Primary Care and HIV: A Focus on Hypogonadism

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Disclosures

I have no financial relationships to disclose.
Goals and Objectives

- Outline the proper way to diagnose hypogonadism in male patients with and without HIV infection
- Describe the effects of testosterone replacement therapy
- Discuss potential side effects of testosterone replacement therapy
Polling Question 1

A male is found to have a low testosterone which is confirmed on repeat testing. The next step in the management of this patient is

A. HIV testing
B. Determination of LH and FSH levels
C. Determination of LH and FSH levels and a pituitary/hypothalamic MRI
D. Initiation of testosterone replacement therapy
Case Presentation

- A middle-aged male presents for routine follow up but mentions that he is concerned about erectile function. He also reports generalized fatigue, though he is wondering if this is due to stress at work and age. He asks, “Doc, do I need testosterone? I hear it’ll help me perform better.”
Erectile Dysfunction

- The consistent or recurrent inability to acquire or sustain an erection of sufficient rigidity and duration for sexual intercourse
Prevalence and severity of ED in aging men in MMAS study

Overall prevalence of ED among men aged 40 to 70 years (n = 1290) was 52%.

J Urol 1994;191:54
Case

- What is the general approach?
  - PDE$_5$ inhibitor therapy (sildenafil et al)
  - Reassure (and ignore)
  - Hypogonadism and/or ED questionnaire
  - Testosterone level
PDE$_5$ Inhibitors (e.g., sildenafil)

“Pfizer Inc.'s new impotence drug set a record for the most prescriptions written during its first week on the market, analysts said Monday, making the launch of Viagra the largest in history.”

➤ LA Times, April 21, 1998
Can we escape talking about Erectile Function??
Polling Question 2

What is it with those bathtubs?
A. They are trying to tell you that you need to be clean for the PGE$_5$ inhibitor to work
B. They are promoting safe sex by having the couple in separate bathtubs
C. There is no meaning whatsoever to the bathtubs
D. The tubs are symbols of relaxing, taking your time, not hurrying, in that a bath is more relaxing than a shower.
Erectile Dysfunction

- In addition to age, the best predictors of ED are diabetes mellitus, hypertension, obesity, dyslipidemia, cardiovascular disease, smoking, and medication use. Obstructive sleep apnea is also a risk factor for ED.
“Regular intercourse has an important role in preserving erectile function among elderly men, whereas morning erection had no association. Continued sexual activity decreases the incidence of erectile dysfunction in direct proportion to coital frequency.”

The American Journal of Medicine (2008) 121, 592-596
Countess: *You are a great lover!*
Boris: *I practice a lot when I’m alone.*

-- “Love and Death” 1975
Case

- What is the general approach?
  - PDE$_5$ inhibitor therapy (sildenafil et al)
  - Reassure (and ignore)
  - Hypogonadism and/or ED questionnaire
  - Testosterone level
Reassure and Ignore

- Of course never ignore your patient!
- Reassurance may be all that is needed
  - This can always be reassessed!
Case

- What is the general approach?
  - PDE$_5$ inhibitor therapy (sildenafil et al)
  - Reassure (and ignore)
  - Hypogonadism and/or ED questionnaire
  - Testosterone level
ADAM Questionnaire

1. Do you have a decrease in libido (sex drive)?
2. Do you have a lack of energy?
3. Do you have a decrease in strength and/or endurance?
4. Have you lost height?
5. Have you noticed a decreased "enjoyment of life"
6. Are you sad and/or grumpy?
7. Are your erections less strong?
8. Have you noticed a recent deterioration in your ability to play sports?
9. Are you falling asleep after dinner?
10. Has there been a recent deterioration in your work performance?
Testosterone Therapy in Men With Hypogonadism: An Endocrine Society* Clinical Practice Guideline

Shalender Bhasin,1 Juan P. Brito,2 Glenn R. Cunningham,3 Frances J. Hayes,4 Howard N. Hodis,5 Alvin M. Matsumoto,6 Peter J. Snyder,7 Ronald S. Swerdloff,8 Frederick C. Wu,9 and Maria A. Yialamas10

JCEM 2018;103:1715-1744
Case Finding Questionnaires (including ADAM)

- “Limited information about the performance properties…”
  “Therefore, we suggest clinicians not use the available case finding questionnaires for detecting T deficiency.”

