Hypogonadism in Men

Alvin B. Lin, MD, FAAFP

ACTIVITY DISCLAIMER

The material presented here is being made available by the American Academy of Family Physicians for educational purposes only. Please note that medical information is constantly changing; the information contained in this activity was accurate at the time of publication. This material is not intended to represent the only, nor necessarily best, methods or procedures appropriate for the medical situations discussed. Rather, it is intended to present an approach, view, statement, or opinion of the faculty, which may be helpful to others who face similar situations.

The AAFP disclaims any and all liability for injury or other damages resulting to any individual using this material and for all claims that might arise out of the use of the techniques demonstrated therein by such individuals, whether these claims shall be asserted by a physician or any other person. Physicians may care to check specific details such as drug doses and contraindications, etc., in standard sources prior to clinical application. This material might contain recommendations/guidelines developed by other organizations. Please note that although these guidelines might be included, this does not necessarily imply the endorsement by the AAFP.
DISCLOSURE

It is the policy of the AAFP that all individuals in a position to control content disclose any relationships with commercial interests upon nomination/invitation of participation. Disclosure documents are reviewed for potential conflict of interest (COI), and if identified, conflicts are resolved prior to confirmation of participation. Only those participants who had no conflict of interest or who agreed to an identified resolution process prior to their participation were involved in this CME activity.

All individuals in a position to control content for this session have indicated they have no relevant financial relationships to disclose.

The content of my material/presentation in this CME activity will include discussion of unapproved or investigational uses of products or devices as indicated:

- Discussion of AUA's stance to use aromatase inhibitors, human chorionic gonadotropin, selective estrogen receptor modulators, or any combination of above to treat men with testosterone deficiency who desire to maintain fertility.

Alvin B. Lin, MD, FAAFP

Physician, Solo private practice, Las Vegas, Nevada

Dr. Lin completed his medical degree at the Bowman Gray School of Medicine (now the Wake Forest School of Medicine) in Winston-Salem, North Carolina, and completed his family medicine residency at Merrithew Memorial Hospital, Martinez, California, which is part of the UC Davis School of Medicine network of affiliated residency programs. For three years, he gained experience as a locum tenens physician, working under a dozen state licenses. He completed a fellowship in geriatric medicine at Pitt County Memorial Hospital, Greenville, North Carolina, in conjunction with the Brody School of Medicine at East Carolina University, and then joined the faculty for five years. Subsequently, he was recruited to advance the science of hypogonadism and healthy aging in a private, cash-based practice in Las Vegas, Nevada. He restarted his academic career part-time at the University of Nevada School of Medicine (now the UNLV School of Medicine) and then joined the full-time faculty in 2010, advancing to associate professor of family medicine from 2012 to 2016. In October 2016, Dr. Lin made the leap to solo practice. He lectures for the Nevada Academy of Family Physicians, chairs the AAFP’s Geriatric Medicine Live Course, and serves as faculty for the AAFP’s Care of Chronic Conditions Live Course and for various Knowledge Self-Assessments (KSAs).
Learning Objectives

1. Recognize the pathophysiology and the classification of primary and secondary hypogonadism, as well as the causes of HG associated with each classification.

2. Diagnose HG by appropriate laboratory testing, understand when differential diagnosis is required, when to order an MRI as indicated in men with secondary HG, when to order pituitary imaging, when to order bone densitometry studies, and when to refer to an endocrinologist.

3. Recognize and manage HG comorbidities.

4. Develop treatment plans that consider complications of treatments for other conditions, and that include monitoring and follow-up.

Audience Engagement System

Step 1

Step 2

Step 3
Recognize the pathophysiology and the classification of primary and secondary hypogonadism, as well as the causes of HG associated with each classification

AES Question #1

Examples of primary hypogonadism include

a) Klinefelter’s syndrome
b) Kallman syndrome
c) Mumps orchiectomy
d) Androgen deprivation therapy
e) Both a) & c)
Definitions & Pathophysiology

• Male hypogonadism
  – Inadequate production of testosterone leading to clinical symptoms
  – Timing
  – Etiology

Definitions & Pathophysiology

• Male hypogonadism
  – Inadequate production of testosterone
  – Timing
    • Congenital
      – Klinefelter syndrome (XXY)
    • Acquired
  – Etiology
Definitions & Pathophysiology

• Male hypogonadism
  – Inadequate production of testosterone
  – Timing
    • Congenital
    • Acquired
      – Puberty
      – Adulthood
  – Etiology

