MALE HYPOGONADISM

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Topics

- What is male hypogonadism and how to diagnose it.
- What is age-related hypogonadism
- Difference between age-related and classical hypogonadism
- Why diagnose and treat hypogonadism
- What are the risks of testosterone treatment for hypogonadism
Definitions

- Androgen deficiency
  - Low serum testosterone level
  - Also called biochemical hypogonadism

- Clinical Hypogonadism*
  - Symptoms associated with low testosterone AND
  - Inadequate testicular function
    - Low testosterone and sperm production

*Endocrine Society Guidelines, 2010
Etiology

- Primary hypogonadism
  - Testicles do not respond to hormonal stimulation
  - Increased FSH and LH

- Secondary hypogonadism
  - Deficiency of LH and FSH
    - Defect in hypothalamus or pituitary

- Mixed

FSH = follicle stimulating hormone
LH = Luteinizing hormone
Categories of Male Hypogonadism

- **“Classic”**
  - Low T (testosterone) due to known underlying medical condition
    - Primary hypogonadism
      - Klinefelter syndrome, mumps orchitis, orchiectomy
    - Secondary hypogonadism
      - pituitary pathology, Kallman Syndrome, chronic opioid use
  - May present in young through elderly population

- **Age-related (Andropause)**
  - Low T due to decreased T production that accompanies aging
  - Mixed hypogonadism (evidence of both primary and secondary etiologies)
Presentation depends on timing and degree of testosterone deficiency

- Fetal Period
- Childhood
- Puberty
- Adult

T level

- Micro-penis
- Cryptorchidism
- Absent puberty
- Partial puberty
- ED/Infertility
- Hypogonadal Sx

ED = erectile dysfunction
Sx = symptoms
Testosterone Measurements

- Types of measurements
  - Total Testosterone
    - SHBG-T + Alb-T + Free-T
  - Free Testosterone
  - Bioavailable Testosterone
    - Non-SHBG T = Free T + Alb-T

- No consensus
  - Most studies and guidelines use total T
  - FT or BioT useful when TT is borderline – low normal range

SHBG= sex hormone binding globulin
Alb = albumin
Free-T = FT = free testosterone
BioT = bioavailable testosterone
TT = total testosterone
Circadian Rhythm

- Testosterone best measured in morning
  - Less variation in older men

Clin Endocrinol 2003 Jun;58(6):710
What is a normal T level

- How is it defined
  - 95% CI of young healthy males
    - Healthy but not specifically “normal sexual function”
    - 2.5% of healthy “normal” men will have levels below this range

CI = confidence interval
Indications for Treatment

- **Endocrine society, 2010**
  - Treat classic hypogonadism, conflicted on age associated hypogonadism
  - Symptoms +
    - T below lower limit (95% CI) for young men
      - T < 280 - 300 ng/dl or local lab determined reference ranges.
      - OR
    - T in low normal range + low free T

- **ASA, ISSAM, EAU, EAA 2008**
  - Symptoms +
    - T < 230 ng/dL OR
    - T 230 - 350 ng/dL AND FT < 65 pg/mL

- **EMAS, 2013**
  - 3 Sexual Symptoms +
  - T < 320 AND FT < 64 pg/mL
Androgen Deficiency and Male Hypogonadism

- All “guidelines” require symptoms of hypogonadism

- Low T alone is insufficient

- Prevalence of low T is > prevalence of hypogonadism
Low Testosterone, Hypogonadism and Age

T declines ~ 0.4 – 1 % per year
FT and BioT ~ 2 % per year

Low T alone

Low T + Symptoms: 5.6%
(T < 300 + FT < 5 ng/dl)

and MMAS , J Endo Metab 1991
Diagnosis of Hypogonadism

- **Morning testosterone level**
  - Diurnal variation

- **If low, repeat T level**
  - 15% of young healthy men will have low T at some point in a 24hr period
  - 30% of men will have a normal T in follow-up

- **LH, (FSH)**

- **Prolactin if LH inappropriately low**

- **Pituitary MRI if**
  - Elevated prolactin (>~ 2x normal)
  - T < 150 without elevation in LH
  - Other clinical indicators
    - Sx of intracranial lesion

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Brambilla et al., Clin Endo 2007. 67:853
Endocrine Society Guidelines 2010
Symptoms - More Specific

