)

NOTE HIGH BACKGROUND PREVALENCE OF SYMPTOMS WITH NORMAL TESTOSTERONE LEVELS

(Wu et al New Eng J Med 2010)
Multiple Correspondence (2D-Cluster) Analysis
(Low T and sexual symptoms form syndromic association)

Total Testosterone Threshold <11 nmol/liter

- Normal testosterone level
- Low testosterone level

Symptoms:
- Sexual
- Physical
- Psychological

No symptoms

(Wu et al New Eng J Med 2010)
Thresholds for Symptoms and Testosterone to Diagnose LOH

Minimal criteria for diagnosis of LOH can be based on the presence of at least 3 sexual symptoms with total T <11.0 nmol/L and free T of <220 pmol/L.

Based on Strengths of Associations Between

Increasing Number of Sexual Symptoms with
Low Total Testosterone (tT) and Low Free Testosterone (fT)

Multiple logistic regression models: odds ratios OR (95% CI) for low T - reference: no symptom

Wu et al New Eng J Med 2010
What to do now for symptomatic diabetic men with low testosterone?

Clinical strategy
Management issues
Testosterone Rx of Symptomatic Androgen Deficient Older Men

What to do now?

• Document signs and symptoms consistent with testosterone deficiency
• Document serum testosterone deficiency
• Identify and treat relevant underlying/co-morbid conditions especially obesity
• Identify conditions that contraindicate T Rx
• Treat older men that meet these criteria with testosterone for 3 – 6 months
• Monitor patient response (benefits and AE)
Algorithm for the Management of Suspected Symptomatic Hypogonadism in Diabetic Men
Algorithm for the Management of Suspected Symptomatic Hypogonadism in Diabetic Men

Symptoms/signs of hypogonadism or osteopenia/porosis
Algorithm for the Management of Suspected Symptomatic Hypogonadism in Diabetic Men

1. Symptoms/signs of hypogonadism or osteopenia/porosis
2. Measure morning Total T
   - Low < 8 nmol/L
   - Borderline 8 - 12 nmol/L
3. Repeat T + LH, FSH, PRL to confirm low total or free T
4. High gonadotrophins
5. Low/normal gonadotrophins
6. Exclude contraindications
7. Trial of T Rx
8. Monitor response
9. Review diagnosis
10. Investigate pituitary & other causes
11. Manage accordingly

Reference range young men
- Total T 10 - 35 nmol/L
- Calc free T 250 – 700 pmol/L
Algorithm for the Management of Suspected Symptomatic Hypogonadism in Diabetic Men

Symptoms/signs of hypogonadism or osteopenia/porosis

Measure morning Total T

- Low <8 nmol/L
- Borderline 8 - 11 nmol/L
- Normal >11 nmol/L

Reference range young men
Total T 10 - 35 nmol/L
Calc free T 250 – 700 pmol/L
Algorithm for the Management of Suspected Symptomatic Hypogonadism in Diabetic Men

Symptoms/signs of hypogonadism or osteopenia/porosis

Measure morning Total T

Low <8 nmol/L

Borderline 8 - 11 nmol/L

High gonadotrophins

Low/normal gonadotrophins

Exclude contraindications

Trial of T Rx

Monitor response

Review diagnosis

Investigate pituitary & other causes

PDE5-I treatment

Erectile/sexual dysfunction

Seek other causes

Reference range young men
Total T 10 - 35 nmol/L
Calc free T 250 – 700 pmol/L
Algorithm for the Management of Suspected Symptomatic Hypogonadism in Diabetic Men

Symptoms/signs of hypogonadism or osteopenia/porosis

Measure morning Total T

Low <8 nmol/L

Repeat T + LH, FSH, PRL
Confirms low total or free T

High gonadotrophins

Exclude Contraindications:
  Hct, DRE normal,
  PSA <4 ng/mL

Trial of T Rx

Monitoring:
  Clinical response
  T, Hct, DRE, PSA
  BMD

Borderline 8 - 11 nmol/L

Normal >11 nmol/L

Seek other causes

Reference range young men
  Total T 10 - 35 nmol/L
  Calc free T 250 – 700 pmol/L
Algorithm for the Management of Suspected Symptomatic Hypogonadism in Diabetic Men