• Male hypogonadism
  – Inadequate production of testosterone
  – Timing
  – Etiology
    • Primary
    • Secondary
Congenital

• For whatever reason, if not enough testosterone during fetal development, genetic male may present with
  – Female genitalia
  – Ambiguous genitals
  – Underdeveloped male genitals

Puberty

• Inadequate or lack of testosterone in puberty can manifest as
  – Decreased development of muscle mass
  – Lack of deepening of voice
  – Lack of male pattern hair distribution
  – Decreased development of penis & testicles
  – Development of breast tissue (gynecomastia)
Adulthood

• Inadequate or lack of testosterone in adulthood can manifest as
  – Erectile dysfunction
  – Infertility
  – Decrease in beard & body hair
  – Decrease in muscle mass
  – Development of breast tissue (gynecomastia)
  – Loss of bone mass (osteoporosis)

Adulthood

• Inadequate or lack of testosterone in adulthood can also manifest as
  – Fatigue
  – Decrease in sex drive
  – Difficulty concentrating
  – Hot flashes
Primary Hypogonadism

• aka primary testicular failure
  – Congenital
  – Acquired

  • Klinefelter syndrome (XXY)
  • Undescended testicle (if not corrected early on)

– Acquired
Primary Hypogonadism

• aka primary testicular failure
  – Congenital
  – Acquired
    • Chemotx or XRT
    • Hemochromatosis & other liver disease esp EtOH
    • Injury
    • Mumps orchitis

Secondary Hypogonadism

• Testicular malfunction due to pituitary or hypothalamic issue
  – Congenital
  – Acquired
Secondary Hypogonadism

• Testicular malfunction due to pituitary or hypothalamic issue
  – Congenital
    • Kallmann syndrome
      – Hypothalamic malfunction
      – Look for hyposmia or anosmia
  – Acquired

Secondary Hypogonadism

• Testicular malfunction due to pituitary or hypothalamic issue
  – Congenital
  – Acquired
    • Inflammatory diseases
      – Histiocystosis
      – Sarcoidosis
      – Tuberculosis
Secondary Hypogonadism

- Testicular malfunction due to pituitary or hypothalamic issue
  - Congenital
  - Acquired
    - Medications
      - Androgen deprivation therapy
      - Opioids
      - Spironolactone

- Obesity
- Pituitary tumor
  - Also surgery or XRT for other brain tumors
Secondary Hypogonadism

- Testicular malfunction due to pituitary or hypothalamic issue
  - Congenital
  - Acquired
    - Concurrent illnesses
    - HIV/AIDS
    - Normal aging!

Diagnose HG by appropriate laboratory testing, understand when differential diagnosis is required, when to order an MRI as indicated in men with secondary HG, when to order pituitary imaging, when to order bone densitometry studies, and when to refer to an endocrinologist.
AES Question #2

Differential diagnosis for hypogonadism includes

a) Depression
b) Hemochromatosis
c) Marijuana use
d) Opioid use
e) All of the above

Differential Diagnosis

- Anemia
- Depression
- Diabetes
- Hemochromatosis
- Hypothyroidism
- Life stressors

- Medications
  - Androgen deprivation tx
  - Opioids
  - Spironolactone
- Obesity
- Poor health habits
  - Alcohol & marijuana abuse
Primary vs Secondary Hypogonadism

• In the presence of low testosterone
  – 1o hypogonadism = elevated FSH & LH
    • Primary testicular failure so pituitary sending lots of signal to testicles which aren’t responding
  – 2o hypogonadism = low to normal FSH & LH
    • Testicles underperforming b/c not receiving enough signal to produce testosterone and/or sperm

Choosing Wisely

• Don’t prescribe testosterone therapy unless there is biochemical evidence of testosterone deficiency
  – Endocrine Society 10/16/13
Choosing Wisely

• Don’t prescribe testosterone therapy unless there is laboratory evidence of testosterone deficiency
  – American Society for Clinical Pathology 2/3/15

Choosing Wisely

• Don’t prescribe testosterone or testosterone products to men contemplating/attempting to initiate pregnancy
  – American Society for Reproductive Medicine 4/13/15
Choosing Wisely

• Don’t prescribe testosterone to men with erectile dysfunction who have normal testosterone levels
  – American Urological Association 2/21/13
  – Updated 5/9/16, 5/26/17 & 7/9/18

AES Question #3

To meet laboratory guidelines for hypogonadism, you must know
  – 1) which laboratory performed test
  – 2) how laboratory performed test
  – 3) when laboratory performed test
  – 4) all of the above
What’s in a name?

