

ENDO 2018

THE ENDOCRINE SOCIETY'S 100TH ANNUAL MEETING & EXPO

Testosterone Therapy in Men with Hypogonadism: An Endocrine Society Clinical Practice Guideline

Guideline Overview & Case Discussions

Clinical Guideline Authors

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Plenary Panel

Ann Danoff, MD (*Endocrine Society Annual Meeting Steering Committee, Clinical Chair*)

Brad Anawalt, MD (*Session Moderator*)

Shalender Bhasin, MD (*Panelist*)

Glenn Cunningham, MD (*Panelist*)

Alvin Matsumoto, MD (*Panelist*)

Maria Yialamas, MD (*Panelist*)

Plenary Format

1. Overview of Testosterone Guidelines (Dr. Bhasin)
2. Case #1: Diagnosis of Male Hypogonadism (Dr. Matsumoto)
 - a. 2 multiple choice questions with audience response
 - b. Panel discussion of diagnosis case
 - c. Q&A related diagnosis of male hypogonadism
 - *Audience may submit questions re diagnosis of male hypogonadism at any time during first case*
3. Case #2: Treatment of Male Hypogonadism (Dr. Cunningham)

Same format as Case #1
4. Case #3 Monitoring During Testosterone Therapy (Dr. Yialamas)

Same format as Case #1

Overview of Testosterone Guidelines

Shalendar Bhasin, MD

Guideline Development Process and Values

- The ES selected the expert panel and its Chair.
- The panel included a cardiologist (Hodis), primary care expert (Yialamas), and a member of the European Academy of Andrology (Wu).
- The panel worked by consensus – items on which there was strong disagreement were generally not included.
- Evidence-based recommendations followed the *Grading of Recommendations, Assessment, Development, and Evaluation (GRADE)* approach.
- In addition to the evidence, the task force considered “values”
 - Greater emphasis on shared decision-making in the decision to treat and perform prostate monitoring
 - “*Primum non nocere*”

Systematic Reviews and Meta-Analyses

Unique aspects of the systematic reviews:

- Included trials that recruited men who met the ES criteria for the diagnosis of hypogonadism
- Focus on outcomes that were clinically relevant, patient-important, and ascertained using validated instruments
- Included recent large controlled trials of TRT including the TTrials

Efficacy:

- Significant improvement in libido, erectile function & sexual activity
- No statistically significant difference in energy or mood
- Benefits in correcting unexplained and explained anemia and volumetric bone density of the spine and hip (TTrials data)

Safety:

- Significantly higher frequency of erythrocytosis (hematocrit >54%)
- No significant change in lower urinary tract symptoms