Symptoms/signs of hypogonadism or osteopenia/porosis

Measure morning Total T

Low <8 nmol/L

Repeat T + LH, FSH, PRL
Confirm low total or free T

High gonadotrophins

Exclude Contraindications: Hct, DRE normal, PSA <4 ng/mL

Trial of T Rx

Low/normal gonadotrophins

Investigate pituitary & other causes: PRL, MR pit, Drugs, Ferritin

Manage accordingly

Borderline 8 - 11 nmol/L

Normal >11 nmol/L

Seek other causes

Reference range young men
Total T 10 - 35 nmol/L
Calc free T 250 – 700 pmol/L
Algorithm for the Management of Suspected Symptomatic Hypogonadism in Diabetic Men

Symptoms/signs of hypogonadism or osteopenia/porosis

Measure morning Total T

Low <8 nmol/L

Repeat T + LH, FSH, PRL; Confirm low total or free T

High gonadotrophins

Exclude Contraindications: Hct, DRE normal, PSA <4 ng/mL

Trial of T Rx

Monitoring: Clinical response T, Hct, DRE, PSA, BMD

Low <220 pmol/L

Investigate pituitary & other causes: PRL, MR pit, Drugs, Ferritin

Manage accordingly

Borderline 8 - 11 nmol/L

Repeat T + SHBG → Calc. or Eq. Dial. Free T

Low <220 pmol/L

Investigate pituitary & other causes: PRL, MR pit, Drugs, Ferritin

Seek other causes

Low >220 pmol/L

Seek other causes

Physician judgement on Rx

Normal >11 nmol/L

Seek other causes

Reference range young men

Total T 10 - 35 nmol/L
Calc free T 250 – 700 pmol/L
When is Testosterone the right treatment for the diabetic patient with ED?

- **T <8 nmol/L**
  - Hypogonadism probably the main cause of ED and TRT is treatment of choice

- **T >11 nmol/L**
  - Hypogonadism unlikely, PDE5-I treatment of choice

- **T 8 -11 nmol/L**
  - PDE5-I alone first, add TRT in case of failure, or
  - TRT alone first, add PDE5-I in case of failure
  - PDE5-I with TRT from start may accelerate the recovery?
Potential Risks of Testosterone in Older Men

- Erythrocytosis
- Obstructive sleep apnoea
- Prostate health
- Cardiovascular health
### The Testosterone (T) Trial in Older (>65 yr)

**Sponsor:** University of Pennsylvania  
**Collaborators:**  
- National Institute on Aging (NIA)  
- National Institute of Neurological Disorders and Stroke (NINDS)  
- Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)  
- National Heart, Lung, and Blood Institute (NHLBI)  
- Abbott

<table>
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<tr>
<th>Arms</th>
<th>Assigned Interventions</th>
</tr>
</thead>
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<tr>
<td><strong>Active Comparator:</strong> Testosterone gel</td>
<td>Drug: AndroGel® (testosterone gel)AndroGel or placebo is applied to the shoulders, abdomen or upper arms once a day. Subjects will be instructed to wash their hands after application and not to have contact with women or children while the gel is wet. They will also be asked not to bathe or get this area wet for five hours after application. The initial dose of AndroGel will be 5.0 g (containing 50 mg of testosterone) once a day.</td>
</tr>
<tr>
<td><strong>Placebo Comparator:</strong> Placebo gel</td>
<td>Drug: AndroGel® (testosterone gel)AndroGel or placebo is applied to the shoulders, abdomen or upper arms once a day. Subjects will be instructed to wash their hands after application and not to have contact with women or children while the gel is wet. They will also be asked not to bathe or get this area wet for five hours after application. The initial dose of AndroGel will be 5.0 g (containing 50 mg of testosterone) once a day.</td>
</tr>
</tbody>
</table>

- **Estimated Enrollment:** n = 800  
- **Study Start Date:** November 2009  
- **Estimated Study Completion Date:** June 2015  
- **Estimated Primary Completion Date:** November 2014 (Final data collection date for primary outcome measure)
The Testosterone Trial

• Seven coordinated RCTs to determine if testosterone treatment will *benefit* elderly men who have low testosterone and conditions low testosterone may cause

• \( n = 790 \) enrolled

• Treatment testosterone gel for 12 months

• Assessments:-
  • Primary endpoints powered at 90% for each trial
  • Multiple secondary and exploratory endpoints for each trial
  • Not powered to assess *adverse effects* of testosterone