JCEM 2018;103:1715-1744
Case

What is the general approach?
- $\text{PDE}_5$ inhibitor therapy (sildenafil et al)
- Reassure (and ignore)
- Hypogonadism and/or ED questionnaire
- Testosterone level
Testosterone levels and sexual function

JCEM 91:1323–1328, 2006
European Male Aging Study

BMI < 25

BMI 25-30

OBES

JCEM 2006;93:2737
Table 4. Conditions in Which There Is a High prevalence of Low T Concentrations and for Which We Suggest Measurement of Serum T Concentrations

- Pituitary mass, radiation to the pituitary region, or other diseases of the sellar region
- Treatment with medications that affect T production or metabolism, such as opioids and glucocorticoids
- Withdrawal from long-term AAS use
- HIV-associated weight loss
- Infertility
- Osteoporosis or low trauma fracture
- Low libido or erectile dysfunction
Measuring Testosterone:
--not as easy as we hope--

- Reliable assay (liquid chromatography-tandem mass spectrometry is the best, but is more expensive and not routine)
- Diurnal variation
- “Free” versus total levels
Polling Question 3

What method of testosterone measurement is routinely done for your patients?

A. Liquid chromatography-tandem mass spectrometry
B. A commercially available immunoassay kit
C. An assay certified by the CDC Hormone Standardization Program for Testosterone
D. I haven’t the slightest clue
In 2013, AMC Endocrinology and Clinical Chemistry reviewed the AMC CLIA assay performance and established these levels for men. This assay could not determine reliable norms for children and females.

Post op orchiectomy patients
Testosterone: Age and Time of Day

J Clin Endocrinol Metab 1983;56:1278–81
Endocrine Society Recommendations: Testosterone Measurement

“Clinicians should measure total testosterone concentrations on two separate mornings when the patient is fasting…and should use an accurate and reliable method.”
What About Free Testosterone?
Testosterone Metabolism

- Testosterone (T)
- 5α reductase
- Aromatase
- DHT
- E2
- 17 Ketosteroids
- Tissues
- Hepatic inactivation
- Excretion
What About Free Testosterone?

- Consider when SHBG can be altered
- Caveat: most FT levels calculate from total T, so if that assay is not reliable, neither is FT. Best: use equilibrium dialysis. Do not use analog based FT assays
Free & Bioavailable Testosterone calculator

These calculated parameters more accurately reflect the level of bioactive testosterone than does the sole measurement of total serum testosterone. Testosterone and dihydrotestosterone (DHT) circulate in plasma unbound (free approximately 2 - 3%), bound to sex hormone-binding globulin (SHBG) and weakly bound to nonspecific proteins such as albumin. The SHBG-bound fraction is biologically inactive because of the high binding affinity of SHBG for testosterone. Free testosterone measures the free fraction, biologically active plus weakly bound to albumin.

**Albmin**: 4.3 g/dL

**SHBG**: 300 nmol/L

**Testosterone**: 10 ng/dL

Calculate

**Free Testosterone**

**Bioavailable Testosterone**

Explanation and examples

Disclaimer: Results from this calculator should NOT be solely relied upon in making (or refraining from making) any decision in any case/circumstances without the prior consultation of experts or professional persons. No responsibility for correctness or suitability for any given purpose.

WARNING! The calculated free and bioavailable testosterone are reliable in most clinical situations, but should not be relied upon in situations with potential massive interference by steroids binding to SHBG; e.g., in women during pregnancy or inducing high levels of DHT (e.g. transdermal DHT, oral testosterone) or mesterolon

This calculator was developed at the Hormonology department, University Hospital of Gent, Belgium. If you have suggestions to improve this calculator or for further questions or help contact us Dr. Tom Fiers or Prof. Dr. J.M. Kaufman.
HIV and Hypogonadism
“Wasting syndrome in AIDS: pathophysiologic mechanisms and therapeutic approaches”

“Effects of Potent Antiretroviral Therapy on Free Testosterone Levels and Fat-Free Mass in Men in a Prospective, Randomized Trial: A5005s, a Substudy of AIDS Clinical Trials Group Study 384”
- *Clinical Infectious Diseases*, Volume 45, Issue 1, July 2007
Where Are We in 2021?

- HIV has become a chronic comorbidity with an (almost) normal life expectancy
- Multicenter AIDS Cohort Study (MACS) found a rate of hypogonadism of 24.5 in HIV+ versus 7.8% in HIV- individuals*
- SHBG levels appear to be higher in treated HIV+ patients, with no explanations

MACS: Longitudinal Free T levels

- 10 year follow up
- 182 HIV+ vs. 267 HIV- individuals
- Mean age 48.8
Multicenter German 50/2010 Study

- 322 Men > 50
- Three arms: HIV+; HIV- with DM; HIV- without DM
- Testosterone deficiency defined as calculated Free T < 65 pg/mL
- Hypogonadism defined as testosterone deficiency and positive Aging Male Symptoms Survey.

