Hypogonadism: the sixth factor in the Metabolic Syndrome?

Kiara Hennessey, PGY-4
Department of Urologic Sciences
University of British Columbia
Objectives

- To understand the clinical association between late onset hypogonadism (LOH) and atherosclerotic cardiovascular disease (CVD)
- To understand the shared biological causes of LOH and CVD
- Effect of androgen replacement therapy on CVD risk

Previous Grand Rounds

- Testosterone (T) biochemistry
- Physiology of T
- Dx of T deficiency syndrome (TDS)
- Tx options
- Concerns regarding TRT
- Monitoring and follow-up
True or false?

- Androgens, testosterone (T) in particular, are the cause of a consistent male : female ratio of 2 : 1 incidence of coronary heart disease mortality.

True or false?

- T replacement therapy increases risk of CVD.
“Gladly I think of the days when all my members were limber, all except one.
Those days are certainly gone. Now all my members are stiff. All except one.”

- Johann Wolfgang von Goethe (1749-1832)

LOH

“LOH is a clinical and biochemical syndrome associated with advancing age and characterized by symptoms and a deficiency in serum testosterone levels”

ISA, ISSAM, EAU, EAA, ASA recommendations 2009

LOH

• AKA...
  Testosterone deficiency syndrome
  Andropause
  Androgen decline in the aging male (ADAM)
  Partial ADAM (PADAM)
  Androgen deficiency syndromes
  Combined primary and secondary hypogonadism
  Male Climacteric
  Male menopause


Diagnosis of LOH

• Exclude confounders: illness or medications
• ≥ 1 symptom of hypogonadism

<table>
<thead>
<tr>
<th>Low libido</th>
<th>Decreased BMD and osteoporosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erectile dysfunction</td>
<td>Decreased vitality</td>
</tr>
<tr>
<td>Decreased muscle mass and strength</td>
<td>Depressed mood</td>
</tr>
<tr>
<td>Increase body fat</td>
<td></td>
</tr>
</tbody>
</table>

PLUS

low T level

No consensus on lower limit:
  Above 12 nmol/L does not require replacement
  Below 8 nmol/L usually benefits from T replacement
  In between 8 and 12 nmol/L → free T assay or SHBG level

Prevalence LOH

- 20% of men >60 yrs
- 50% of men >80 yrs

• TT -1.6% per year
• FT -2-3% per year

Mechanism of LOH

- ↓ production of T result from changes at all levels of HPA
  - ↑ gonadotropins, testicular response to hCG reduced (1° hypogonadism)
  - altered GnRH secretion (2° hypogonadism)
  - ↓ LH pulse frequency and amplitude (2° hypogonadism)
  - ↓ androgen receptor concentration in some target tissues

Effects of LOH

- Osteoporosis
- Sexual dysfunction
- Alzheimer’s
- Frailty
- **OBESITY**
- **DM**
- **DYSLIPIDEMIA**
- **HTN**
- **CVD?**

Metabolic Syndrome (MS)

MS

• Co-occurrence of metabolic risk factors for both type II DM and CVD

• AKA...
  Syndrome X
  Insulin resistance syndrome
  Deadly quartet
  Obesity, dyslipidemia syndrome