• First results anticipated summer 2015
The Testosterone Trial

<table>
<thead>
<tr>
<th>Trial</th>
<th>Primary End Point</th>
<th>Subjects</th>
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</thead>
<tbody>
<tr>
<td>Physical Function</td>
<td>Distance walked in 6 minutes</td>
<td>390</td>
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<tr>
<td>Sexual Function</td>
<td>Sexual activity by questionnaire</td>
<td>470</td>
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<tr>
<td>Vitality</td>
<td>Vitality by questionnaire</td>
<td>474</td>
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<tr>
<td>Cognitive Function</td>
<td>Delayed paragraph recall</td>
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<td>Anaemia</td>
<td>Haemoglobin</td>
<td>112</td>
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<td>Cardiovascular</td>
<td>Coronary artery plaque volume</td>
<td>168</td>
</tr>
<tr>
<td>Bone</td>
<td>Volumetric BMD by DEXA</td>
<td>203</td>
</tr>
</tbody>
</table>
Are you male? Aged 50 - 74?

You have the opportunity to join T4DM, a research study using diet and testosterone treatment to prevent type 2 diabetes.

• 1500 men with low T (8 - 11 nmol/L) and impaired GTT
• 4 Australian states
• Diet and exercises
• T injection v placebo
• 24 month treatment
• Incident T2DM – 1° endpoint
Conclusions 1

- Testosterone decreases with age, mostly because of obesity; this is preventable and can be reversible with weight reduction strategies.

- Sexual symptoms with low testosterone are the best criteria for identifying hypogonadism in ageing men, due to non-specificity of other symptoms and unproven causal relationships.

- Diagnosis of androgen deficiency in diabetic men with low T is particularly challenging because of the frequent co-morbid presence of obesity and sexual dysfunction.
Conclusions 2

• Preliminary data suggest positive metabolic effects of T therapy on glycemic control and insulin resistance in men with T2DM and MetS.

• Current evidence is insufficient (few, small and short studies only) to support T as a metabolic or anti-obesity drug.

• Real benefits (clinical outcomes) and safety of T therapy in T2DM and MetS need confirmation by large-scale and longer RPCTs.

• Serum testosterone should be measured in men with T2DM who have symptoms suggestive of T deficiency (including ED).
Conclusions 3

- Obese patients with low T should be advised that losing weight can improve both their hormonal and metabolic health.
- Management of diabetic men with hypogonadal symptoms and indications for TRT should adhere to the principles established for non-diabetic hypogonadal men.
- PDE5 – Is remain the mainstay of ED management in diabetic men with normal T (>11 nmol/L).
- Combination treatment with TRT may be indicated in those failing to respond to PDE5-Is alone in those with low levels of low T (<11 nmol/L).
Acknowledgements

Giovanni Corona,
Sexual Medicine & Andrology
University of Florence, Florence, Italy
Endocrinology Unit
Medical Department, Ospedale Maggiore
Bologna, Italy

Jacques Buvat,
CETPARP, Lille, France
THANK YOU
Conclusions 2

• LOH is a biomarker of poor general and cardiometabolic health from obesity, insulin resistance - opportunity for prevention

• Obesity is associated with *reversible* functional hypothalamic hypogonadism (analogous to hypothalamic amenorrhea)

• Management should be expectant with *interim* hormone replacement to improve symptoms and maintain sex hormone dependent functions appropriate to age and individual

• Long term risks of T treatment in older men are unknown – carefully monitoring of AEs required
Clinical implications 2

- LOH is rare, 2.1% usually in older men, associated with obesity and co-morbidity
- LOH is relatively stable and persists in individuals with obesity and insulin resistance
- LOH is associated with
  - multiple end organ deficits compatible with (but not necessarily caused by) testosterone deficiency
  - 5-fold increase in mortality over 4.5 years
  - Individual sexual symptoms and low T both associated with increased mortality additively
- Sexual dysfunction and/or low testosterone are important portals to improving older men’s general and cardiometabolic health
Conclusions 2

• Best practice guidelines based on opinions rather than strong evidence – still evolving
• HRT for ageing men currently should not be routine clinical practice
• High diagnostic rigour essential
• Careful assessment/explanation of overall benefits/risks with individual patients
• Re-assess and review diagnosis regularly before and after starting treatment
Summary & Conclusions 1