Exp Clin Endocrinol Diabetes. Published online: 2021-01-21
## Results

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>MLWH</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone Deficiency</td>
<td>34.5%</td>
<td>35.0%</td>
<td>44.9%</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>3.5%</td>
<td>7.7%</td>
<td>14.3%</td>
</tr>
</tbody>
</table>

Postel et al. Functional Hypogonadism and Testosterone Deficiency in Aging Males With and Without HIV-infection. *Experimental and Clinical Endocrinology & Diabetes; eFirst*
Results

Total T

SHBG

Controls  MLWH  DM

MLWH  18.9557
Controls  15.4704
T2D  12.6300

MLWH  63.6437
Controls  46.7945
T2D  39.6932
Results

Postel et al. Functional Hypogonadism and Testosterone Deficiency in Aging Males With and Without HIV-infection. *Experimental and Clinical Endocrinology & Diabetes*
Hypogonadism and DM

- Up to 30% of patients with DM may have hypogonadism\(^1\)
- Meta review (43 studies) found testosterone levels on average were 76 ng/ml lower in men with DM than those without\(^2\)

2. Ding et al., JAMA. 2006;295(11):1288
Diagnosis of Hypogonadism (Endo Society)

- Diagnosis requires consistent and unequivocally* low free or total testosterone levels and the presence of symptoms.

* Good assay, no recent illness, etc.

JCEM 2018;103:1715-1744
What next?

- Determine the etiology: is it primary hypogonadism or secondary ("Hypogonadotropic") hypogonadism
HPG Axis

Exogenous Sex Hormones

Inhibins
Sex Steroids

Cortical Input

Brain (hypothalamus)

GnRH

Pituitary

LH, FSH

Gonads
(ovaries, testes)

Sex Hormones

Tissues

(+)

(-)

(+)

(+)

(-)

(-)

(+)

(-)

(+)
Diagnosis of hypogonadism is confirmed

Measure LH and FSH

LH and FSH
low or inappropriately normal
(Secondary hypogonadism)

LH and FSH
high
(Primary hypogonadism)

Consider potentially reversible functional causes, Table 1*
  Measure prolactin, iron saturation
  Evaluate other pituitary hormones (if clinically indicated)
  Pituitary MRI (if indicated)

Obtain karyotype to diagnose Klinefelter syndrome (if clinical indication)

Table 1. Classification of Hypogonadism and Causes of Primary and Secondary Hypogonadism

<table>
<thead>
<tr>
<th>Primary Hypogonadism</th>
<th>Secondary Hypogonadism</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORGANIC</td>
<td></td>
</tr>
<tr>
<td>KS</td>
<td>Hypothalamic/pituitary tumor</td>
</tr>
<tr>
<td>Cryptorchidism, myotonic dystrophy, anorchia</td>
<td>Iron overload syndromes</td>
</tr>
<tr>
<td>Some types of cancer chemotherapy, testicular irradiation/damage, orchidectomy</td>
<td>Infiltrative/destructive disease of hypothalamus/pituitary idiopathic hypogonadotropic hypogonadism</td>
</tr>
<tr>
<td>Orchitis</td>
<td></td>
</tr>
<tr>
<td>Testicular trauma, torsion</td>
<td></td>
</tr>
<tr>
<td>Advanced age</td>
<td></td>
</tr>
<tr>
<td>FUNCTIONAL</td>
<td></td>
</tr>
<tr>
<td>Medications (androgen synthesis inhibitors)</td>
<td>Hyperprolactinemia</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>Opioids, anabolic steroid use, glucocorticoids</td>
</tr>
<tr>
<td>Alcohol and marijuana abuse</td>
<td>Nutritional deficiency/excessive exercise</td>
</tr>
<tr>
<td>Systemic illness*</td>
<td>Severe obesity, some sleep disorders</td>
</tr>
<tr>
<td>Nutritional deficiency/excessive exercise</td>
<td>Organ failure (liver, heart, and lung)*</td>
</tr>
<tr>
<td>Comorbid illness associated with aging*</td>
<td></td>
</tr>
</tbody>
</table>

*Combined primary and secondary hypogonadism, but classified to usual predominant hormonal pattern. Adapted with permission from Bhasin et al. (7).
"Surveys of middle-aged and older men with secondary hypogonadism and sexual dysfunction have revealed a low prevalence of hypothalamic–pituitary abnormalities. ...(consider) performing this procedure (MRI) in men with panhypopituitarism, persistent hyperprolactinemia, serum TT < 150 ng/dL or symptoms of tumor mass effect (e.g., visual impairment, visual field defect, or new onset headache)."
Testosterone Therapy
FIG. 1. All-cause mortality according to deciles of total testosterone adjusting for age, BMI, waist to hip ratio, current smoking, alcohol use, and exercise. The squares represent point estimates for HRs, the lines indicate 95% CIs. The median total testosterone values for deciles 1–10 were 171, 209, 241, 266, 288, 314, 338, 370, 422, and 507 ng/dl, respectively.
Polling Question 4

