The epidemiology and burden of male hypogonadism

Professor Siegfried Meryn
Definitions of hypogonadism

Hypogonadism in men is a clinical syndrome that results from failure of the testis to produce physiological levels of testosterone (androgen deficiency) and a normal number of spermatozoa due to disruption of one or more levels of the hypothalamic-pituitary testicular axis.

Endocrine Society clinical practice guideline

“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)”

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

Prevalence of hypogonadism
Incidence of hypogonadism in aging men reported by the BLSA*

*Baltimore Longitudinal Study of Aging

Epidemiology of hypogonadism/TDS

• The prevalence of hypogonadism is high; however, estimates differ the according to the definition used:
  – Hypogonadism in Males (HIM) Study (N=2,126): **crude prevalence 38.7%** in men ≥ 45 years (total testosterone <300ng/mL)
  – BLSA (N=890): prevalence rates by tT (<325ng/dL) were **12%, 19%, 28%** and **49%** in men in their 50s, 60s 70s and 80s, respectively
  – Data from the Boston Area Community Health (BACH) study showed an incidence of symptomatic androgen deficiency of **5.6%** among men aged 30–79 years
  – Massachusetts Male Aging Study (MMAS) (N=1,709): reported a **prevalence of 12.3%** for hypogonadism among men aged 40–70 years, with tT <200ng/dL and at ≥3 clinical features of androgen deficiency
  – An analysis of studies from seven European countries found a prevalence of **20% of moderate and severe symptoms** of hypogonadism (on the Aging Male Symptoms [AMS] scale

Prevalence of hypogonadism reported in the Hypogonadism in Males (HIM) study*

*In patients presenting to a doctor's office

Prevalence of hypogonadism in aging men in a general population in the BLSA

Harman SM et al. J Clin Endocrinol Metab 2001;86(2):724-731
Main causes of TDS
Classification: primary and secondary hypogonadism

Hypothalamus → GnRH → Pituitary gland → LH → Testis → Testosterone → Androgen receptor → Target cell → Effect

Primary hypogonadism
Secondary hypogonadism

GnRH – gonadotrophin releasing hormone
LH – luteinizing hormone
## Causes of hypogonadism

<table>
<thead>
<tr>
<th>Primary congenital</th>
<th>Secondary congenital</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Klinefelter’s syndrome</td>
<td>– Isolated GnRH deficiency</td>
</tr>
<tr>
<td>– Noonan’s syndrome</td>
<td>– Isolated LH deficiency</td>
</tr>
<tr>
<td>– Inborn errors of testosterone biosynthesis</td>
<td>– Prader-Willi syndrome</td>
</tr>
<tr>
<td>– Androgen resistance states</td>
<td>– Laurence-Moon-Biedl syndrome</td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary acquired</td>
<td>Secondary acquired</td>
</tr>
<tr>
<td>– Undescended testes</td>
<td>– Pituitary tumours &amp; infarct</td>
</tr>
<tr>
<td>– Bilateral torsion of the testes</td>
<td>– Trauma</td>
</tr>
<tr>
<td>– Bilateral orchitis</td>
<td>– Craniopharyngioma</td>
</tr>
<tr>
<td>– Orchidectomy</td>
<td>– Hyperprolactinaemia (1° &amp; 2°)</td>
</tr>
<tr>
<td>– Gonadal toxins (radiotherapy &amp; chemotherapy)</td>
<td>– Haemochromatosis</td>
</tr>
<tr>
<td>– Acute and chronic systemic disease</td>
<td>– Neurosarcoid</td>
</tr>
<tr>
<td></td>
<td>– Ageing</td>
</tr>
</tbody>
</table>
Hypothalamic causes of hypogonadism

• **Idiopathic Hypogonadotrophic Hypogonadism (IHH) and Kallmann’s Syndrome**
  – Due to insufficient secretion of GnRH from the hypothalamus

• **Delayed puberty (pubertas tarda)**
  – Most common cause of delayed puberty is constitutional growth delay (CGD), due to individual differences in maturation of the hypothalamus

• **Other ‘hypothalamic’ causes of hypogonadism**
  – Underweight, anorexia nervosa
  – Prader–Labhart–Willi syndrome and Angelman’s syndrome
  – Laurence–Moon–Bardet–Biedl syndrome
Hypophyseal (pituitary) causes of hypogonadism

- Inadequate secretion of LH and FSH cause hypogonadism, as the testes are not sufficiently stimulated to function properly
  - Hormone analysis typically reveals reduced levels of FSH, LH and testosterone
  - Gonadotropins increase in hypothalamic secondary hypogonadism (following repeat GnRH stimulation if necessary), however, no increase in gonadotropins is seen if the disorder is hypophyseal in origin