- Dose-response modelling of symptom probability and T levels with population data can provide *rigorous evidence* to *establish* criteria for diagnosis of ‘LOH’ in ageing men
- Diagnosis of hypogonadism can be based on the presence of ≥3 sexual and total T <11 nmol/L and free T <220 pmol/L
- Prevalence of LOH in the general population using evidence-based criteria ~2.1%
Summary & Conclusions 2

• Secondary hygogonadism is related to obesity & general health - not truly LOH
• Primary hypogonadism is associated with ageing
• Compensated hypogonadism *may* be a real entity - is it a forerunner of primary hypogonadism?
• High ‘background’ prevalence of non-specific symptoms unrelated to low T in older men confounds the diagnosis of LOH
Potential Risks of Testosterone in Older Men

- Erythrocytosis
- Prostate health
- Cardiovascular health
Effects of Testosterone on Erythropoiesis are Greater in Older Men than Young Men

(Coviello et al JCEM 2008)
# Relative Risks (RR) of Erythrocytosis in Testosterone Therapy in Older Men

<table>
<thead>
<tr>
<th>First author, year (Ref.)</th>
<th>RR</th>
<th>95% CI</th>
<th>$I^2$</th>
</tr>
</thead>
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<tr>
<td></td>
<td></td>
<td>Lower boundary</td>
<td>Upper boundary</td>
</tr>
<tr>
<td>Erythrocytosis</td>
<td>3.15</td>
<td>1.56</td>
<td>6.35</td>
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<tr>
<td>Bhasin, 2007 (30)</td>
<td>3.00</td>
<td>0.32</td>
<td>27.74</td>
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<td>Copenhagen Study Group, 1986 (38)</td>
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<td>Snyder 1999a, 1999b, 2001 (58, 59, 19)</td>
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<td>Marks, 2006 (10)</td>
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<td>Sih, 1997 (56)</td>
<td>8.00</td>
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<td>Steidle, 2003(a) (20)</td>
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<td>Steidle, 2003(b) (20)</td>
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<td>0.97</td>
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<td>Drinka, 1995 (39)</td>
<td>6.11</td>
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<td>Merza, 2006 (53)</td>
<td>2.85</td>
<td>0.32</td>
<td>25.07</td>
</tr>
</tbody>
</table>

(Fernandez-Balsells et al JCEM 2010)
Androgens & Prostate Carcinogenesis (Borsland 2000)

• **Animal Models**
  - T & DHT are complete but *weak carcinogens*
  - T is a *strong tumour promotor* especially in the presence of chemical carcinogens

• **Human prostate cancer**
  - Latency & doubling time extremely long
  - Prostate cancer cells are androgen-dependent – basis of androgen ablation Rx
  - Numerous molecular mechanisms involved
    - Androgen – dependent (promotion & protection)
    - Androgen – independent, chronic inflammation
  - Epidemiological evidence inconsistent
Endogenous Sex Hormones Were Not Associated with Increased Risk or Grades of Prostate Cancer in 3886 Cases and 6438 Controls
A Collaborative Analysis of 18 Prospective Studies (Roddam et al 2008)

<table>
<thead>
<tr>
<th>Hormone</th>
<th>No. of case patients/No. of control subjects</th>
<th>RR (95% CI)</th>
<th>RR &amp; 95% CI</th>
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<td>1</td>
<td>784/1302</td>
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<tr>
<td>2</td>
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<tr>
<td>4</td>
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<tr>
<td>5</td>
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<tr>
<td><strong>Free testosterone</strong></td>
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<td>2</td>
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<td>0.83 (0.64 to 1.08)</td>
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<td><strong>Androstanediol glucuronide</strong></td>
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<td><strong>SHBG</strong></td>
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<td>2</td>
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<td>5</td>
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<td>0.86 (0.75 to 0.98)</td>
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</table>
No Significant Effect of Testosterone Therapy on the Incidence of the Need for Prostate Biopsy or Prostatic Cancer - Meta-Analysis up to 2008

