The clinical picture of male hypogonadism

Professor Myles Spar
Classic signs and symptoms
Definitions

“Late onset hypogonadism (LOH, also referred to as age-associated testosterone deficiency [TDS]) is a clinical and biochemical syndrome associated with advancing age and characterized by symptoms and a deficiency in serum testosterone levels (below the young healthy male reference range)

“This condition may result in significant detriment in the quality of life and adversely affect the function of multiple organ systems”

ISA, ISSAM, EAU, EAA and ASA recommendations, 2009

“TD [testosterone deficiency] is a clinical and biochemical syndrome frequently associated with age and comorbidities, and characterized by a deficiency in testosterone and relevant symptoms

“It may affect the function of multiple organ systems and result in significant detriment in the quality of life, including alterations in sexual function”

International Society for Sexual Medicine (ISSM), 2010

Symptoms and signs suggestive of male hypogonadism

<table>
<thead>
<tr>
<th>More specific symptoms and signs</th>
<th>Others less specific symptoms and signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Incomplete or delayed sexual development, eunuchoidism</td>
<td>• Decreased energy, motivation, initiative, and self-confidence</td>
</tr>
<tr>
<td>• <strong>Reduced sexual desire (libido) and activity</strong></td>
<td>• Feeling sad or blue, depressed mood, dysthymia</td>
</tr>
<tr>
<td>• <strong>Decreased spontaneous erections</strong></td>
<td>• Poor concentration and memory</td>
</tr>
<tr>
<td>• Breast discomfort, gynaecomastia</td>
<td>• Sleep disturbance, increased sleepiness</td>
</tr>
<tr>
<td>• Loss of body (axillary and pubic) hair, reduced shaving</td>
<td>• Mild anaemia (normochromic, normocytic, in the female range)</td>
</tr>
<tr>
<td>• Very small (especially &lt;5 mL) or shrinking testes</td>
<td>• <strong>Reduced muscle bulk and strength</strong></td>
</tr>
<tr>
<td>• Inability to father children, low or zero sperm count</td>
<td>• Increased body fat, body mass index</td>
</tr>
<tr>
<td>• Height loss, low trauma fracture, low bone mineral density</td>
<td>• Diminished physical or work performance</td>
</tr>
<tr>
<td>• Hot flushes, sweats</td>
<td></td>
</tr>
</tbody>
</table>

Bhasin et al. J Clin Endocrinol Metab 2010;95;2536–2559.
### Classification of male hypogonadism

<table>
<thead>
<tr>
<th>Secondary hypogonadism</th>
<th>Hypothalamus Pituitary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary hypogonadism</td>
<td>Testes</td>
</tr>
<tr>
<td>Target organ resistance</td>
<td>Androgen receptor defect</td>
</tr>
<tr>
<td></td>
<td>5α-reductase deficiency</td>
</tr>
<tr>
<td></td>
<td>Aromatase deficiency</td>
</tr>
<tr>
<td></td>
<td>Target tissues for testosterone, estradiol and DHT</td>
</tr>
</tbody>
</table>

Bhasin et al. J Clin Endocrinol Metab 2010;95;2536–2559.
The typical presentation – the man with hypogonadism
Diagnosing male hypogonadism

• The difficulties in making the diagnosis in borderline cases are confounded by the symptoms of hypogonadism being non-specific

and

• That there has been no consensus as to the level of testosterone which is considered to be consistent with the diagnosis as well as which fraction of testosterone should be assayed
Diagnostic evaluation of adult men with suspected hypogonadism

History and physical symptoms and signs

Morning Total T

- **Low T**
  - Exclude reversible illness, drugs, nutritional deficiency
  - Repeat T (use free or bio T, if suspect altered SHBG)
  - LH+FSH
  - SFA (if sterility issues)

- **Confirmed low T (eg, total T<300ng/dL) or free or bioavailable T < normal (eg, free T <5ng/dL)**
  - Low T, low or normal LH+FSH
  - Low T, high LH+FSH

Follow up

- **Normal T, LH+FSH**

FSH = follicle stimulating hormone
LH = luteinising hormone
SFA = seminal fluid analysis
SHBG = sex hormone binding globulin
T = testosterone

Men presenting with hypogonadism

Subject characteristics

- Male patient: 42 years of age
- Patient reported weight gain that did not respond significantly to effects of diet and exercise
- Complained of sleep apnoea, loss of libido, erectile dysfunction (ED), fatigue, depression and hypertension (up to 165/100 mmHg)
- No medication for his condition
- Physical examination:
  - Normal external genitalia,
  - Female type of pubic hair and lipomastia
- Aging Males’ Symptoms Scale (AMS) questionnaire: 50 points – severe androgen deficiency symptoms
- International Index of Erectile Function (IIEF) score: 12 points (moderate ED)
  - Beck Depression Inventory: 20 points – fulfils criteria of severe depression
- Transrectal ultrasound revealed normal prostate volume (20 mL) without any signs of pathology

