CONSIDERATIONS BEFORE TESTOSTERONE THERAPY
WHAT’S UP WITH THE T?

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29 yo man presents to your clinic for hypogonadism

Told several years ago that his T was low, and was treated with T gel for a short duration, but not continued over time

Total testosterone - undetectable

BMI 42

Would you treat him with testosterone?
Stopped growing about age 13
Has never needed to shave
Short compared to family members
Lifelong ED
Lifelong history of headaches
Physical exam notable for height 5'2", bilateral gynecomastia, small testes (8cc, soft)
Now what?
Please consider:

1) Is my patient really hypogonadal?
2) WHY?
3) What is the likelihood that it is reversible?
4) What is the benefit of T therapy for this patient?
**T will look low, but bioT may be normal**

**T will look normal/high, but bioT may be low**

Free T = unbound T  
Bioavailable = unbound + albumin bound
WHAT IS THE ASSAY METHOD USED AT MAINE MED?

- Total T – Nordx, Chemiluminescent assay
- Bio T/Free T – Send outs to Mayo
- Total T measured by LC/MS
- Free T - measured by equilibrium dialysis
- BioT - ammonium sulfate precipitation of SHBG
We suggest the measurement of morning total testosterone level by a reliable assay as the initial diagnostic test. (2)
IS ONE 8 AM MEASUREMENT ENOUGH?

- 1022 patients referred for ED, Lille, FR
- 107 found to have low T (< 300 ng/dl)
- Repeat sample in 98 - 39 patients had normal results (38%)
- Lesson: Get more than one sample!

We recommend confirmation of the diagnosis by repeating measurement of total testosterone. (1 | ☐ ☐ ☐ ☐)

8 AM Biot was low when my patient was in the hospital for pneumonia – is he hypogonadal?

- Iglesias, et al, Endocrine epub Sept 2014
- 1st examined 150 male patients in Madrid > 65 admitted to medical wards – 53% were hypogonadal (< 200 ng/dl)
- They examined 43 of these patients one month after discharge

We suggest that an evaluation of androgen deficiency should not be made during an acute or subacute illness. (2 | ☹☼☼ ☼)

Iglesias, et al Endocrine Jun 2014
ONCE YOU HAVE ESTABLISHED THAT THE PATIENT IS HYPOGONADAL:

Primary = testicular disorders
Secondary = pituitary or hypothalamic disorders
Late-onset hypogonadism

H&P: Development, fertility, headaches, visual field changes, brain injuries, testicular injuries or infections, duration of symptoms, systemic illnesses
The Hypothalamic-Pituitary-Gonadal Axis

**Hypothalamus**

**GnRH →**

**Pituitary**

- **FSH**
- **Sertoli Cells**
- **Inhibin**

**Spermatogenic Axis**

**Hypothalamus**

**GnRH →**

**Pituitary**

- **LH**
- **Leydig Cells**
- **Testosterone**

**Androgenic Axis**
Study of 3369 European men, ages 40-70, 150 excluded for known pituitary disease or disease known to affect T.

Single morning T, E2, LH, FSH, SHBG = 300 ng/dl

PRIMARY HYPOGONADISM

- LH/FSH high – primary defect is at testes
- Infertility/gynecomastia more likely
- Congenital
  - Klinefelters – 1/1000 live male births, karyotype usually 47 XXY
  - Bilateral cryptorchidism/varicocele
- Acquired
  - Infectious – Mumps orchitis
  - Ketonconazole
  - Trauma/torsion
KLINEFELTER SYNDROME

One of most common forms of male primary hypogonadism and infertility

Incidence:
- 1:600 live male births
- 5-10% of azoospermics

Genotype:
- 47, XXY (pure) (0.2% male conceptions and 0.1% live births)
- Chromosome studies on MR males reveal extra X in 0.45-2.5%
- 46, XY/47, XXY (mosaic)
- XXXY, XXXXY or XXYY

Presentation
- Hormonal levels are variable
- Testosterone may be low normal to normal range
- Some have no secondary sexual developmental changes and others are indistinguishable from healthy males

SECONDARY HYPOGONADISM

- Testosterone is low
- LH/FSH are low or inappropriately normal
- Suggests hypothalamic/pituitary dysfunction
  - Congenital
  - Suppression of gonadotrophs
  - Damage to gonadotrophs
Idiopathic hypogonadotopic hypogonadism (IHH)

• Congenital GnRH deficiency
• Various syndromes/phenotypes
• Kallman’s syndrome – associated with anosmia, product of KAL-1 gene involved in smell and also migration of GnRH secreting neurons
SUPPRESSION OF GONADOTROPINS

- Hyperprolactinemia
- GnRH analogs (leuprolide)
- Exogenous sex steroids – weight lifters/athletes, megasterol
- Opioid administration
  - 74% men on LAO, 34% on SAO! Rubenstein et al, Clin J Pain Oct 2013
- Diabetes
- Obesity
- Acute illness
- Corticosteroid administration
DAMAGE TO PITUITARY GONADOTROPHS

- Tumors – benign/malignant
- Infiltrative disease – sarcoid, hemochromatosis, tuberculosis

Consider MRI in secondary hypogonadism
AREN'T PITUITARY TUMORS RARE?
IS MRI REALLY WORTH THE COST?