<table>
<thead>
<tr>
<th>Study</th>
<th>RR</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
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<th>Control Events</th>
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<td>Harman, 2003</td>
<td>4.09</td>
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<td>Nair, 2006</td>
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<td>0.55</td>
<td>38.63</td>
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<td>Snyder 1999, 2001</td>
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<td>27.94</td>
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<td>Prostate Biopsy</td>
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<tr>
<td>Amory, 2004 &amp; Page, 2005</td>
<td>2.00</td>
<td>0.19</td>
<td>20.61</td>
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<td>1 / 24</td>
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<td>Emmelot-Vonk, 2008</td>
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<td>0.01</td>
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<td>2 / 110</td>
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<td>Marks, 2006</td>
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<td>0.09</td>
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<td>4 / 19</td>
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<td>Snyder 1999, 2001</td>
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<td>0.12</td>
<td>72.05</td>
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<td>0 / 54</td>
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<td>Steidle, 2003</td>
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<td>0.08</td>
<td>33.53</td>
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<td>0 / 99</td>
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<td><strong>0.28</strong></td>
<td><strong>2.28</strong></td>
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</table>

(Fernández-Balsells JCEM 2010)
Prostate Cancer and Testosterone

9.1 No conclusive evidence testosterone therapy increases the risk of prostate cancer or BPH.

- No evidence that testosterone treatment converts sub-clinical to clinically detectable prostate cancer (Level 4, grade C)

- Testosterone can stimulate growth and aggravate symptoms in locally advanced & metastatic cancer (Level 2a, grade A)

- Long-term data are not available to determine whether there is any additional risk from testosterone replacement.

- Hypogonadal older (>45 yr) men should be counselled on the potential risks and benefits of testosterone replacement before treatment, and carefully monitored thereafter (Level 3, Grade A)

(ISA, EAA, ISSAM & EAU 2009)
Prostate Cancer and Testosterone

9.2 Prior to T therapy, a man's risk of prostate cancer must be assessed using, as a minimum, DRE and serum PSA.

- Assessment can be improved by incorporating other risk predictors such as age, family history, and ethnicity/race.

- Several tools exist to assist in assessing prostate cancer risk (e.g. online prostate cancer risk calculator\(^1\)) but…..
  - these have not been validated for patients with LOH.
  - If the patient and physician feel that the risk is sufficiently high, further assessment may be desirable (Level 2a, grade B)

- Pre-treatment prostate ultra-sound examinations or biopsies are not recommended as routine

1. Parekh et al 2006; Thompson et al 2006

(ISA, EAA, ISSAM & EAU 2009)
Absolute Contraindications for Testosterone Treatment

• Prostate cancer
• High-grade PIN
• History of breast cancer
Relative Contraindications for Testosterone Treatment

- Treated prostate cancer
- Severe urinary obstructive symptoms (IPSS symptom score >21) due to BPH
- Untreated sleep apnoea
- Severe heart, renal or liver failure
- Polycythaemia
Conclusions 1

- Testosterone decreases with age mostly because of obesity and poor health - may be a biomarker of poor health
- Low testosterone with sexual symptoms most reliable diagnostic criteria for hypogonadism in ageing men, corroborated by end organ deficits
- Late onset hypogonadism is a relatively rare condition: it is potentially preventable and may be reversible
- Sexual dysfunction and/or low testosterone are important portals to improving men’s general health
Testosterone action Tissue Target Function- Glucose Homeostasis

- ↑ Glut4 Muscle, Liver, Adipose
- ↑ IR Liver
- ↑ IRS-1, 2 Muscle, Adipose, Akt Muscle
- ↑ Protein kinase C Muscle
- ↑ Phosphofructokinase Muscle
- ↑ Hexokinase Muscle
- ↑ UQRCB Muscle
- ↑ Glycogen synthase Muscle
- ↓ Glycogen phosphorylase Muscle, Glycogen breakdown.
- ↑ G6PD Muscle

Glucose transporter protein involved in cellular glucose uptake
- Insulin signalling.
- Insulin receptor signalling pathway.
- Insulin receptor signalling pathway.
- Key regulatory enzyme in glycolysis.
- Key regulatory enzyme in glycolysis.
- Oxidative phosphorylation in mitochondrial respiration.
- Glycogenesis.
- Rate limiting enzyme in the
Low testosterone

Adipocyte Obesity

Adipokines, pro-inflammatory molecules, free fatty acids

Hypothalamic, pituitary and testicular hypofunction

Oestrogen

Other features of the metabolic syndrome
Insulin resistance

Vascular disease
Endothelial dysfunction
Vascular stiffness
Erectile dysfunction

Potential causal pathways between testosterone, adipose tissue dysfunction and vascular disease
Low testosterone