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total testosterone (nmol/L)</td>
<td>5.0</td>
<td>13–33.5</td>
</tr>
<tr>
<td>SHBG</td>
<td>33.9</td>
<td>12.9–61.7</td>
</tr>
<tr>
<td>Leptin (ng/mL)</td>
<td>16.8</td>
<td>&lt;12.0</td>
</tr>
<tr>
<td>Insulin (mU/L)</td>
<td>17.5</td>
<td>4.1</td>
</tr>
<tr>
<td>Estradiol</td>
<td>164</td>
<td>20–240</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>152.0</td>
<td>NA</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>44.4</td>
<td>29.8</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>141</td>
<td>96.0</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td>140/90</td>
<td>–</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>5.5</td>
<td>3.3–5.2</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>1.3</td>
<td>0.9–2.6</td>
</tr>
<tr>
<td>LDL (mmol/L)</td>
<td>3.4</td>
<td>0.0–3.7</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>2.3</td>
<td>0.1–2.2</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.0</td>
<td>3.05–6.38</td>
</tr>
<tr>
<td>Total PSA (ngml/L)</td>
<td>0.4</td>
<td>0.0 – 4.0</td>
</tr>
</tbody>
</table>
Physical examination of adult men with suspected hypogonadism

- Comprehensive history
- General internal examinations (incl. blood pressure)
- Secondary sexual characteristics: virilisation (decreased body hair, decreased beard growth)
- Testicular examination, noting size and consistency (approximate ranges of normal adult testes)
- Body mass index (BMI)
- Waist circumference
- Body proportions (e.g. female fat distribution)
- Pubic hair (density, distribution)
- Penis (size)
- Scrotum (pigmentation etc.) and testis (masses, volume, etc.)
- Spermatic cord (varicocele)
- Gynaecomastia
Hormonal diagnosis

• Basic diagnosis in male hypogonadism always includes assessment of testosterone, FSH and LH
  – Testosterone reveals endocrine activity of testis (be aware of circadian rhythm)
  – LH and FSH are indicators for pituitary functions and allow etiological assessment of hypogonadism
• Increased gonadotropins indicate primary hypogonadism, decreased gonadotropins in combination with decreased T suggest secondary hypogonadism
Clinical symptoms of hypogonadism are less clearly identifiable in older men because of age related changes.

The questionnaires combine the assessment of the most prevalent symptoms of men with low testosterone to a helpful diagnostic tool.

Questionnaires include: the St. Louis Questionnaire and the Aging Males’ Symptoms scale (AMS)
Recent publication of 2 major sets of guidelines have provided some clarity when making a diagnosis

• There are no generally accepted lower limits of normal and it is unclear whether geographically different thresholds depend on ethnic differences or on the physician’s perception

• However, there is general agreement that:
  – TT above 12 nmol/L (346 ng/dL) or free T above 250 pmol/L (7.2 ng/dL) do not require substitution
  – TT below 8 nmol/L (231 ng/dL) or free T below 180 pmol/L (5.2 ng/dL) require substitution
  – In symptomatic men with TT levels between 8 to 12 nmol/L, a trial of testosterone therapy can be considered

TT = total testosterone

Co-morbidities in patients with male hypogonadism
Common co-morbidities

- Cardiovascular disease
- Diabetes
- Obesity and the metabolic syndrome
- Osteoporosis
Prevalence of hypogonadism in 831 men with Coronary Artery Disease – The South Yorkshire Study

Number of patients (%)

- tT <7.5 nmol/L and/or bT <2.5 nmol/L: 23.4%
- tT <12 nmol/L and/or bT <4 nmol/L: 52.6%

Pugh et al. J Am Col Cardiol. 2003;41:p344A
Percentage of type 2 diabetic men with low and borderline low testosterone levels per decade

Osteoporosis

• In 50% of cases or more, male osteoporosis is secondary to another pathological process

• Principal amongst these secondary causes of osteoporosis in men are:
  – Corticosteroid usage
  – Hypogonadism

• Each accounts for about 20% of the total incidence of male osteoporosis

Osteoporosis: not just a female disease!

- 25–30% of hip fractures occur in men
- 25% die of it in the short term and 25% die of it in the longer term
- Only 20% return to their former quality of life; many more need assistance with activities of daily living
- 51% suffer from depression (Coolsaet, Aging Male congress 2002)
Proportion of hypogonadal men in patients with hip fractures

Bone mineral density (BMD)

Hypogonadal patients on androgen therapy regularly show an increase in BMD. Testosterone acts in two different ways:

1. Directly stimulates the bone-building osteoblasts
2. Indirectly inhibits the bone-resorbing activity of the osteoclasts via its metabolite estradiol
Longitudinal relationship between hypogonadism and incidence of depression in elderly men*

*Mean age 62.4 years; n=278

Increasing evidence of metabolic syndrome
What is metabolic syndrome?

