Hypogonadism & “Adrenal Fatigue”

BRYAN PRIMARY CARE CONFERENCE
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Disclosures

- No relevant financial disclosures and no conflicts of interest
How many times a week do you hear an add for “Low T” on TV or Radio?

- A. ONCE
- B. TWICE
- C. THREE TIMES
- D. FOUR TIMES
Objectives

**Diagnosis**
Screening & case detection
Primary vs Secondary
Determining the etiology

**Treatment**
Considerations Prior to Treatment
Potential Adverse Effects
T Replacement Options

**Monitoring**
Timing of Lab Draws
Parameters to follow

What do you do as a provider when asked about "Low T"?

- AACE Guidelines – last updated 2002
- AUA Guideline – Feb 2018
- Endocrine Society Guidelines – May 2018
  - Task force formulated Evidence based recommendations using the best available research.
  - Emphasis: informing the patient of potential benefits & risks of testosterone treatment; the monitoring of treatment; shared decision making; general preventive care measures; and basic principles of androgen deficiency screening, diagnosis, and treatment.
  - Strength of recommendations
    - Strong recommendation – “we recommend”
    - Conditional recommendation - “we suggest”
    - Followed by the quality of evidence 1-4 (1 being low-quality ⇒ 4 high quality)
Who should we be screening for low T?

- *guidelines recommend AGAINST routine screening of men in the general population
- Evidence
  - Lack of consensus on the extent to which hypogonadism is an important public health problem
  - The benefits and risks of long-term T therapy on outcomes in asymptomatic men with low T remain unclear
  - Screening for hypogonadism does not fulfill the necessary criteria to justify population-level screening

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

Adapted with permission from Bhasin et al. (7).
What are the clinical Signs & Symptoms?

Table 3. Symptoms and Signs Suggestive of T Deficiency in Men

<table>
<thead>
<tr>
<th>Specific symptoms and signs</th>
<th>Testosterone levels exhibit diurnal and day-to-day variations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of body hair</td>
<td>Confirm low T - ~30% of men with an initial low T have normal T on repeat measurement</td>
</tr>
<tr>
<td>Reduced testicular volume</td>
<td>*levels can be suppressed by food intake or glucose</td>
</tr>
<tr>
<td>Reduced muscle mass</td>
<td>Measure total T concentrations on two separate mornings when the patient is fasting.</td>
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Diagnosis

- **Unequivocally and Consistently** low serum total testosterone and/or free testosterone concentrations + **clinical symptoms**
  - Testosterone levels exhibit diurnal and day-to-day variations
  - Confirm low T - ~30% of men with an initial low T have normal T on repeat measurement
  - *levels can be suppressed by food intake or glucose

  Symptoms + TWO fasting am low T levels
In men who have conditions that alter sex hormone-binding globulin (SHBG) or Total T is at or near the lower limit, free T should be measured.

Men with normal Free T levels do not require testosterone therapy.

Now that you have made the diagnosis of Low T...
What’s next?

THE WHY?
**Primary Hypogonadism**

- Results in low T concentrations, impairment of spermatogenesis and elevated gonadotropin levels
- Causes of primary hypogonadism:
  - Klinefelter syndrome (KS)
  - cryptorchidism
  - some types of cancer chemotherapy
  - radiation of the tests
  - trauma
  - torsion
  - infections orchitis
  - HIV infection
  - anorchia syndrome
  - myotonic dystrophy

**Secondary Hypogonadism**

- Results in low T concentrations, impairment of spermatogenesis and low or inappropriately normal gonadotropin levels
- Causes of secondary hypogonadism
  - hyperprolactinemia
  - severe obesity
  - iron overload syndromes
  - use of opioids
  - glucocorticoids
  - androgen-deprivation therapy w/GnRH agonist
  - androgenic-anabolic steroid (AAS) withdrawal syndrome
  - idiopathic hypogonadotropic hypogonadism
  - hypothalamic or pituitary tumors or infiltrative disease
  - head trauma
  - pituitary surgery or radiation
Functional Vs Organic - Clinical Implications

Organic hypogonadism: caused by congenital, structural, or destructive disorders resulting in permanent hypothalamic, pituitary, or testicular dysfunction (primary or secondary hypogonadism).

Functional hypogonadism: caused by conditions that suppress gonadotropin and T concentrations but that are potentially reversible with treatment of the underlying etiology.
Case Study

- 55 y/o M  PMH: Hypogonadism, OSA, DM2, HTN, tobacco use, GERD, psoriasis, obesity.
- FH: brother died age 53, had DM2, OSA, was found dead on his couch without CPAP.
- States he hasn’t felt well, lost all the hair on his legs and arms, didn’t feel like he was getting anywhere.
- In January 2018 found low T clinic, filled out online survey, had labs done, states he was told his testosterone was the lowest they’d seen at “7”. Was started on Test 140mg IM q week, anastrazole and oral hcg.
- The patient isn’t sure why his testosterone was so low, he never asked.