MS

• Several definitions

<table>
<thead>
<tr>
<th>NCEP definition</th>
<th>WHO definition</th>
<th>International Diabetes Foundation definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 3 of following:</td>
<td>Hyperinsulinemia or fasting plasma glucose ≥ 110 mg/dL. PLUS</td>
<td>Central obesity (Waist circumference &gt; 94 cm in Caucasian men and &gt; 80 cm in women). PLUS any 2 of the following:</td>
</tr>
<tr>
<td>• Fasting glucose greater than or equal to 110 mg/dL.</td>
<td></td>
<td>• Triglycerides &gt; 1.7 nmoL (150 mg/dL)</td>
</tr>
<tr>
<td>• Abdominal obesity with waist circumference ○ &gt; 102 cm in men ○ &gt; 88 cm in women</td>
<td>• Abdominal obesity with waist to hip ratio ○ &gt; 0.9 in men ○ &gt; 0.85 in women</td>
<td>• Reduced HDL &lt; 1.03 nmoL (40 mg/dL) in males or &lt; 1.22 nmoL (50 mg/dL) in females</td>
</tr>
<tr>
<td>• Serum triglycerides ≥ 150 mg/dL.</td>
<td>• Dyslipidemia ○ Serum triglycerides ≥ 150 mg/dL or HDL cholesterol &lt; 35 mg/dL.</td>
<td>• Raised blood pressure &gt; 130 mmHg systolic or 85 mmHg diastolic</td>
</tr>
<tr>
<td>• Serum HDL &lt; 40 mg/dL.</td>
<td>• Blood pressure ≥ 140/90 mmHg</td>
<td>• Raised fasting blood glucose &gt; 5.6 nmoL (100 mg/dL)</td>
</tr>
<tr>
<td>• Blood pressure ≥ 130/85 mmHg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MS- definition

- NCEP/ATPIII and IDF, most widely used
- Relative value for prognosis/management similar

NCEP/ATPIII: any 3 of 5 traits

1. **Abdominal obesity** - waist circumference > 102cm in men, > 88cm in women
2. **Serum triglycerides** - ≥ 1.7 mmol/L or drug treatment
3. **Serum HDL** - < 1mmol/L in men and < 1.3mmol/L in women or drug treatment
4. **Blood pressure** - ≥ 130/85mmHg or drug treatment
5. **Fasting plasma glucose** - ≥ 5.6mmol/L or drug treatment


MS- prevalence and risk factors

- Increasing
  - NHANES (1999-2002): 34.5%

- Risk factors

<table>
<thead>
<tr>
<th>Obesity</th>
<th>Low income</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Inactivity</td>
</tr>
<tr>
<td>Race</td>
<td>High carbohydrate diet</td>
</tr>
<tr>
<td>Family history</td>
<td>Soft drink consumption</td>
</tr>
<tr>
<td>Postmenopausal status</td>
<td>Atypical antipsychotics</td>
</tr>
<tr>
<td>Smoking</td>
<td>No ETOH consumption</td>
</tr>
</tbody>
</table>

Ford et al, JAMA. 2002; 287:356.
MS- Implications

• Risk factor for DM II, CVD, and mortality
  – Meta-analysis of 16 multi-ethnic cohort studies:
  – 3 meta-analyses:
    RR CVD is 1.53-2.18
    RR all-cause mortality is 1.27-1.60

• Fatty liver, CKD, PCOS, OSA, Gout

MS- Implications

• ↑ metabolic risk ➔ RF clustering, insulin resistance (IR)
• Not simply obesity:
  Framingham population
  Obesity: no sig ↑ risk DMII or CVD
  Obesity + MS: 10x ↑ risk DMII and 2x ↑ risk CVD
  Normal weight + MS: 4x ↑ risk DMII, 3x ↑ risk CVD

Risk differs as a function of insulin sensitivity
MS- controversy

• A true “syndrome”?
  – Lack of single definition
  – Lack consistent thresholds
  – Different phenotypes
  – Inclusion of pts with clinical CVD, DMII
  – Unclear unifying pathogenesis
  – Sub-clinical CVD
  – Other RF, ex. inflammatory markers, not included
  – CVD risk not greater than risk sum of its parts


MS- Implications

• Key clinical implication
  – Identify patients at high metabolic risk
    • presence of one component ➔ look for others
    • aggressive lifestyle modification ➔ weight loss, exercise
    • evaluation of RFs regularly
    • risk algorithms to target pts for Rx intervention

LOH and MS

• The sixth factor?

