SMSNA Hypogonadism Colloquium: Update

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Objectives

- To review the concept and purpose of the SMSNA White Paper: Adult Onset Hypogonadism (AOH)

- To enhance understanding of hypogonadism as a clinical health problem requiring proper recognition and management
Sexual Medicine Society of North America Colloquium on Adult Onset Hypogonadism AOH

- Convened in Washington DC, August 2015
- Consisted of experts in men’s health, sexual medicine, urology, endocrinology and methodology (members and non-members of the SMSNA)
- Purposed to create a document describing AOH as a clinical syndrome that can be rigorously evaluated and properly treated
SMSNA Colloquium on Adult Onset Hypogonadism
Participants (18 experts)

- Mohit Khera, MD, MBA MPH
- Shehzad Basaria, MD
- Gregory A. Broderick, MD
- Culley C. Carson III, MD
- Adrian S. Dobs, MD, MHS
- Martha M. Faraday, PhD
- Irwin Goldstein, MD
- Lawrence S. Hakim, MD
- Wayne J. G. Hellstrom, MD
- Ravi Kacker, MD
- Tobias S. Köhler, MD, MPH
- Jesse N. Mills, MD
- Martin Miner, MD
- Hossein Sadeghi-Nejad, MD
- Allen D. Seftel, MD
- Ira D. Sharlip, MD
- Stephen J. Winters, MD
- Arthur L. Burnett, MD, MBA
SMSNA Colloquium on Adult Onset Hypogonadism: Process

- All participants declared potential conflicts of interest
- The colloquium was funded by the SMSNA Foundation with an educational grant from Repros Therapeutics Inc. (NB: no industry participation in the evidence selection, discussion or creation of the document)
- Literature was reviewed as evidence and critiqued by colloquium participants
- Participants delivered presentations and contributed written compositions
- Document was assembled by a principal writing team and submitted through peer-review process of evaluation and publication (now accepted in Mayo Clinic Proceedings)
Description of the Health Problem

- Clinical scenario of men who present with low testosterone and associated signs and symptoms accompanied by low or normal gonadotropin levels

- This clinical “syndrome” is distinct from classical primary (testicular failure) or secondary (pituitary or hypothalamic failure) hypogonadism, possibly having elements of both classical presentations

- This syndrome is designated Adult Onset Hypogonadism (AOH) because it occurs commonly in men of middle-age and older

- A conceptual framework for this syndrome will guide its diagnosis, treatment and follow-up
Characteristics of Secondary, Primary, and Compensated Hypogonadism in Aging Men: Evidence from the European Male Aging Study

- **Primary Hypogonadism**
  - \( TT < 10.4 \text{ nmol/L} \) (300 ng/dl)
  - \( LH > 9.4 \text{ U/L} \)

- **Secondary Hypogonadism**
  - \( TT < 10.4 \text{ nmol/L} \)
  - \( LH < 9.4 \text{ u/L} \)

- **Eugonadal**
  - \( TT > 10.4 \text{ nmol/L} \)
  - \( LH < 9.4 \text{ U/L} \)

- **Compensated Hypogonadism**
  - \( TT > 10.4 \text{ nmol/L} \)
  - \( LH > 9.4 \text{ u/L} \)

Men classified as having secondary hypogonadism with low \( T \) accompanied by low or normal \( LH \) manifest a presentation consistent with AOH.
These co-morbidities are difficult to separate from the influence of aging, but they may not be solely an aging phenomenon.
Diagnosis

Signs/symptoms of AOH, particularly poor morning erection, low sexual desire, erectile dysfunction (Wu et al., 2010); other possible symptoms include reduced muscle mass, increased body fat, fatigue, decreased concentration/memory, osteopenia/porosis, gynecomastia, reduced sexual hair, hot flashes; NOTE: delay work-up if patient recovering from acute/subacute illness

History, physical examination, and morning total testosterone (TT; by reliable assay)

Low or borderline low T (e.g., T<280-300 ng/dl or lower limit in reference laboratory)

Exclude drug effects, other known causes of low T; Repeat morning TT (by reliable assay) + LH/FSH, SHBG; if SHBG abnormality suspected or T is borderline low, then measure free T or bioavailable T