What worries you most about this presentation?

- A. The level of his testosterone (7ng/dL)
- B. His history of sleep apnea
- C. The medications he’s being given (Testosterone, HCG, anastrazole)
- D. The patient isn’t sure why his testosterone was so low
Case Study

- Pt presented to ER July 2018 c/o dizziness, arm pain and chest pain.
- 7/16/18: CTH: 1.9x2.3x2.2cm pituitary mass, stalk deviated to the right. 7/16/18: MRI brain: large pituitary mass, some mass effect on inferior margin of optic chiasm, some encroachment/indentation upon cavernous sinus distribution bilaterally.
- 7/18/18 ACTH 17.7, PRL 20.3H**, u osm 823, AM cortisol 6.3, total test 710.5ng/dL (*on exogenous T, last shot 7/9/18), LH 0.5, FSH 2.4, IGF1 25L (61-200), CBC: WBC 13.8H, HGB 13.9, CMP: cr 1.1, ALT 16, TSH 1.2, fT4 1.3ng/dL.
- Patient underwent transphenoidal resection 8/2018.
- 12/14/18 T test 10ng/dL, free T 0.5%, LH 0.8 L, FSH 2.1.

The Why:

Men with secondary hypogonadism require additional diagnostic evaluation to exclude:

- hyperprolactinemia (prolactinoma)
- head trauma
- iron overload syndromes
- hypothalamic or pituitary tumors
- infiltrative or destructive hypothalamic-pituitary diseases
- genetic disorders associated with gonadotropin deficiency – Prader-Willi, Kallmann syndrome
When to get pituitary MRI:

- Consider cost-effectiveness of pituitary imaging
- Surveys of middle age/older men reveal low prevalence of H/P abnormalities
- Severe secondary hypogonadism (e.g., serum T < 150 ng/dL (5.2 nmol/L)
- Panhypopituitarism
- Persistent hyperprolactinemia
- Symptoms or signs of tumor mass effect (such as new-onset headache, visual impairment, or visual field defect) are present.

Considerations Prior to Therapy

- HGB/HCT
  - T increases Hgb/Hct, effects related to dose and circulating concentrations
    - (more so in older men than in young men)
  - The hct level at which the risk of neuro-occlusive or CV events increase is not known, if >54% stop T, evaluate for other causes (OSA, PCV). Periodic phlebotomy a consideration.
- PSA
  - PSA should be measured in men over 40 years of age prior to initiating testosterone therapy to exclude a prostate cancer diagnosis. (Clinical Principle* AUA)
  - Inform patients of the absence of evidence linking testosterone therapy to the development of prostate cancer.
  - Patients with testosterone deficiency and a history of prostate cancer should be informed that inadequate evidence to quantify the risk-benefit ratio of testosterone therapy. (Expert Opinion)
Screen and treat obstructive sleep apnea

- Some symptoms may improve: erectile function, low sex drive, anemia, bone mineral density, lean body mass, and/or depressive symptoms.
- Evidence is inconclusive whether testosterone therapy improves cognitive function, measures of diabetes, energy, fatigue, lipid profiles, and quality of life measures.

Counsel patients that, at this time, it cannot be stated definitively whether testosterone therapy increases or decreases the risk of cardiovascular events.

### Considerations Prior to Therapy

- Untreated severe OSA
- Elevated hematocrit
- MI or stroke within the last 6 months
- Thrombophilia

### Table 7. Conditions in Which T Administration Is Associated With a High Risk of Adverse Outcomes and for Which We Recommend Against Using T

<table>
<thead>
<tr>
<th>Very high risk of serious adverse outcomes</th>
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<tbody>
<tr>
<td>Metastatic prostate cancer</td>
</tr>
<tr>
<td>Breast cancer</td>
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</table>

<table>
<thead>
<tr>
<th>Moderate to high risk of adverse outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unevaluated prostate nodule or induration</td>
</tr>
<tr>
<td>Unevaluated PSA &gt; 4 ng/mL (&gt;3 ng/mL in individuals at high risk for prostate cancer, such as African Americans or men with first-degree relatives who have prostate cancer)</td>
</tr>
<tr>
<td>Hematocrit &gt; 48% (&gt;50% for men living at high altitude)</td>
</tr>
<tr>
<td>Severe LUTS associated with benign prostatic hypertrophy as indicated by AUAI/PPS &gt; 19</td>
</tr>
<tr>
<td>Uncontrolled or poorly controlled congestive heart failure</td>
</tr>
<tr>
<td>Desire for fertility in the near term</td>
</tr>
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Adapted with permission from Bhasein et al. (10).