6.6% with "serious" pathology

**Results of pituitary imaging 164 men with ED and secondary hypogonadism**

<table>
<thead>
<tr>
<th>Type of Abnormality</th>
<th>Number (%)</th>
</tr>
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<tbody>
<tr>
<td>None</td>
<td>137 (83.5%)</td>
</tr>
<tr>
<td>Empty sella</td>
<td>11 (6.7%)</td>
</tr>
<tr>
<td>Pituitary adenoma (mm)</td>
<td></td>
</tr>
<tr>
<td>&lt; 5 mm</td>
<td>5 (3%)</td>
</tr>
<tr>
<td>5-9</td>
<td>5 (3%)</td>
</tr>
<tr>
<td>10 or more</td>
<td>4 (2.4%)</td>
</tr>
<tr>
<td>Hypothalamic lesion</td>
<td>2 (1.2%)</td>
</tr>
</tbody>
</table>

(Adapted from Table 2)
21% in the lowest quintile had significant pathology

Prevalence of serious hypothalamic or pituitary imaging abnormalities (HPIA) by quintiles (Q) of serum testosterone in 164 men with erectile dysfunction.

Citron, Urology, 1996
DO I REALLY NEED TO DO ALL THOSE TESTS?

- Not in every case
- Use your clinical judgment
- In general, it is NOT normal for men to develop hypogonadism and causes need to be considered in every case.
- Once T therapy is started, it can be more difficult to evaluate the etiology
Labs on presentation 9:36 am
- T <7, Free T < 0.2
- LH 0.1
- FSH 0.6
- Prolactin 640 (4.1-18.4)
- Other pituitary function testing normal
- Started on cabergoline 0.5 mg twice weekly
- 4 week follow up prolactin: 19.2 ng/ml (4.1-18.4)
- Testosterone pending with next lab draw
1.1.1. **Further evaluation of men deemed androgen deficient**

We recommend measurement of serum LH and FSH levels to distinguish between primary (testicular) and secondary (pituitary-hypothalamic) hypogonadism. (1 | ☐☐☐☐)

In men with secondary hypogonadism, we suggest further evaluation to identify the etiology of hypothalamic and/or pituitary dysfunction. This evaluation may include measurements of serum prolactin and iron saturation, pituitary function testing, and magnetic resonance imaging of the sella turcica. (2 | ☐☐☐☐)

In men with primary testicular failure of unknown etiology, we suggest obtaining a karyotype to exclude Klinefelter syndrome, especially in those with testicular volume less than 6 ml. (2 | ☐☐☐☐)

We suggest measurement of bone mineral density by using dual-energy x-ray absorptiometry (DXA) scanning in men with severe androgen deficiency or low trauma fracture. (2 | ☐☐☐☐)
FIG. 1. An approach for the diagnostic evaluation of adult men suspected of having androgen deficiency. FSH = follicle-stimulating hormone; LH = luteinizing hormone; MRI = magnetic resonance imaging; SFA = seminal fluid analysis; SHBG = sex hormone-binding globulin; T = testosterone

1. History and physical (symptoms and signs)
   - Morning Total T
     - Low T 
       - Exclude reversible illness, drugs, nutritional deficiency
       - Repeat T [use free or bioavailable T, if suspect altered SHBG] LH+FSH
         - SFA [if fertility issue]
     - Confirmed low T [Low total T*; or free or bioavailable T**]
       - Low T, low or normal LH+FSH (secondary hypogonadism)
         - Prolactin, iron, other pituitary hormones, MRI
           [under certain circumstances*]
       - Low T, high LH+FSH (primary hypogonadism)
         - Karyotype
           [Klinefelter syndrome]
     - Normal T, LH+FSH
   - Normal T
     - Follow up
WHAT IF I DO THE WORKUP BUT DON'T FIND A CAUSE?
COULD IT BE HIS AGE? 
DOES T DECLINE WITH AGE?

Wu, et al. JCEM 2008
93

600 mg/dl
400 mg/dl
IS HIS WEIGHT TO BLAME?
WHAT IS “LATE-ONSET HYPOGONADISM”?

Basaria S. 

- Age-related decline in testosterone, not due to any clear organic phenomenon
- Aging is associated with fatigue, muscle weakness, sexual dysfunction, obesity and mood changes
- ? cause or effect of declining testosterone
- Studies showing benefit are limited
- Safety studies limited and unclear
- Variable definitions of LOH, many studies using CLIA, single data point, not time specific
- EMAS study - tried to identify symptoms which have a negative correlation with T - only sexual symptoms (decreased sexual thoughts, morning erections, erectile dysfunction)
- No correlation with difficulty climbing stairs, concentration, and 29 others.
Estimated Number of Men with a Prescription Claim for a Testosterone Product from U.S. Outpatient Retail Pharmacies, Stratified According to Age, 2010–2013.