• Total Testosterone

• Free Testosterone
  – Total T minus (SHBG bound T) minus (albumin bound T)

• Bioavailable Testosterone
  – Total T minus (SHBG bound T)

You Say To-may-toe, I Say To-mah-toe

• ARUP Electrochemiluminescence Immunoassay (ECLIA)
  – 300-1080ng/dL 18-39yo M
  – 300-890ng/dL 40-59yo M
  – 300-720ng/dL >60yo M

• LabCorp ECLIA
  – 264-916ng/dL >18yo M
  – 348-1197ng/dL >19yo M (same URL referenced in 2017)
You Say To-may-toe, I Say To-mah-toe

• Quest Immunoassay
  – 250-827ng/dL adult M
• Quest LC/MS/MS
  – 250-1100ng/dL >18yo M

Circadian Rhythm

• Testosterone level
  – Peaks in AM
    • Screening is most accurate before 10AM (test time often mandated by athletic commissions)
  – Varies from day-to-day
    • Endocrine Society recommends obtaining 2 results prior to starting therapy
When to order a pituitary MRI?

• Obtain pituitary imaging to exclude pituitary and/or hypothalamic tumor or infiltrative disease if
  – Severe 2o hypogonadism w/T <150ng/dL
  – Panhypopituitarism
  – Persistent hyperprolactinemia

*J Clin Endocrinol Metab. May 2018; 103(5):1-30*

When to order a pituitary MRI?

• Obtain pituitary imaging to exclude pituitary and/or hypothalamic tumor or infiltrative disease if
  – Symptoms or signs of tumor mass effect
    • New-onset headache
    • Visual impairment
    • Visual field defect

*J Clin Endocrinol Metab. May 2018; 103(5):1-30*
When to order a DEXA?

- Measure bone mineral density of lumbar spine and/or femoral neck after 1-2yr of TRT in hypogonadal men w/osteoporosis

*J Clin Endocrinol Metab.* May 2018; 103(5):1-30

When to call the Urologist?

- Obtain urologic consultation if
  - PSA incr >1.4ng/mL within 12mo of initiating TRT
    - Expect incr of 0.3ng/mL in younger men, 0.44ng/mL if older
  - PSA confirmed >4ng/mL at any time
  - Digital rectal examination detects prostate abnormality
  - Substantial worsening of LUTS

*J Clin Endocrinol Metab.* May 2018; 103(5):1-30
Develop treatment plans that consider complications of treatments for other conditions, and that include monitoring and follow-up.

AES Question #4

Which of the following is/are true?

a) Injectable testosterone is the best form of TRT
b) TRT may be offered to men who are contemplating future fertility in the near term
c) TRT may be offered to men w/PSA >4 prior to evaluation
d) Oral TRT is a safe & viable option
e) None of the above
TRT Pros & Cons

- Buccal
  - Expensive & it’s a pinch btwn cheek & gum
- Cream/gel
- Injection
- Oral
- Patch
- Pellet
TRT Pros & Cons

- Buccal
- Cream/gel
  - Expensive, messy & *transference*
  - No peak & trough
  - Some are site specific ie axilla or thigh
- Injection
- Oral
- Patch
- Pellet

TRT Pros & Cons

- Buccal
- Cream/gel
- Injection
  - Cheap but (potentially) painful!
  - Need to worry about peak & trough effect
- Oral
- Patch
- Pellet
TRT Pros & Cons

- Buccal
- Cream/gel
- Injection
- Oral
  - Liver toxicity esp peliosis hepatis
  - SO DON’T PRESCRIBE THIS
- Patch
- Pellet

TRT Pros & Cons

- Buccal
- Cream/gel
- Injection
- Oral
- Patch
  - Expensive + adhesive dermatitis
  - No peak & trough effect
- Pellet
TRT Pros & Cons

• Buccal
• Cream/gel
• Injection
• Oral
• Patch
• Pellet
  – Not cheap plus difficult to adjust dose
  – Infection & extrusion

New Kids on the Block

• Testosterone Cypionate & Enanthate (old school)
  – Inject 75-100mg/wk or 150-200mg/2wk
• Testosterone UNDECANOATE (new school)
  – Inject 750mg
  – Followed by 750mg 4wk later
  – Then 750mg q10wk
  – Restricted distribution