Abbreviations: AUAI, America Urological Association; IPSS, International Prostate Symptom Score.
Testosterone Therapy: Mode of replacement

<table>
<thead>
<tr>
<th>Topical gels:</th>
<th>Androgel, Fortesta, Testim, Testosterone (generic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical solutions:</td>
<td>Axiron, Testosterone (generic)</td>
</tr>
<tr>
<td>Transdermal patches:</td>
<td>Androderm, Testosterone (generic)</td>
</tr>
<tr>
<td>Intranasal gels:</td>
<td>Natesto</td>
</tr>
<tr>
<td>Buccal tablets:</td>
<td>Striant</td>
</tr>
<tr>
<td>Pellet implants:</td>
<td>Testopel</td>
</tr>
</tbody>
</table>

**ester prodrugs of testosterone in oil solutions for intramuscular injection:**

| Testosterone enanthate | Delatestryl, Testosterone Enanthate (generic) |
| Testosterone cypionate | Depo-Testosterone, Testosterone Cypionate (generic) |
| Testosterone undecanoate | Aveed |

Clomid

- The long-term impact of exogenous testosterone on spermatogenesis should be discussed with patients who are interested in future fertility.
  - Testosterone will suppress GnRH, LH, FSH thereby reducing spermatogenesis.
- Clomid: GnRH Agonist
  - *The efficacy and safety of clomid in hypogonadotropic hypogonadism has not been demonstrated in randomized trials*
Monitoring Men Receiving T Therapy

- Eval T level at 3-12 mos after treatment initiation and then annually to assess whether symptoms have responded to treatment and whether the pt is suffering any adverse effects.
- Ck Hct at baseline, 3-6 mos after starting treatment and then annually.
- If Hct >54%, stop therapy until Hct returns to a safe level, eval for hypoxia and sleep apnea, reinitiate with a reduced dose.
- Measure BMD after 1-2 yrs of T therapy in hypogonadal men w/osteoporosis.
- Men 55-69 yrs & men 40-69 who are at increased risk of prostate cancer (and who choose prostate monitoring), perform DRE and ck PSA level prior to T treatment, and then in accordance w/guidelines for prostate CA screening depending on age and race of pt.

Timing of Lab Draw When Monitoring T Levels

**Monitor T concentrations 3-6 mo after initiation of T therapy.** Therapy should aim to raise serum T concentrations into the mid-normal range.

- Injectable T enanthate or cypionate: measure serum T concentrations midway between injections. If mid-interval T is >600 ng/dl (24.5 nmol/L) or <350 ng/dl (14.1 nmol/L), adjust dose or frequency.
- Transdermal gels: assess T concentrations 2-8 h following the gel application, after the patient has been on treatment for at least 1 wk, adjust dose to achieve serum T concentrations in the mid-normal range.
- Transdermal patches: assess T concentrations 3-12 h after application; adjust dose to achieve T concentration in the mid-normal range.
- Buccal T bioadhesive tablet: assess concentrations immediately before or after application of fresh system. T pellets: measure T concentrations at the end of the dosing interval. Adjust the number of pellets and/or the dosing interval to maintain serum T concentrations in the mid-normal range.
- Oral T undecanoate: monitor serum T concentrations 3-5 h after ingestion with a fat containing meal.
- Injectable T undecanoate: measure serum T levels at the end of the dosing interval just prior to the next injection and aim to achieve nadir levels in low-mid range.

Goal is achieve T levels in the mid-normal range.

Educate patients to have labs drawn at the correct time in order to prevent undue medication adjustment and additional labs.
Would you treat?

- 47 y/o M c/o fatigue, steady weight gain over the past 5 years, low libido requests T level be checked.
- SH: Married, 3 kids, works varying shifts in factory, non smoker
- ROS: endorses fatigue, daytime somnolence, knee pain, otherwise negative.
- Fasting 8am Total testosterone 237ng/dL (250-1100)

Would you do anything else?

- A. Repeat fasting testosterone
- B. Repeat fasting testosterone + SHBG + free testosterone
- C. Do no other testing
Additional Labs

- Repeat fasting 8am total T 242ng/dL (250-1100), free T nl 40.8 (35-155)
- SHBG 19 (10-57)

Would you treat?

- A. YES
- B. NO
The term itself has often been loosely defined as a “weakening or burnout” of the adrenal glands in response to chronic stress.

Unlike the well-recognized disorders of either adrenal insufficiency or Cushing syndrome, *adrenal fatigue* appears to exist as a hybrid condition.