- 20x increase in T sales in the past decade
- Most common ICD code: testicular hypofunction, NOS
- 80% of T users in the US are men ages 40-74
- Average duration of therapy: 6 months
- Health claims data analysis – 28% of men with new rx for Thad no T measurement at all
In young hypogonadal men with classical androgen deficiency syndromes testosterone therapy

- Improves sexual function (esp libido)
- Improves sense of well being/mood
- Increases bone density
- Increases muscle strength
- Decreases fat mass
- ? Improved insulin sensitivity

WHAT ARE THE BENEFITS TO T THERAPY IN YOUNG MEN?
- Decreased fertility
- May stimulate growth of pre-existing breast or prostate cancers
- T may increase Hct > 50%, exacerbate untreated OSA, severe lower urinary tract symptoms, severe CHF

Risks and benefits are not so clear in LOH
Weak evidence that there is some improvement in sexual function

Improvement in sexual function probably less than that seen in PDE inhibitors

DOES T IMPROVE SEXUAL FUNCTION IN LOH?
Erectile function

Sexual desire

Intercourse satisfaction

Orgasmic function

Overall satisfaction

Change in IIEF scores with sildenafil alone or in combination with testosterone or placebo. The study included assessments during week −13, a sildenafil dose-optimization phase (weeks −7 to 0) (shaded areas), and a 14-week post-randomization period. The day of randomization was designated as day 0. Higher IIEF scores reflect better erectile function. IIEF = International Index of Erectile Function.
- **Muscle strength:**
  - Increases muscle strength and lean body mass
- **Cognitive function:**
  - Inconclusive
- **Mood:**
  - Inconclusive
- **Fracture:**
  - Increased lumbar spine BMD, no change at hip, no fracture data
- **Falls:**
  - No data

**WHAT ABOUT OTHER BENEFITS?**
Is there an increased cardiovascular risk with treatment for older men?

Unknown - NO RCT data

FDA reviewed 5 retrospective studies:

- RCS - 2 showed increased risk of CV events, 2 showed decrease overall mortality, 1 showed no change in hospitalization for MI

- MA - One showed increased risk of CV endpoints, the other showed no increased risk

To date, there is no definitive evidence that increasing serum testosterone concentrations in these men is beneficial and safe, and the need to replace testosterone in older men who lack a distinct, well-recognized cause of hypogonadism remains debatable.
"Effects of Testosterone Administration for 3 Years on Subclinical Atherosclerosis Progression in Older Men with Low or Low-Normal Testosterone Levels" by Basaria, et al.

308 men over age 60 with low T (Total 100-400 ng/dl free T < 50)

156 received T gel, 152 received placebo for 3 years, treatment group titrated dose to achieve T levels 500-900 ng/dl.

Measured carotid intima thickness, coronary artery calcium, sexual function, and health-related QOL.

- Sexual function score
  - Erectile Function
  - Orgasmic function
  - Sexual desire
  - Intercourse satisfaction
  - Overall desire

Graph showing total score with 95% CI: 3.1 (-0.5 to 6.6), P = 0.09

Data points for months: 0, 6, 18, 36

Counts: 117, 112, 100, 97, 110, 100, 98, 85
University of Pennsylvania and others

- 800 men ages 65 and older with T < 250
- Randomized to T gel or control, titrating T dose

Outcomes specifically studied:
- Physical function (6 minute walk distance)
- Vitality
- Cognitive function
- Sexual function
- Cardiovascular - change in CAC, sq fat, HOMA-IR, A1c change
- Bone - Volumetric bone density, DEXA
- Anemia
Can age-related changes in testosterone be attenuated by lifestyle intervention? Does weight loss or gain change T?
3369 European men recruited, aged 40-79
2736 followed up 4.4 years later

Camacho, et al.
European Journal of Endocrinology 2013 (168)

2 nmol/L = 58 ng/dl
6 nmol/L = 173 ng/dl
STUDIES OF TESTOSTERONE WEIGHT LOSS IN TYPE 2 DIABETES

Grossman, M 2011 review article in JCEM
Reviewed studies looking at weight loss and T in patients with type 2 diabetes

FIG. 1. Effect of weight loss on testosterone levels. Each data point refers to an individual study, and the size of the data point is proportional to the size of the study, ranging from 10 (87) to 58 men (83); refer to Supplemental Table 1. Numbers correspond to reference numbers as cited in the manuscript. The study by Khoo et al. (84) included two distinct populations of men depicted separately, men with (84a) and men without (84b) diabetes.

Grossman, M JCEM Aug 2011
Testosterone therapy has beneficial effects on several organ systems for men with classical androgen deficiency syndromes.

LOH is a gradual, age-related decline in testosterone, and it is not known whether testosterone therapy in these men is beneficial and safe.

Be sure you have made the right diagnosis, and excluded secondary causes before beginning therapy.

Discuss the unknowns with your patients.

Tune in later!
THE END

THANK YOU
33 Healthy Young Men
Study looking at T as contraception
Treated with T enanthate 200 mg IM weekly


Open bars = pretreatment
Shaded bars = on T enanthate weekly x 20 weeks

TREATMENT SUPPRESSES ENDOGENOUS T PRODUCTION