Normal Hx and physical exam; Normal T (T>280-300 ng/dl)

No AOH; seek other causes

Confirmed low T with low bioavailable T; assess PRL; pituitary work up (i.e., MRI) if total T<150 ng/dl

Low T w/ low or normal LH+FSH = AOH; exclude TRT contraindications (e.g., elevated Hct, breast Ca, severe sleep apnea, severe cardiac failure); begin TRT w/ lifestyle modifications; Investigate for T2DM, HL, NAFLD; manage if present

High LH+FSH, normal PRL = primary hypogonadism

Exclude contraindications for TRT (e.g., elevated hematocrit, breast Ca, severe sleep apnea, severe cardiac failure)

Low/normal LH+FSH; elevated PRL

Investigate pituitary + other causes (e.g., iron studies, other AP hormones; MRI if symptoms of mass effect or TT<150 ng/dl)

No identifiable cause; exclude TRT contraindications

Identified cause

TRT w/ lifestyle modifications and comorbidity management

Successful; monitor TT, FBC

Failure; review diagnosis

TRT with lifestyle modifications and comorbidity management

Manage or refer
Treatment and Follow-Up

Man with AOH signs/symptoms AND repeatedly low TT AND documented LH+FSH values; contraindications to TRT excluded; lifestyle modifications discussed as necessary; presence of comorbidities requiring management evaluated

 Desire to maintain fertility

 Stimulation of endogenous T secretion (if LH not elevated); SERM or hCG

 Follow-up at 3 and 6 mos, then annually; signs/symptoms, weight, TT, Hct, PSA; at 6 mos; if total T < 400 ng/dL and no improvement, then consider dose increase with reassessment in another 3-6 mos;

 If hematocrit > 54%, then stop TRT until Hct decreases to safe level; evaluate for hypoxia and sleep apnea; reinstate TRT at reduced dose

 Measure BMD of lumbar spine and/or femoral neck after 1-2 y of TRT in men w/ osteoporosis or low trauma fracture

 In men aged ≥40 years w/ baseline PSA > 0.6 ng/ml, perform DRE and check PSA before TRT, at 3 to 6 mos, and then based on prostate cancer screening guidelines

 Evaluate formulation-specific adverse events at each follow-up visit

 Not improved after 3-6 mos; consider discontinuation; search for other causes/treatments

 No desire to maintain fertility

 TRT after discussion regarding risks/benefits of various formulations
FDA Drug Safety Communication: FDA cautions about using testosterone products for low testosterone due to aging; requires labeling change to inform of possible increased risk of heart attack and stroke with use.

This information is an update to the FDA Drug Safety Communication: FDA Evaluating Risk of Stroke, Heart Attack, and Death with FDA-Approved Testosterone Products issued on January 31, 2014.

Safety Announcement

[03-03-2015] The U.S. Food and Drug Administration (FDA) cautions that prescription testosterone products are approved only for men who have low testosterone levels caused...
FDA Drug Safety Communication

- Required Label Changes
  - Clarify the approved uses of testosterone meds
  - Add information about a possible increased risk of heart attacks and strokes in patients taking testosterone
- FDA concerned about TRT to relieve symptoms in men who have low T for no apparent reason other than aging
- Requiring manufacturers of approved TRT products to conduct well-designed trial
FDA Drug Safety Communication

- TRT Approved for Use
  - Primary Testis Failure
    - Genetics or Chemotherapy Damage
  - Secondary Hypogonadism
    - Hypothalamus or Pituitary Failure

- Safety and Efficacy of TRT for Age-Related Hypogonadism not established

- Diagnosis of Hypogonadism
  - At least 2 separate morning lab tests
FDA Drug Safety Communication

- Weigh potential risk of major adverse CV outcome and other risks against benefit for each patient
- Inform patients of potential increased CV risk
- Encourage patients to read Medication Guide
- Report adverse events involving TRT to FDA
Consensus Statement

Adult Onset Hypogonadism (AOH) is a measurable syndrome characterized by low T, associated symptoms, and low or normal gonadotropin levels. Men with AOH who are candidates for treatment with T should be counseled regarding the benefits and risks of treatment. Patients who are treated should be monitored regularly.