Patients are told that they are suffering from the negative impacts of excess cortisol while also being told that their adrenal glands are unable to effectively produce enough of this hormone.
History of “Adrenal Fatigue”

- Beginning in the 1920s Adrenal Cortical Extract (ACE) from cows and other animals was used to treat Adrenal Insufficiency.
- Once more effective, synthetic purified products became available ACE became obsolete.
- In 1949 Dr. John W Tintera began giving ACE to people as a treatment of hypoadrenalism and hypoglycemia, prescribing it to people who had neither of these diagnoses.
- Symptoms: excessive fatigue, nervousness, irritability, depression, weakness, lightheadedness, faintness, insomnia, HA, inability to concentrate.
- Findings were published in Women’s Day.
- New York Medical Society and Westchester Medical Society advised him to abandon his “hypoglycemia” treatment.
- His ideas continued to be promoted by the Hypoglycemia Foundation (which he founded himself in the 1950s).
- 1968 Journal of the American Medical Association called the ideas promoted erroneous and bizarre.
- 1978 FDA sent letters to 78 drug companies advising them that ACE products risked undertreating true AI due the low potency of these products, which could lead to life threatening complications.

Adrenal Insufficiency

- True Adrenal Insufficiency is a serious disorder.
- Diagnosed by an ACTH stimulation test.
  - Baseline Cortisol followed by 30 and 60 minute cortisol after receiving 250mcg Cortrosyn (synthetic ACTH).
  - Blood levels should rise to >18ug/dL.
- There is no good medical evidence supporting reference ranges of salivary cortisol.
  **with the exception of late night salivary cortisol which we use to screen for Cushing’s Syndrome.**
The Endocrine Society and the Hormone Health Network have published official position statements addressing the issue. These statements clearly describe the symptoms of true disorders of the adrenal gland, and then suggest that patients who believe they are suffering from those symptoms undergo validated testing by an endocrinologist. For the patients who do not have clear symptoms or whose hormonal testing falls into the normal range, most practice guidelines encourage the patients to seek lifestyle approaches to improve stress and wellness. Despite these well-intentioned publications, most patients continue to latch on to the idea of adrenal imbalance, often seeking solace from nonphysician providers or buying glandular supplements on their own.

Is there proof of adrenal dysfunction?

Neurologists and psychiatrists have researched HPA pathways in post-traumatic stress disorder. Patients with trauma have documented evidence of changes in the circadian patterns of cortisol release, elevation of corticotropin-releasing hormone [CRH] in the central nervous system, and alterations in the architecture and neuronal structure of their brains. CRH has been shown to steer the stress response within the sympathetic nervous system and does not respond to traditional negative feedback after exposure to glucocorticoids in extrahypothalamic circuits. Patients who complain of adrenal fatigue may be experiencing chronic stress-related neuronal changes within their limbic system. They may have developed maladaptive neurohormonal responses such that any additional stress or burden feels overwhelming and unbearable to them.
How do I treat my patient?

- Listen to them, get a good history
- Find out what is going on in their day to day lives
- Has there been a traumatic event? What stressors are they facing? Job/kids/health/financial/emotional/mental
- Diet, exercise, sleep, water
- Evaluate for other causes, rule out other medical conditions, vitamin deficiencies, sleep apnea, hypothyroidism, anemia, depression, anxiety, hypogonadism, etc.
- Educate them on the lack of evidence/science regarding “adrenal fatigue” as it is not a true diagnosis, whilst not offending them, dismissing their symptoms or making them feel you don’t care.
- Explain the harm in taking adrenal fatigue supplements (i.e. long term suppression of HPA axis)
- Understand they are suffering and may be desperate to feel better.
- Introduce other forms of treatment

Referral to a behavioral health specialist is beneficial, but may give the patient the message that “it’s all in my head”

There is evidence for the use of several mind-body techniques including meditation, yoga, and tai chi in not only improving a person’s quality of life but also in changing and improving the structure of the brain previously exposed to trauma.

There are small studies that also support other integrative approaches like acupuncture, and herbal remedies in improving fatigue and energy levels in patients with functional somatic disorders and chronic stress.
Summary

- Establish the diagnosis of hypogonadism with two fasting testosterone levels + symptoms
- Determine WHY hypogonadism is present
- Treat functional causes of hypogonadism
- Monitor testosterone levels at appropriate times depending on method of delivery
- Monitor for adverse side effects
- "Adrenal Fatigue" is a not true diagnosis.
- Patients are suffering and symptoms should not be dismissed.
- Patients should be evaluated for other diagnoses that may be causing their symptoms
- Build rapport with your patient, guide them away from potentially harmful supplements and lead them to other forms of symptom management.

References

- Mulhall et al. Evaluation and Management of Testosterone Deficiency: AUA Guideline 2018
References

- [https://hormonesdemystified.com/adrenal-fatigue-a-fraud-perpetrated-on-unsuspecting-patients](https://hormonesdemystified.com/adrenal-fatigue-a-fraud-perpetrated-on-unsuspecting-patients)