A man without testicles (and not receiving testosterone) cannot get erections

A. True
B. False
Testosterone and Erectile Function

Sites of action of Testosterone

Testosterone Therapy

- EBM For hypogonadal men (T < 300):
  - Statistically significant, clinically mild improvements in libido and erectile function
  - Increased lean muscle mass, decreased fat mass: for older men, +/- improved fatigue
  - Minor improvements in mood, no discernable benefit to cognitive function

JCEM 2018;103:1715-1744
Figure 1. Prevalence of Androgen Replacement Therapy, by Formulation

- Overall
- Gel
- Injection
- Oral
- Patch

But Then Something Happened

Figure 1. Total and New Testosterone Use Among Men 30 Years or Older in the United States, 2002-2016

JAMA 2018;320:200-202
Vigen et al (JAMA)

- Reported a hazard ratio of 1.29

*JAMA*. 2013;310(17):1829-1836
Testosterone and ASCD

- With much conflicting data, the FDA stated “..the studies presented in the petition have significant limitations that weaken their evidentiary value for confirming a causal relationship..”
- But the FDA did require drug makers to change labeling. The European Medicines Agency did not (2014)
Testosterone and CV Harm?

Figure 1. Total and New Testosterone Use Among Men 30 Years or Older in the United States, 2002-2016

3: FDA communication  4: FDA advisory committee  
5: FDA label change

JAMA 2018;320:200-202
Endocrine Society Guidelines: Testosterone and CV Risks

- Insufficient RCTs to answer the question
- “Most meta-analyses have not shown a significant association between T treatment and CV events, MACE, or deaths”

JCEM 2018;103:1715-1744
Testosterone: Adverse Effects

- Cardiovascular effects?
- Erythrocytosis (Hct > 54%): can be seen, more common in older men.
- Reduced fertility
- Growth of metastatic prostate cancer

JCEM 2018;103:1745-1754
Testosterone and Prostate

- “There is no strong evidence for the association between prostate cancer risk and T concentrations”
- “However, … T administration promotes the growth of metastatic prostate cancer … we recommend against T supplementation in men with prostate cancer and suggest assessing prostate cancer risk prior to treatment.”

JCEM 2018;103:1745-1754
Testosterone and Prostate

- “T therapy does not worsen lower urinary tract symptoms (LUTS) in men who do not have severe LUTS prior to treatment.”
- “We do not know whether T worsens LUTS in men who have severe LUTS at baseline, because such men have been excluded from T trials.”
ES Guidelines: Summary

- Diagnosis of Hypogonadism: ONLY in men with signs and symptoms and unequivocally and consistently low serum total and/or free T concentrations
- Recommend against routine screening in the general population
- Distinguish between primary and secondary causes

*J Clin Endocrinol Metab* 2018;103:1715-1744
ES Guidelines: Summary

- Recommend T therapy in hypogonadal men
  - Caveats: men planning fertility; breast or prostate cancer; palpable prostate nodule or PSA > 4; ↑ Hct; untreated sleep apnea; severe LUTS; recent MI or stroke; uncontrolled heart failure
ES Guidelines: Summary

- T therapy For Older Hypogonadal Men (55-69)
  - “Discuss potential benefits and risks” (specifically prostate)
  - Men over 65: suggest against routinely prescribing T therapy in men with low T. If symptoms are present, individualize

- Monitoring
  - If PSA > 1.4 ng/mL increase, or value > 4.0, urologic consultation
Summary and Final Thoughts

- Treating associated conditions is probably best (diabetes, obesity, narcotic use) but hardest
- HIV positive patients require special consideration in establishing the diagnosis of hypogonadism
Post-test Polling Question (A repeat of question 1)

A male is found to have a low testosterone which is confirmed on repeat testing. The next step in the management of this patient is

A. HIV testing
B. Determination of LH and FSH levels
C. Determination of LH and FSH levels and a pituitary/hypothalamic MRI
D. Initiation of testosterone replacement therapy
HIV - HCV - PrEP - PEP
Clinical Consultations
For Providers in Upstate NY

Call or E-mail for a consultation:
518-262-6864
Monday – Friday 8:00 a.m. – 4:30 p.m.
prokopw@amc.edu

If you have experienced an occupational exposure such as a needle stick, please call 518-262-4043. You will be given an opportunity on the telephone menu to speak to a physician 24 hours a day.