- Impaired sexual development, eunuchoidism
- Decreased libido
- Decreased spontaneous erections
- Breast discomfort, gynecomastia
- Loss of body hair (pubic, axillary, facial)
- Small testes
- Low sperm count (< 10 ml/ml)
- Low bone density, height loss, easy bone fracture
- Hot flashes, sweats

“Sometimes it hides like a frightened turtle”
Less Specific Symptoms/Signs

- Lethargy, decreased motivation, self-confidence
- Depression
- Poor concentration and memory
- Sleep disturbance, increased sleepiness
- Mild anemia
- Reduced muscle bulk/strength
- Increased body fat, BMI (body mass index)
- Diminished physical/work performance
Testosterone levels in symptomatic and asymptomatic men

EMAS. NEJM 2010
Testosterone levels do not separate symptomatic from asymptomatic men

- No study had defined a level of T that consistently separates those that will respond to treatment from those that will not.

- Each symptom may be caused by things other than low testosterone

- The testosterone level at which symptoms develop may vary by
  - symptom
  - patient
Symptoms and testosterone levels

A Sexual Symptoms and Total Testosterone
- Decreased frequency of morning erection
- Erectile dysfunction
- Decreased frequency of sexual thoughts

B Sexual Symptoms and Free Testosterone
- Decreased frequency of morning erection
- Erectile dysfunction
- Decreased frequency of sexual thoughts

C Physical Symptoms and Total Testosterone
- Decreased vigorous activity
- Difficulty walking >1 km
- Decreased bending

D Physical Symptoms and Free Testosterone
- Decreased vigorous activity
- Difficulty walking >1 km
- Decreased bending

E Psychological Symptoms and Total Testosterone
- Fatigue
- Loss of energy
- Sadness

F Psychological Symptoms and Free Testosterone
- Fatigue
- Loss of energy
- Sadness

EMAS. NEJM 2010
Thresholds for Symptoms

- Chance of Sx greater below threshold than above it
- Pts may have Sx with levels above threshold
- Different symptoms have different thresholds
- Most thresholds are around 300 ng/dL
Low T and Symptoms

If testosterone is low, older men are more likely to have symptoms than younger men BUT 47.6% of older men with low T were asymptomatic.

Why Diagnose and Treat Hypogonadism?

- To diagnose significant medical conditions
- To identify patients who will benefit from treatment
- Treatment will relieve symptoms
- Treatment will protect against future pathologies
Conditions Associated with hypogonadism

- Obesity
- NIDDM (non-insulin dependent diabetes mellitus)
- Hypertension
- COPD (chronic obstructive pulmonary disease)
- Renal failure
- Reduced bone mineral density
- HIV
- Metabolic Syndrome
Comorbidities and LOH

- Obesity
- Type 2 diabetes mellitus
- Predicted CV risk
- Chronic diseases
- Metabolic syndrome
  - Waist circumference (>102 cm)
  - Triglycerides (>150 mg/dl)
  - Glycemia (>100 mg/dl)
  - HDL (< 40 mg/dl)

Age adjusted risk for EMAS-defined LOH
Late onset Hypogonadism (LOH) and Comorbidities

![Graphs showing LOH prevalence by age bands, BMI categories, and levels of co-morbidity.](EMAS. NEJM 2010)
Comorbidities: Causation or Association?

- Does low testosterone cause disease or is it due to disease?
- Does treatment of hypogonadism improve the underlying disease/condition?
Goal of testosterone Rx

- How high should T level be with Treatment?
  - No evidence based guidelines
    - Endocrine Guidelines
      - Classic Hypogonadism
        - Mid range of healthy young men
          - 400 – 700 ng/dL
      - Age associated hypogonadism
        - If you decide to treat
          - Lower range of healthy young men
            - 400 – 500 ng/dL

RX = treatment
Inconsistent Criteria for Treatment

- Pt with Sx and $T < 300$
  - Treat to get $T > 400$

- Pt with Sx and $T > 300$ but $< 400$ (normal FT)
  - Leave him with $T < 400$

- Since we don’t know the risks of long-term T therapy, many organizations suggest only treating if $T$ is lower than lower limit for young men.
IOM Report

- Need RCTs (randomized controlled trials)
  - Short-term efficacy trials in Older Men
    - Sample size < 500 men for 1 year
  - If efficacy is shown, then perform long-term safety/risks and benefits studies
    - Sample size 5000
    - Observational studies of limited value
      - Uncontrolled
      - Selection bias
  - Studies in Middle aged men should wait for results in older men