NCEP/ATPIII: any 3 of 5 traits

1 Abdominal obesity- waist circumference > 102cm in men, > 88cm in women
2 Serum triglycerides- ≥ 1.7 mmol/L or drug treatment
3 Serum HDL- < 1mmol/L in men and < 1.3mmol/L in women or drug treatment
4 Blood pressure- ≥ 130/85mmHg or drug treatment
5 Fasting plasma glucose- ≥ 5.6mmol/L or drug treatment
6 Late Onset Hypogonadism?
LOH and CVD

• Observational studies:

  – Over 40 studies: $T \alpha$ coronary heart disease?
    • None, positive correlation
    • Many, CHD $\alpha \downarrow T$


LOH and CVD

• Observational studies:

  • Some, well designed
    – English et al. 2000: FT and BT reduced in angio- determined CHD compared to control.
    • Corrected for CVD RFs

LOH and CVD

• Indirect evidence

– Androgen suppression therapy for prostate cancer
  • Metabolic complications
    – weight gain, IR, dyslipidemia, HTN, CVD
  • Earlier onset of fatal MI in men >65


LOH and CVD

• Indirect evidence:
  – Non-coronary atherosclerosis
    • Carotid atherosclerosis
      – Age-related in Tα degree & progression of carotid atherosclerosis1-2
        • Intimal thickness predicts CVD mortality3
    • Aortic atherosclerosis
      – T independently 1/α aortic degree & progression atherosclerosis4
    • Peripheral arterial disease
      – FT α with ABI in elderly men, independently5

LOH and CVD

• Indirect evidence:

Relief of anginal symptoms and ischemia

Studies from 1940-present
– Multiple RCTS\(^1,2,3\):
  • T Rx \(\downarrow\) anginal sx
  • T Rx \(\uparrow\) time to 1mm ST depression on stress-testing
    – Lower baseline T, \(\uparrow\) effect; maintained if concurrent anti-anginal Rx


LOH and CVD

• Indirect evidence:

  • Relief of anginal symptoms and ischemia
    – T \(\uparrow\) coronary A diameter and flow:
      • large body evidence in humans and animals, \textit{in vivo and in vitro}
      • effect \(\downarrow\) with age\(^1\)
      • in men with CHD\(^2\)
      • mediated by action on calcium channel, independent of AR?\(^3\)

LOH and CVD

• Indirect evidence:
  
  • Mortality
    – Rancho Bernardo prospective cohort study
      \( \downarrow \) TT and BT \( \alpha \) \( \uparrow \) overall mortality, independently
      • Lowest quartile (TT<8nmol/L) 40% \( \uparrow \) risk death
        [HR 1.4 [CI 1.14-1.71]]
      and predicts CV death [HR 1.38 [CI 1.02-1.85]]


LOH and CVD

• Indirect evidence:
  
  • Mortality
    – EPIC Norfolk prospective case-control study
      baseline T 1/\( \alpha \) all cause and CVD mortality

LOH and CVD

• T Rx in 1° or 2° CVD prevention?
  – no trial of sufficient size or duration
  – current studies are small, brief, poorly designed
• Absence of this data
  – examination of T’s relationship with CVD RFs


LOH and body composition
LOH and body composition

• Hypogonadism → loss muscle mass, gain visceral fat
  – Observational studies:
    • TT, FT 1/α waist circumference\(^1\)
    • TT, FT α central obesity vs general obesity\(^1\)
    • T level predicts central obesity\(^2\)
    • Hypogonadal men → ↑ fat mass\(^2\)


LOH and body composition

• Hypogonadism → loss muscle mass, gain visceral fat
  – Intervenational studies:
    • GnRH Rx in healthy men or prostate CA → ↑ fat mass\(^1,2\)
    • Weight ↓ in obese men following gastroplasty → ↑ T\(^3\)

LOH and obesity

T replacement and body composition

- ↑ T → ↑ fat-free mass, ↓ in visceral adiposity\(^1\)
  - Meta-analysis of 16 RCTs
  - Tx to physiologic T levels, includes older men

- ↑T → ↑ visceral adipocyte [AR] and ↓ fat mass\(^2\)

LOH and body composition

- Summary:
  - T↓ visceral obesity in aging men
  - visceral fat predisposes to MS, DM, CVD

LOH and IR/ DMII

- Hypogonadism ➔ IR, DMII

  - Observational studies:
    - T 1/α glucose and insulin levels¹
    - ↓ T in DMII, 33% prevalence hypogonadism²
    - GnRH Rx in prostate CA➔ ↓ insulin sensitivity⁴
    - ↓ T α future DM II⁵

LOH and IR/ DMII

• Findings vary as to whether the α of T with DM occurs independently of obesity

• Role of LOH in *pathogenesis* of DMII?
  