Adipocyte
Obesity

Hypothalamic, pituitary and testicular hypofunction

Adipokines, pro-inflammatory molecules, free fatty acids

Other features of the metabolic syndrome
Insulin resistance

Vascular disease
Endothelial dysfunction
Vascular stiffness
Erectile dysfunction

Potential causal pathways between testosterone, adipose tissue dysfunction and vascular disease
Diabetes Mellitus

Testosterone treatment:
- Diagnosis
- Indications
- Benefits
- Risks
- Alternatives

Obesity & Metabolic Syndrome

Erectile (Sexual) Dysfunction

Low Testosterone (T) Hypogonadism
Diabetes Mellitus

Low Testosterone (T)
Hypogonadism

Testosterone treatment:
- Diagnosis
- Indications
- Benefits
- Risks
- Alternatives

Obesity & Metabolic Syndrome

Erectile (Sexual) Dysfunction

Low Testosterone (T) Hypogonadism
Relationship between testosterone, vascular disease and adipose tissue dysfunction

- Low testosterone
- Hypothalamic, pituitary and testicular hypofunction
- Cardiovascular disease
  - Endothelial dysfunction
  - Vascular stiffness
  - Erectile dysfunction

- Oestrogen
- Obesity and adipose tissue dysfunction
- Novel therapeutic targets from adipose tissue
  - Newly discovered molecules and known adipokines, pro-inflammatory adipokines and lipids
- Other features of the metabolic syndrome including insulin resistance
The Gonadal-Obesity-Adipocytokine-Axis.
## Comparison of Prostate Cancer Incidence

<table>
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<th>Study Cohort</th>
<th>Haider (Unpub)</th>
<th>Yassin (Unpub)</th>
<th>Zitzmann (Unpub)</th>
<th>PLCO [1]</th>
<th>ERSPC [2]</th>
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<tr>
<td>N</td>
<td>255</td>
<td>261</td>
<td>334</td>
<td>38,343</td>
<td>72,891</td>
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<tr>
<td>Follow-up</td>
<td>5.5 years</td>
<td>5.5 years</td>
<td>15 years</td>
<td>7 years</td>
<td>11 years</td>
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<tr>
<td>PCa cases</td>
<td>3</td>
<td>6</td>
<td>0</td>
<td>2,820</td>
<td>6,963</td>
</tr>
<tr>
<td>Proportion</td>
<td>1.2%</td>
<td>2.3%</td>
<td>0</td>
<td>7.35%</td>
<td>9.6%</td>
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<tr>
<td>Incidence per 10,000 patient years</td>
<td>30.3</td>
<td>54.4</td>
<td>0</td>
<td>116</td>
<td>96.6</td>
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</tbody>
</table>

Long-Term Changes in the DPPOS (Diabetes Prevention Program Outcomes Study)

The DPP Research Group, Diab Care 35: 731-737 (2012)
Total Testosterone in men with Type 2 Diabetes

Meta-analysis 20 studies 1982 - 2005

Ding L et al. JAMA 295:1288-1299

Barnsley Study n=355

Total T 12.7 ± 0.3 nmol/l (2.9 – 39.0) NR 8.3-41

SHBG 32.5 ± 1.1 nmol/l (5.1 - 129) NR 15-100

Prevalence of Hypogonadism in Men with Type 2 Diabetes

Total testosterone (TT)

- Percentage of men with low TT
  - TT < 8 nmol/l
  - TT < 12 nmol/l

Bioavailable testosterone (BT) and calculated free testosterone (cFT)

- Percentage of men with low BT, cFT
  - BT < 2.5 nmol/l
  - BT < 4 nmol/l
  - cFT < 0.255 nmol/l