- Metabolic syndrome is the name given to a group of risk factors that occur together and markedly increase the risk of an individual developing coronary heart disease, stroke or type 2 diabetes.

- Components of metabolic syndrome include:
  - Abdominal obesity
  - Dyslipidaemia
    - Particularly hypertriglyceridaemia and low HDL-cholesterol
  - Hyperglycaemia
  - Hypertension
  - Insulin resistance

THE ICEBERG EFFECT

Type 2 diabetes

- Atherosclerosis
- Pro-inflammatory
- Pro-thrombotic
- Hypertension
- Dyslipidaemia
- Glucose intolerance
- Hyperinsulinaemia
- Insulin resistance
- Abdominal obesity
Definitions of metabolic syndrome

For a person to be defined as having the metabolic syndrome they must have:

<table>
<thead>
<tr>
<th>Impaired Glucose Tolerance, Impaired Fasting Glucose, Insulin Resistance or Type 2 Diabetes plus any two or more of the following factors:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal (central) obesity</td>
</tr>
<tr>
<td>Waist circumference: men &gt;102 cm (&gt;40 in); women &gt;88 cm (&gt;35 in)</td>
</tr>
<tr>
<td>Raised triglycerides</td>
</tr>
<tr>
<td>≥150 mg/dL</td>
</tr>
<tr>
<td>Reduced HDL cholesterol</td>
</tr>
<tr>
<td>Men &lt;40 mg/dL; women &lt;50 mg/dL</td>
</tr>
<tr>
<td>Raised blood pressure</td>
</tr>
<tr>
<td>Blood pressure ≥130 and/or ≥85 mmHg</td>
</tr>
<tr>
<td>FPG</td>
</tr>
<tr>
<td>≥110 mg</td>
</tr>
</tbody>
</table>

FPG = Fasting plasma glucose

Relationship between metabolic syndrome (MetS) and testosterone deficiency (TD)

Androgen/testosterone deficiency (Hypogonadism)

Obesity  Hypertension  Dyslipidaemia  Hyperglycaemia  Insulin resistance

Metabolic syndrome

Risk of having metabolic syndrome by testosterone level in 1,865 non-diabetic men

Odds ratio

<table>
<thead>
<tr>
<th>Model</th>
<th>Description</th>
<th>tT 23.4-51.7 nmol/L</th>
<th>tT 17.0-23.3 nmol/L</th>
<th>tT 1.1-16.9 nmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>Adjusted for age category</td>
<td>p&lt;0.001*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>Adjusted for age, smoking, alcohol, CVD, socioeconomic status</td>
<td>p&lt;0.001*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 3</td>
<td>Adjusted for age, smoking, alcohol, CVD, socioeconomic status, and BMI</td>
<td></td>
<td>p=0.002*</td>
<td></td>
</tr>
</tbody>
</table>

*for linear trend

Hypogonadism is likely a fundamental component of the metabolic syndrome. Testosterone treatment may not only treat hypogonadism, but may also have tremendous potential to slow or halt the progression from metabolic syndrome to overt diabetes or cardiovascular disease.

Increasing evidence of CV risk
Addressing the myth

• It has been considered for a long time that testosterone is associated with cardiovascular imbalance
• Not supported by epidemiological studies: in more than 40 cross-sectional studies none found an association of testosterone treatment with CVD
• In contrast about half of the studies that assessed the relationship between T levels and coronary heart disease (CHD) found lower levels in these patients

New spectrum of CV complications of low testosterone levels

Potentially modifiable cardiovascular risk factors by testosterone

- Visceral obesity
- Insulin resistance/diabetes
- Hypercholesterolaemia
- Hypertension
- Coagulation
- Inflammation
Low testosterone increases the risk of atherosclerosis in 504 elderly men: The Rotterdam Study

RR1 = Relative Risk for severe aortic atherosclerosis adjusted for age
RR2 = Relative Risk for severe aortic atherosclerosis adjusted for age BMI, SBP, TC, HDL-C, DM (yes/no), smoking (ever/never), and alcohol intake (4 cat.)