  OR
  
  is obesity the common link?

```
hypogonadal-obesity-adipocytokine cycle
```

T replacement and IR/ DMII

• RCTs
  
  – not specific to aging male
  
  – Tx to physiologic T

• ↑T ➔ ↓IR in hypogonadal, non-diabetic men¹
  
  • associated ↓ central obesity

• ↑T ➔ ↓HbA₁c , fasting glucose, IR, insulin dose in hypogonadal men with DM²
  
  • associated ↓ central obesity

LOH and IR/ DM II

• Summary:
  – Regardless of mechanism: +/- via central obesity
    • ↓ T α IR
    • IR predisposes to MS, DM, CVD

LOH and dyslipidemia

• ↓ T → atherogenic lipid parameter

  – Observational studies:
    • ↓ T → ↓ HDL, ↑ TG and LDL independent of other RFs

T replacement and dyslipidemia

• Meta-analysis of 17 RCTs
  – $\uparrow$ T $\rightarrow$ $\downarrow$ total cholesterol in hypogonadal men

LOH and dyslipidemia

• Summary:
  – $\downarrow$ T $\alpha$ dyslipidemia
  – Dyslipidemia $\alpha$ atherosclerosis, CVD

LOH and HTN

- Observational studies:
  - ↓ T ➔ ↑ sBP

T replacement and HTN

- No effect on HTN


LOH and HTN

• Summary:
  – Possible trend: T 1/α BP
  – HTN α DM, MS, CVD

LOH and atherosclerotic mediators

• Pro-thrombotic factors and inflammatory cytokines
  – Observational and interventional studies:
    • T 1/α pro-thrombotic factors\(^1\)
    • T α fibrinolytic agents\(^1\)
    • T 1/α pro-inflammatory cytokines\(^2\)
  – Both key mediators in atherosclerosis

LOH and atherosclerotic mediators

T replacement and atherosclerotic mediators

- RCTs
  - T can beneficially regulate inflammatory cytokines (TNFs, ILs) in men with CHD\(^1\)
  - T ↓ prothrombotic factors\(^2\)

LOH and atherosclerotic mediators

• Summary:
  – ↓ Tα ↑ mediators of atherosclerosis
  – Atherosclerosis ➔ CVD

True or false?

• Androgens, testosterone (T) in particular, are the cause of a consistent male : female ratio of 2 : 1 incidence of coronary heart disease mortality
True or false?

- T replacement therapy increases risk of CVD

Summary

- Existing evidence ➔ low T is a significant RF for CVD
  - 1/α RFs for CVD, relieves sx of MI and ischemia
    - Potential to slow or halt progression of DM or CVD
    - Physicians should evaluate for MS in all men dx with hypogonadism and *vice versa*

- Caution with studies
  - Heterogeneous design
  - Gonadal status at baseline and tx T goals, route and preparation
  - Length of studies
  - Specific to aging male
  - Pt comorbidities
Take home messages

• T Rx to restore T within physiological range
  – Favourable effect on RFs
  – Reduces myocardial ischemia
• Cellular mechanisms mediating effect need further elucidation
• Little known about the suitability or comparative efficacy of different preparations within CV system
• Safety of T Rx in pts with normal serum levels, unknown

Take home messages

• Current evidence: likely effects of T on overall CVD risk – neutral or beneficial effect
  However...
  Need appropriately powered, long duration RCTs in aging male with CVD primary endpoints
• Traditional benefits of T (sexual function, mood, QOL...) should remain primary goals of T Rx
  – Possible beneficial effects on other parameters including CVD are emerging
  – Premature to recommend T tx solely to decrease CV risk
• Absolute CI and relative CI
• Adverse side effects
  – Until answers available, must balance risk/benefit
Questions?

Thank you

FOOTNOTE: the “Listening to children cry in the middle of the night” gland is not shown due to its small and underdeveloped nature. Best viewed under a microscope.