*J Clin Endocrinol Metab. May 2018; 103(5):1-30*
New Kids on the Block

• Nasal Testosterone
  – 5.5mg/pump
  – 1 pump each nostril TID
  – Max 6 pumps/d
  – Adjust dosing based upon T level achieved

When to avoid using TRT

• Use of TRT is associated w/very high risk of serious adverse outcomes in
  – Metastatic prostate CA
  – Breast CA
When to avoid using TRT

• Use of TRT is associated w/moderate to high risk of adverse outcomes in
  – Unevaluated prostate nodule or induration
  – Unevaluated PSA >4ng/mL
    • >3ng/mL in those at high risk
      – African American
      – Men w/1st degree relatives w/prostate CA
  – Severe LUTS w/AUA/IPPS >19

J Clin Endocrinol Metab. May 2018; 103(5):1-30

When to avoid using TRT

• Use of TRT is associated w/moderate to high risk of adverse outcomes if
  – Hematocrit >48%
    • >50% for men living at high altitude
  – Uncontrolled or poorly controlled congestive heart failure
  – Desire for fertility in near term

J Clin Endocrinol Metab. May 2018; 103(5):1-30
How to monitor TRT

• Evaluate at 3-12mo after treatment initiation and then annually to assess whether symptoms have responded to treatment and whether patient is suffering from any adverse events

J Clin Endocrinol Metab. May 2018; 103(5):1-30

How to monitor TRT

• Monitor T concentration 3-6mo after initiating TRT
  – Therapy should aim to raise serum T concentration into mid-normal range
  – If using
    • Injectable T cypionate or enanthate: measure serum T concentration midway btwn injections & adj dose/freq if >600ng/dL

J Clin Endocrinol Metab. May 2018; 103(5):1-30
How to monitor TRT

• Monitor T concentration 3-6mo after initiating TRT
  – Therapy should aim to raise serum T concentration into mid-normal range
  – If using
    • Injectable T undecanoate: measure serum T concentration at end of dosing interval just prior to next injection; aim for nadir in low-mid range

J Clin Endocrinol Metab. May 2018; 103(5):1-30
How to monitor TRT

• Monitor T concentration 3-6mo after initiating TRT
  – Therapy should aim to raise serum T concentration into mid-normal range
  – If using
    • Buccal tablet: measure serum T concentration immediately before or after application of fresh tablet
    • Pellets: measure serum T concentrations at end of dosing interval & adj number of pellets and/or dosing interval

How to monitor TRT

• Check hematocrit at baseline, 3-6mo after starting treatment, and then annually
• If hematocrit >54%, stop TRT until hematocrit decr to safe level
  – Evaluate for hypoxia & sleep apnea
  – Reinitiate at reduced dose
How to monitor TRT

• For men 55-69yo (and for those 40-69yo at incr risk for prostate cancer),
  – Perform digital rectal examination & check PSA before initiating treatment
  – Perform digital rectal examination & check PSA 3-12mo after initiating treatment
  – And then in accordance w/prostate cancer screening guidelines for age & race

And in this corner . . .
AES Question #5
We should screen all men for hypogonadism
a) True
b) False

AES Question #6
We should routinely offer TRT to all hypogonadal men
a) True
b) False
Summary of Endocrine Society Guidelines

• Recommend diagnosing hypogonadism in men with symptoms & signs of testosterone deficiency and unequivocally & consistently low serum total T and/or free T concentrations
• Recommend AGAINST routine screening of general population for hypogonadism

J Clin Endocrinol Metab. May 2018; 103(5):1-30

Summary of Endocrine Society Guidelines

• In men with hypogonadism,
  – Distinguish between primary (testicular) and secondary (pituitary-hypothalamic) hypogonadism by measuring LH & FSH
  – Evaluate further to identify etiology of hypothalamic, pituitary and/or testicular dysfunction

J Clin Endocrinol Metab. May 2018; 103(5):1-30
Summary of Endocrine Society Guidelines

• Recommend TRT in hypogonadal men to induce & maintain secondary sex characteristics and to correct symptoms of T deficiency

Summary of Endocrine Society Guidelines

• Recommend AGAINST TRT in men planning fertility in near term
• Recommend AGAINST TRT in men with
  – Breast or prostate CA
  – PSA >4ng/mL (or >3ng/mL in high risk)

*J Clin Endocrinol Metab. May 2018; 103(5):1-30*
Summary of Endocrine Society Guidelines