Testosterone and Aging, IOM Report, 1995
Sexual Function after T Rx

- Increased libido
- Sexual thoughts
- Attention to erotic stimuli
- Increased frequency and duration of nocturnal erections
- ED – less so than libido
  - T level correlated poorly with presence of ED in men > 60

Basaria S. Lancet 2014; 383:1250
Korenmann et al. J Clin Endocrinol Metab. 1990; 71:963
Reyes-Vallejo et al. J Sex Med. 2007, 4:1757
Effects of T Rx on Body Composition

- Fat and muscle
  - Decreased fat mass
  - Increased lean body mass
  - Increased muscle strength
    - Not all studies
- Effects are modest at best

Basaria S. Lancet 2014; 383:1250
Endo Soc Guidelines 2010
Bone Density

- Hypogonadal men have decreased bone density and increased fracture risk
  - Best correlated with estrogen levels

- Treatment increases bone density
  - Increase in lumbar but not femoral neck
    - Need larger better studies
  - Effect on fracture rate?
    - No studies

Behre et al. J Clin Endo Metab. 1997; 82:2386
Psychological Symptoms

- Some evidence of improvement but inconsistent results:
  - Quality of life
  - Mood
  - Depression
  - Cognition
T Rx and Type 2 Diabetes

- Evidence for improvement in:
  - Fasting glucose
  - HbA1c
  - Triglycerides

Corona et al. Best Practice & Res Clin Endo & Met 2013. 27:557
T Rx and Metabolic Syndrome

- Evidence for improvement in:
  - Fasting blood Sugar
  - HOMA Index
  - Triglycerides
  - Waist circumference

HOMA = Homeostasis model assessment

Corona et al. Best Practice & Res Clin Endo & Met 2013. 27:557
Summary of Treatment

- Evidence exists of benefit for a variety of symptoms, signs, co-morbidities
  - Those with very low testosterone likely show clearer benefit
    - Not the majority of testosterone use
  - Many classic hypogonadal patients are
    - Older
    - do not have extremely low T levels
    - similar to age associated hypogonadism patients
    - Evidence suggests improvement for both groups in some Sx

- Lack of large RCTs
Potential Risks

- Erythrocytosis
- Prostate
- Cardiovascular
- Infertility
- Lipids
- Sleep apnea
Spermatogenesis

- Exogenous Testosterone is a contraceptive
  - Suppresses LH and FSH secretion
  - Patients become azoospermic
  - Alternate methods of increasing testosterone should be used in men wanting to retain fertility
    - Clomiphene
    - hCG (human chorionic gonadotropin)
    - Aromatase inhibitors
Erythrocytosis

- Most frequent adverse event
  - 5x increase compared to placebo
  - More common with IM testosterone and older men
  - Incidence
    - Injections ~44%
    - Transdermal ~ 15%

- Unclear if risk of thrombotic events is increased
  - Not polycythemia vera

- Management (if hematocrit > 54%)
  - Reduce dose, stop therapy
  - Phlebotomy
Prostate

- BPH (benign prostatic enlargement)
  - TRT (testosterone replacement therapy) does not cause obstructive voiding symptoms

Pearl et al. J Urol 2013; 190:1828
Prostate cancer

- Does testosterone treatment cause prostate cancer?
  - Probably not
    - no single large treatment study

- Epidemiologic Studies
  - T levels not related to risk of PCa
    - 18 studies: Roddam et al. JNCI 2008. 100:170
    - REDUCE Trial – 3255 men

- Treatment Studies
  - No increase in rate of Prostate Cancer or clinically significant PSA elevation
    - Meta-analysis of controlled trials of TRT
Cardiovascular Events

- Does testosterone treatment increase rate of
  - CV events
  - Mortality

- There is data suggesting it is safe and it is not safe
CV Events and mortality studies summary

- Studies are observational
  - Substantial uncorrected bias cannot be eliminated
    - Cannot correct for why some patients were treated and others were not
    - May show correlation when in fact there is none

- Cannot determine cause and effect
  - Hypothesis generating

- Will need large RCT to determine safety
  - CVD (cardiovascular disease)- Thousands of participants
Conclusions

- Clinical hypogonadism is common
  - Many symptoms and co-morbidities are associated with low testosterone

- Criteria for who to treat is controversial
  - Cannot clearly separate those that benefit from those that do not
    - Symptoms and signs are multifactorial and nonspecific

- Reasonable evidence exists that treatment is beneficial for some Sx/signs
  - Both classical and age-associated hypogonadism

- Long-term safety will not be determined without large RCTs.