Testosterone and coronary artery disease (CAD)

- Bioavailable testosterone (BT) levels significantly reduced in males with CAD
  - Approximately 1 in 4 men (23.4%) with coronary artery disease (CAD) have serum levels of testosterone within the clinically hypogonadal range (93.5% positive ADAM questionnaire)
- TRT improves anginal symptoms and cardiac ischaemia

Association of testosterone and CV risk factors in healthy adult men: The Telecom Study

Cholesterol concentration (mmol/L)

- Low testosterone
- Normal testosterone

- Triglycerides: p<0.001
- HDL-C: p<0.01
- LDL-C: p<0.01

Androgens and CV risk

• Both androgen deficiency and androgen excess are associated with unfavourable lipid profiles and increased CV risk
• Maintaining androgen levels in the physiological range promotes a favourable lipid profile
• Early studies have been conducted in hypogonadal men with angina and chronic heart failure showing benefit from normalisation of testosterone levels
• More research is needed on CV risk

Correlation between bioavailable testosterone and waist circumference

$r = -0.21$ $p < 0.001$
Visceral fat is an active endocrine organ

- Adipose tissue
- IL-6
- Adipsin (Complement D)
- Adiponectin
- Leptin
- TNFα
- Angiotensinogen
- Insulin
- FFA
- Resistin
- Lactate
- Plasminogen activator inhibitor-1 (PAI-1)

Hypertension
Atherogenic dyslipidaemia
Type 2 diabetes
Atherosclerosis

The Hypogonadal-Obesity-Adipocytokine Hypothesis

Figure 1. The Hypogonadal-Obesity-Adipocytokine hypothesis. (i) High aromatase activity in adipocytes converts testosterone to estradiol. Reduced tissue testosterone facilitates triglyceride storage in adipocytes by allowing (iii) increased lipoprotein lipase activity and stimulating pluripotent stem cells to mature into adipocytes. (iii) Increased adipocyte mass is associated with greater insulin resistance. (iv) Estradiol and adipocytokines TNF-α, IL-6 and leptin (as a result of leptin resistance in human obesity) inhibit the hypothalamic-pituitary-testicular axis response to decreasing androgen levels (blue arrows). Orange arrows depict the hypogonadal-obesity cycle [38]: Green arrow, low testosterone promotes the formation of adipocytes from pluripotent stem cells [49]. +, positive effect; −, negative effect.
Summary

• Hypogonadism needs to be considered in men with a variety of symptoms, including depression

• Hypogonadism is associated with higher risk of heart disease and osteoporosis

• Hypogonadism contributes to metabolic syndrome

• There is a high prevalence of hypogonadism among patients with type 2 diabetes

• Lower testosterone is associated with higher levels of inflammatory biomarkers and cytokines
Spare Slides
Prevalence of hypogonadism in 300 male patients* with Type 2 Diabetes

*mean age 58 years

Kapoor D et al. Diabet Care. 2007;30:911-917
The CNS functions under direct/indirect control of sex steroid hormones
Decline in specific areas of cognitive function in men receiving GnRHa compared to controls

Definitions of metabolic syndrome (1)

International Diabetes Federation (IDF) consensus definition (2006)

<table>
<thead>
<tr>
<th>For a person to be defined as having the metabolic syndrome they must have:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central obesity (defined as waist circumference* with ethnicity specific values) plus any two of the following four factors:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Factor</th>
<th>Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raised triglycerides</td>
<td>≥ 150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality</td>
</tr>
<tr>
<td>Reduced HDL cholesterol</td>
<td>&lt; 40 mg/dL (1.03 mmol/L) in males</td>
</tr>
<tr>
<td></td>
<td>&lt; 50 mg/dL (1.29 mmol/L) in females</td>
</tr>
<tr>
<td></td>
<td>or specific treatment for this lipid abnormality</td>
</tr>
<tr>
<td>Raised blood pressure</td>
<td>systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg</td>
</tr>
<tr>
<td></td>
<td>or treatment of previously diagnosed hypertension</td>
</tr>
<tr>
<td>Raised FPG</td>
<td>≥ 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes</td>
</tr>
</tbody>
</table>

* If BMI is >30kg/m², central obesity can be assumed and waist circumference does not need to be measured.

FPG = Fasting plasma glucose

The IDF consensus worldwide definition of the of the metabolic syndrome. Available at: [http://www.idf.org/webdata/docs/IDF_Meta_def_final.pdf](http://www.idf.org/webdata/docs/IDF_Meta_def_final.pdf)
For a person to be defined as having the metabolic syndrome they must have:

<table>
<thead>
<tr>
<th>Impaired Glucose Tolerance, Impaired Fasting Glucose, Insulin Resistance or Type 2 Diabetes plus any two or more of the following factors:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Central obesity</strong></td>
</tr>
<tr>
<td><strong>Raised triglycerides</strong></td>
</tr>
<tr>
<td><strong>Reduced HDL cholesterol</strong></td>
</tr>
<tr>
<td><strong>Raised blood pressure</strong></td>
</tr>
<tr>
<td><strong>Microalbuminuria</strong></td>
</tr>
</tbody>
</table>