• Recommend AGAINST TRT in men with
  – Elevated hematocrit
  – Untreated severe obstructive sleep apnea
  – Severe LUTS
  – Uncontrolled heart failure
  – Myocardial infarction or stroke in last 6mo
  – Thrombophilia

*J Clin Endocrinol Metab. May 2018; 103(5):1-30*

Summary of Endocrine Society Guidelines

• Recommend AGAINST routinely prescribing TRT to all men >65yo w/low T concentration
• Recommend offer TRT on individualized basis to men >65yo w/low T concentration plus symptoms/conditions suggestive of testosterone deficiency
• Recommend AGAINST TRT for men w/T2DM as means to improve glycemic control

*J Clin Endocrinol Metab. May 2018; 103(5):1-30*
Summary of Endocrine Society Guidelines

• Recommend assessing for response to treatment, if suffering from adverse effects, and if complying w/treatment regimen

J Clin Endocrinol Metab. May 2018; 103(5):1-30

And in the other corner . . .
AES Question #7

Clinical diagnosis of hypogonadism can be made if

a) No signs/symptoms of low T and normal T level
b) Signs/symptoms of low T and lab-defined low T
c) Signs/symptoms of low T and normal T level
d) No signs/symptoms of low T and lab-defined low T

AUA Guideline

- Use total T < 300ng/dL as reasonable cut-off for diagnosis of low T
- Measure total T on two separate early mornings
- Clinical diagnosis of testosterone deficiency is made only if patients have BOTH low T and signs/symptoms of low T

AUA Guideline

• Consider measuring total T in patients w/
  – Unexplained anemia
  – Bone density loss
  – Diabetes
  – Exposure to chemotx
  – Exposure to testicular radiation
  – HIV/AIDS
  – Chronic narcotic use


AUA Guideline

• Consider measuring total T in patients w/
  – Male infertility
  – Pituitary dysfunction
  – Chronic corticosteroid use
  – Even in the absence of signs/symptoms associated w/testosterone deficiency

AUA Guideline

- Validated questionnaires are not currently recommended to either define patients as candidates for TRT or to monitor symptom response in patients on TRT
- In patients w/low T, measure LH
- In patients w/low T & low/normal LH, measure prolactin

*J Urol. Aug 2018;200(2):423-432*

AUA Guideline

- Low T is a risk factor for cardiovascular disease
  - Yet it’s unclear whether TRT incr or decr risk of cardiovascular events
  - TRT should not be initiated for 3-6mo after cardiovascular event

*J Urol. Aug 2018;200(2):423-432*
AUA Guideline

• TRT may result in improvement in
  – Erectile function
  – Low sex drive
  – Anemia
  – Bone mineral density
  – Lean body mass
  – Depression


AUA Guideline

• Evidence is inconclusive whether TRT improves
  – Cognitive function
  – Diabetes
  – Energy
  – Fatigue
  – Lipids
  – Quality of life

AUA Guideline

- Absence of evidence linking TRT to development of prostate CA
- Inadequate evidence to quantify risk:benefit ratio for TRT use in those w/history of prostate CA
- No definitive evidence linking TRT to higher incidence of VTE

AUA Guideline

- Do not prescribe alkylated oral T
- May use aromatase inhibitors, human chorionic gonadotropin, selective estrogen receptor modulators, or any combination of above to treat men w/T deficiency who desire to maintain fertility
- Prescribe commercially available TRT rather than compounded TRT whenever possible

AUA Guideline

- Consider cessation of TRT 3-6mo after commencement in those who experience normalization of total T but fail to achieve sign/symptom improvement

*J Urol.* Aug 2018;200(2):423-432

Best Practice Recommendations
Best Practice Recommendations

• Male hypogonadism is a clinical diagnosis supported by laboratory values
• Evaluation for male hypogonadism should not be started until differential diagnosis has been exhausted

Best Practice Recommendations

• Testosterone replacement therapy should be individualized per patient preferences
• Testosterone replacement therapy must be closely monitored on a regular basis
• Don’t use compounded bio-identical hormone replacement
References

• General Info
  – https://arupconsult.com/content/hypogonadism-male
  – https://labtestsonline.org/understanding/analytes/testosterone/tab/glance/

• ARUP Total Testosterone

• LabCorp Total Testosterone
  – http://bit.ly/LabCorpTestosterone

References

• Quest Total Testosterone Immunoassay
  – http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=30741

• Quest Total Testosterone LC/MS/MS
  – http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=36170
Questions

Contact Information

Alvin Lin
alvinblin@gmail.com