17% TT< 8nmol/l

14% BT <2.5nmol/l
Serum testosterone concentrations (nmol/l; median values) in Finnish men of different ages (X-axis) born in different decades.
Table 6: The effect and significance of age, BMI and birth cohort studied in multivariate regression models adjusted for the other two respective factors. The study population is divided into seven birth cohorts by their birth years. In the analyses, the birth cohorts are compared with the most recent birth cohort (individuals born in 1970–1974); hence, this is the point of reference and given value 1 (significant comparisons are highlighted by bolding, with the respective \( P \) value below).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Testosterone (( \beta + \text{s.e.m.} ))</th>
<th>SHBG (( \beta + \text{s.e.m.} ))</th>
<th>Free testosterone (( \beta + \text{s.e.m.} ))</th>
<th>LH (( \beta + \text{s.e.m.} ))</th>
<th>FSH (( \beta + \text{s.e.m.} ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>(-0.182 + 0.015)</td>
<td>(0.432 + 0.027)</td>
<td>(-0.007 + 0.001)</td>
<td>(0.031 + 0.005)</td>
<td>(0.066 + 0.010)</td>
</tr>
<tr>
<td>(P&lt;0.0001)</td>
<td>(P&lt;0.0001)</td>
<td>(P&lt;0.0001)</td>
<td>(P&lt;0.0001)</td>
<td>(P&lt;0.0001)</td>
<td>(P&lt;0.0001)</td>
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<tr>
<td>BMI</td>
<td>(-0.776 + 0.041)</td>
<td>(-1.842 + 0.075)</td>
<td>(-0.006 + 0.001)</td>
<td>(-0.069 + 0.015)</td>
<td>(-0.028 + 0.027)</td>
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<tr>
<td>(P&lt;0.0001)</td>
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<td>(P&lt;0.0001)</td>
<td>(P&lt;0.0001)</td>
<td>(P=0.294)</td>
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<tr>
<td>Birth cohort</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>(1913–1922)</td>
<td>(9.460 + 0.914)</td>
<td>(8.540 + 1.687)</td>
<td>(0.164 + 0.019)</td>
<td>(1.900 + 0.337)</td>
<td>(3.176 + 0.596)</td>
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<td>(P&lt;0.0001)</td>
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<tr>
<td>(1923–1932)</td>
<td>(6.957 + 0.853)</td>
<td>(5.425 + 1.573)</td>
<td>(0.125 + 0.017)</td>
<td>(0.847 + 0.314)</td>
<td>(2.048 + 0.556)</td>
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<td>(P&lt;0.0001)</td>
<td>(P=0.0006)</td>
<td>(P&lt;0.0001)</td>
<td>(P&lt;0.0001)</td>
<td>(P=0.0071)</td>
<td>(P=0.0002)</td>
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<td>(1933–1941)</td>
<td>(4.969 + 0.828)</td>
<td>(1.552 + 1.528)</td>
<td>(0.109 + 0.017)</td>
<td>(0.599 + 0.305)</td>
<td>(1.427 + 0.540)</td>
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<td>(P&lt;0.0001)</td>
<td>(P=0.310)</td>
<td>(P&lt;0.0001)</td>
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<td>(P=0.050)</td>
<td>(P=0.0008)</td>
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<td>(1942–1951)</td>
<td>(4.947 + 0.839)</td>
<td>(0.979 + 1.549)</td>
<td>(0.120 + 0.017)</td>
<td>(0.636 + 0.309)</td>
<td>(0.974 + 0.548)</td>
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<td>(P&lt;0.0001)</td>
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<td>(P=0.076)</td>
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<td>(1952–1959)</td>
<td>(1.692 + 1.007)</td>
<td>(-1.199 + 1.858)</td>
<td>(0.041 + 0.020)</td>
<td>(0.050 + 0.371)</td>
<td>(0.204 + 0.657)</td>
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<td>(P=0.093)</td>
<td>(P=0.519)</td>
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<td>(P=0.894)</td>
<td>(P=0.756)</td>
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<td>(1960–1979)</td>
<td>(-0.420 + 0.964)</td>
<td>(-2.659 + 1.779)</td>
<td>(-0.001 + 0.020)</td>
<td>(0.056 + 0.355)</td>
<td>(-0.032 + 0.629)</td>
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<td>(P=0.663)</td>
<td>(P=0.135)</td>
<td>(P=0.950)</td>
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<tr>
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<td>P = 0.959</td>
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<td>(1970–1974)</td>
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<td>1</td>
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Primary Prevention of Cardiovascular Disease with a Mediterranean Diet:

Kaplan–Meier Estimates of the Incidence of Outcome Events in the Total Study Population