- Hypopituitarism: insufficiency of the pituitary gland
  - Deficiency of one or more pituitary hormones owing to various diseases
  - Most common cause benign adenoma of the anterior lobe of the pituitary

- Hyperprolactinemia: any non-physiological increase in prolactin
  - Values above 20–25 ng/mL (400–500 mU/L) are deemed to be pathological
  - Prolactin reduces GnRH secretion from hypothalamus, leading to secondary hypogonadism
Testicular causes of hypogonadism

- The testes are bi-functional organs, producing both androgens and sperm
- Hypogonadism may therefore manifest in either reduced production of androgen or disturbed spermatogenesis, or a combination of the two
- Disorders of the testes are described as primary hypogonadism, typically characterised by increased gonadotropins and reduced testosterone

**Forms**

- Congenital and acquired anorchidism
- Malpositioning of the testes
- Orchitis
- Klinefelter's syndrome
- XX-man
- Male pseudohermaphroditism
- Others
Target organ related causes of hypogonadism

- Disorders in which the testicular hormones testosterone and anti-Müllerian hormone and/or the testosterone metabolites DHT [dihydrotestosterone] and estradiol do not function, despite testis function being essentially intact
- This is due to either:
  - Defects in the corresponding receptors, or
  - Lack of activity by the enzyme 5α-reductase or aromatase, which are responsible for converting testosterone to DHT or estradiol
## Secondary causes of hypogonadism

### Systemic diseases which can impair testicular or sexual function
- Diabetes mellitus
- Kidney disease
- Intestinal diseases
- Epilepsy
- Haemochromatosis
- HIV
- Cancer
- Liver cirrhosis
- Sickle cell disease
- Cystic fibrosis
- Leprosy
- Infections

### Exogenous causes
- Radiation, drugs and medication e.g. cytostatics
- Environmental toxins
- Others
Hypogonadism and aging

- With age, testosterone levels fall and there is greater resistance to its action – in part due to rising sex hormone binding globulin (SHBG) levels causing a more marked drop in bioavailable and free testosterone.
- There are a number of terms for the clinical conditions associated with low levels of T in adult males:
  - TDS (Testosterone deficiency syndrome)
  - LOH (Late-onset hypogonadism)
  - Andropause
  - ADAM (Androgen deficiency of the aging/adult male)
  - PADAM (Partial androgen deficiency of the aging/adult male)
- TDS and LOH are considered the most appropriate terms.
- However, the term ‘hypogonadism’ is used in the licensed indications for testosterone replacement therapies.

Late onset hypogonadism (LOH)

“Late onset hypogonadism (LOH, also referred to as age-associated testosterone deficiency syndrome, 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

Down-regulation in late onset hypogonadism

- Reduced LHRH
- Reduced LH
- Increased sensitivity to testosterone

Testosterone
SHBG

Hypothalamus
Pituitary
Testes
The burden of hypogonadism on patients, healthcare providers and systems
Burden on patients

• Symptoms of TDS
  – Sexual dysfunction
  – Cognitive impairment
  – Decreased energy
  – Depressed mood
  – Increased fat mass
  – Loss of muscle mass and strength
  – Reduced bone mineral density

• Impact on functioning:
  – Physical
  – Social
  – Emotional
  – Cognitive
  – Sexual

• REDUCED QUALITY OF LIFE

Hypogonadism increases the risk of morbidity and mortality

- Low androgen levels in men linked with:
  - Depression
  - Osteoporosis
  - Cardiovascular disease
  - Metabolic syndrome/type 2 diabetes

- **Lower life expectancy**
  - US study in men >40 years found men with normal testosterone levels had a mortality rate of 20% compared with a rate of 35% in men with low testosterone levels (>250 ng/dL [>8.7 nmol/L]) over a mean follow-up of 4.3 years
  - Low testosterone increased risk of mortality by 88%
  - Low testosterone levels are associated with all-cause and CV death

Hypogonadism (TDS) and QoL

- Few direct studies of QoL in TDS
  - One study compared 24 men >50 years with BPH and with free T <200 pmol/L and 24 age-matched controls
    - Health-related QoL assessed using SF-12 and psychological well-being components of SF-36 scale
    - Vitality scores and physical symptom scores were significantly worse in TD subjects (p<0.05)
    - No difference was observed in the mental health index
  - The European Male Aging Study is a prospective study investigating aging in 3,369 European men
    - Erectile dysfunction was shown to be an independent predictor of low physical QoL
    - Depression was significantly associated with all sexual function parameters studies

BPH – benign prostatic hyperplasia

Hypogonadism is associated with increased risk of depression (1)

- Retrospective cohort study (level of evidence 2b)
- Hypogonadism defined as total testosterone <200 ng/dL
- Mean age 62.6 years
- Relative risk for depression in patients with hypogonadism = 3.079

<table>
<thead>
<tr>
<th></th>
<th>Depression (+)</th>
<th>Depression (-)</th>
<th>Total</th>
<th>2-year depression incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypogonadism (+)</td>
<td>5</td>
<td>18</td>
<td>23</td>
<td>21.74%</td>
</tr>
<tr>
<td>Hypogonadism (-)</td>
<td>18</td>
<td>237</td>
<td>255</td>
<td>7.08%</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>255</td>
<td>278</td>
<td>8.27%</td>
</tr>
</tbody>
</table>

Hypogonadism is associated with increased risk of depression (2)

- Retrospective cohort study (level of evidence 2b)
- Mean age 67.1 years
- Hypogonadism defined as total testosterone <250 ng/dL
- Relative risk of depression in patients with hypogonadism = 1.784

<table>
<thead>
<tr>
<th></th>
<th>Depression (+)</th>
<th>Depression (-)</th>
<th>Total</th>
<th>2-year depression incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypogonadism (+)</td>
<td>28</td>
<td>123</td>
<td>151</td>
<td>18.54%</td>
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<tr>
<td>Hypogonadism (-)</td>
<td>62</td>
<td>535</td>
<td>597</td>
<td>10.39%</td>
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<tr>
<td>Total</td>
<td>90</td>
<td>658</td>
<td>748</td>
<td>12.03%</td>
</tr>
</tbody>
</table>

Longitudinal relation of hypogonadism and incident depression in 278 elderly men (mean age 62.4 years)

Hypogonadism associated with increased risk of type 2 diabetes (T2D)/metabolic syndrome (1)

- Prospective cohort study (level of evidence 1b)
- Mean age 51.3 years
- Low testosterone defined as $<317 \text{ ng/dl} (<11 \text{ nmol/L})$
- Relative risk for T2D in patients with low testosterone level = 2.242

<table>
<thead>
<tr>
<th></th>
<th>T2D (+)</th>
<th>T2D (-)</th>
<th>Total</th>
<th>11-year T2D incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low testosterone</td>
<td>6</td>
<td>29</td>
<td>35</td>
<td>17.14%</td>
</tr>
<tr>
<td>Normal testosterone</td>
<td>51</td>
<td>616</td>
<td>667</td>
<td>7.64%</td>
</tr>
<tr>
<td>Total</td>
<td>57</td>
<td>645</td>
<td>702</td>
<td>8.11%</td>
</tr>
</tbody>
</table>

Hypogonadism associated with increased risk of type 2 diabetes (T2D)/metabolic syndrome (2)

- Prospective cohort study (level of evidence 1b)
- Mean age 54 years
- Low testosterone defined as <250 ng/dl
- Relative risk for T2D in patients with low testosterone level = 4.255

<table>
<thead>
<tr>
<th></th>
<th>T2D (+)</th>
<th>T2D (-)</th>
<th>Total</th>
<th>9-year T2D incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low testosterone</td>
<td>8</td>
<td>32</td>
<td>40</td>
<td>20.00%</td>
</tr>
<tr>
<td>Normal testosterone</td>
<td>46</td>
<td>944</td>
<td>990</td>
<td>4.70%</td>
</tr>
<tr>
<td>Total</td>
<td>54</td>
<td>976</td>
<td>1,030</td>
<td>5.20%</td>
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</tbody>
</table>
Costs associated with hypogonadism (TDS)

- **Depression**
  - Most costly brain disorder in Europe – in 2004, the total annual cost of depression was approx €118 billion
  - For each person with depression, direct costs of care were around €2000 per year and indirect costs due to morbidity and mortality were estimated at €3500 per year

- **Sexual dysfunction**
  - In a UK study healthcare costs approx £160 (€253) per patient per year (1998)
  - Costs higher for diabetic patients with ED where first-line treatment with PDE5 inhibitors has failed due to undetected TDS and more expensive forms of treatment are required

- **Osteoporosis**
  - Estimated mean cost of a fracture was approx €8500 (France 1999)
  - Loss of work days (for patients and informal carers)

- **Metabolic syndrome**
  - Diabetes costs Medicare in the US $110 billion

*PDE5 – phosphodiesterase type 5

A clear definition of hypogonadism exists
We should only use one term – ‘hypogonadism’
Incidence varies from 5.6% to 49%, depending upon age
Hypogonadism has a demonstrable impact on quality of life
There are clear clinical symptoms for hypogonadism
Untreated hypogonadism places an economic burden on the healthcare system