### Results of Subgroup Analyses

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Combined Mediterranean Diets</th>
<th>Control Diet</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Interaction</th>
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<tbody>
<tr>
<td><strong>Sex</strong></td>
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</tr>
<tr>
<td>Male</td>
<td>107/2178</td>
<td>64/987</td>
<td>0.69 (0.51–0.94)</td>
<td>0.62</td>
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<tr>
<td>Female</td>
<td>72/2819</td>
<td>45/1463</td>
<td>0.73 (0.50–1.07)</td>
<td></td>
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<tr>
<td><strong>Age</strong></td>
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</tr>
<tr>
<td>&lt;70 yr</td>
<td>86/3272</td>
<td>47/1504</td>
<td>0.73 (0.52–1.05)</td>
<td>0.84</td>
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<tr>
<td>≥70 yr</td>
<td>93/1725</td>
<td>62/946</td>
<td>0.71 (0.51–0.98)</td>
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<td><strong>Diabetes</strong></td>
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<tr>
<td>No</td>
<td>58/2572</td>
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<tr>
<td>Yes</td>
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<td>69/1189</td>
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<tr>
<td><strong>Hypertension</strong></td>
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<td></td>
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<tr>
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<td>11/400</td>
<td>1.25 (0.64–2.45)</td>
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<tr>
<td>Yes</td>
<td>139/4112</td>
<td>98/2050</td>
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<tr>
<td><strong>Dyslipidemia</strong></td>
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<td>0.95 (0.64–1.42)</td>
<td>0.06</td>
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<tr>
<td>Yes</td>
<td>102/3620</td>
<td>73/1763</td>
<td>0.60 (0.44–0.80)</td>
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<tr>
<td><strong>Smoking</strong></td>
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</tr>
<tr>
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<td>80/3037</td>
<td>54/1527</td>
<td>0.67 (0.47–0.94)</td>
<td>0.75</td>
</tr>
<tr>
<td>Ever</td>
<td>99/1960</td>
<td>55/923</td>
<td>0.75 (0.54–1.03)</td>
<td></td>
</tr>
<tr>
<td><strong>Family history of premature CHD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>144/3889</td>
<td>87/1890</td>
<td>0.72 (0.55–0.94)</td>
<td>0.97</td>
</tr>
<tr>
<td>Yes</td>
<td>35/1108</td>
<td>22/560</td>
<td>0.75 (0.43–1.29)</td>
<td></td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>18/399</td>
<td>7/164</td>
<td>0.69 (0.29–1.67)</td>
<td>0.05</td>
</tr>
<tr>
<td>25–30</td>
<td>88/2316</td>
<td>37/1085</td>
<td>1.04 (0.71–1.54)</td>
<td></td>
</tr>
<tr>
<td>&gt;30</td>
<td>73/2282</td>
<td>65/1201</td>
<td>0.51 (0.37–0.71)</td>
<td></td>
</tr>
<tr>
<td><strong>Waist</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;Median</td>
<td>87/2561</td>
<td>48/1177</td>
<td>0.76 (0.53–1.08)</td>
<td>0.72</td>
</tr>
<tr>
<td>≥Median</td>
<td>92/2436</td>
<td>61/1273</td>
<td>0.67 (0.48–0.93)</td>
<td></td>
</tr>
<tr>
<td><strong>Waist-to-height ratio</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;Median</td>
<td>81/2549</td>
<td>47/1182</td>
<td>0.74 (0.52–1.06)</td>
<td>0.82</td>
</tr>
<tr>
<td>≥Median</td>
<td>98/2448</td>
<td>62/1268</td>
<td>0.68 (0.50–0.94)</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline score for adherence to Mediterranean diet</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;9 (low)</td>
<td>93/2178</td>
<td>61/1256</td>
<td>0.81 (0.58–1.12)</td>
<td>0.44</td>
</tr>
<tr>
<td>≥9 (high)</td>
<td>86/2819</td>
<td>48/1194</td>
<td>0.64 (0.45–0.92)</td>
<td></td>
</tr>
<tr>
<td><strong>End-point components</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>81/4997</td>
<td>58/2450</td>
<td>0.61 (0.44–0.86)</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>68/4997</td>
<td>38/2450</td>
<td>0.77 (0.52–1.15)</td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>57/4557</td>
<td>30/2410</td>
<td>0.83 (0.54–1.29)</td>
<td></td>
</tr>
</tbody>
</table>

The hazard ratio indicates the relative risk of the event occurring in the Mediterranean Diets group compared to the Control Diet group. A hazard ratio less than 1 suggests a protective effect of the Mediterranean Diets on the primary endpoint.

(Handelsman et al MJA 2013)