Diagnosis

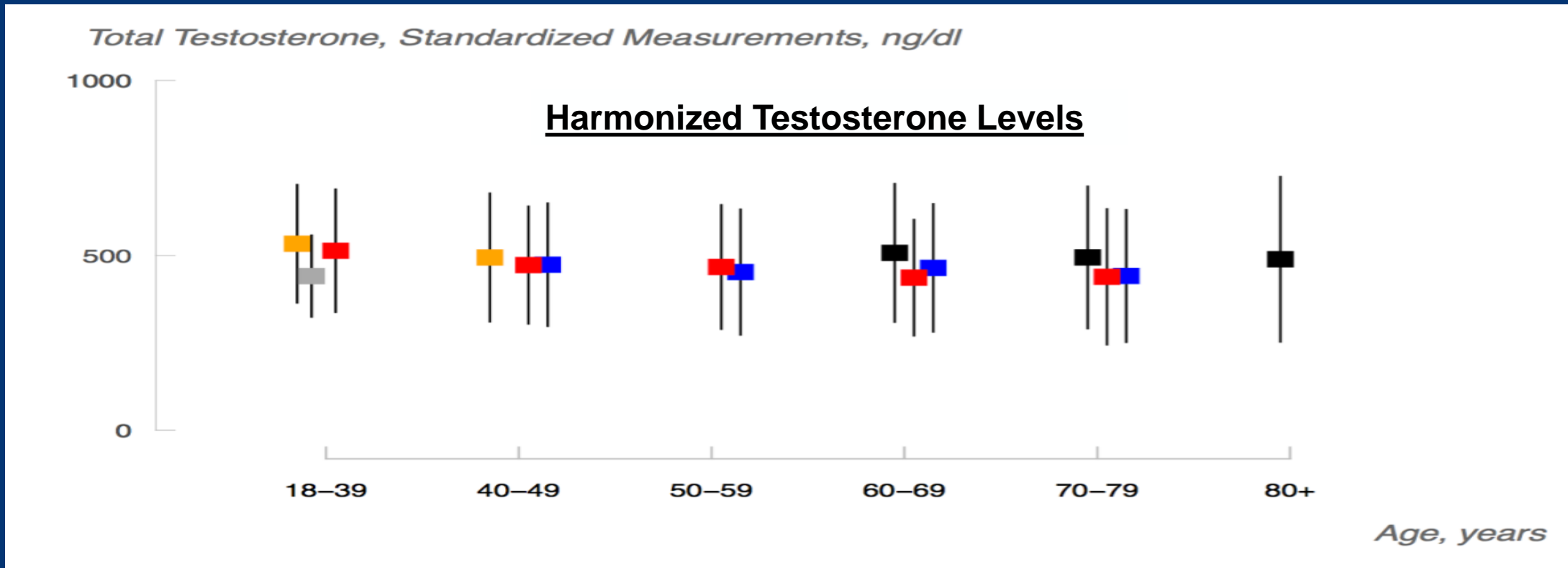
- Emphasis on the use of:
 - Accurate assays, especially LC-MS/MS assays,
 - Labs certified by the CDC's HoSt Program or another accuracy based certifying program
- The use of harmonized reference ranges for total testosterone in CDC-certified laboratories
- A better understanding of testosterone's binding to SHBG and a greater emphasis on free T determination than in the previous guideline

Travison TG, et al. *J Clin Endocrinol Metab.* 2017;102(4):1161-1173.

Goldman AL, et al. *Endocr Rev.* 2017;38:302-324.

Harmonized Testosterone Reference Range

- T assays from four epidemiologic studies cross-calibrated by CDC, and testosterone levels harmonized using Deming's regression
- 2.5th percentile ~264 ng/dL (9.2 nmol/L); 97.5th percentile 916 ng/dL (33 nmol/L)



Androgen Deficiency Syndromes with Increasing Prevalence

- Androgen deficiency associated with opioid use
- Androgenic-anabolic steroid withdrawal hypogonadism

Kanayama G, et al. Addiction 2015; 110:823-831

Coward RM, et al. J Urol 2013; 190:2200-2205

Ali K, et al. Postgraduate Medical Journal 2016; 92:677-68

Basaria S, et al. PAIN 2015; 156:280-288

GRADE Classification of Guideline Recommendations

QUALITY OF EVIDENCE		High Quality	Moderate Quality	Low Quality	Very Low Quality
<i>Description of Evidence</i>		<ul style="list-style-type: none"> Well-performed RCTs Very strong evidence from unbiased observational studies 	<ul style="list-style-type: none"> RCTs with some limitations Strong evidence from unbiased observational studies 	<ul style="list-style-type: none"> RCTs with serious flaws Some evidence from observational studies 	<ul style="list-style-type: none"> Unsystematic clinical observations Very indirect evidence observational studies
STRENGTH OF RECOMMENDATION	Strong (1): “We recommend...” <i>Benefits clearly outweigh harms and burdens, or vice versa</i>	1 ⊕⊕⊕⊕	1 ⊕⊕⊕○	1 ⊕⊕○○	1 ⊕○○○
	Conditional (2): “We suggest...” <i>Benefits closely balanced with harms and burdens</i>	2 ⊕⊕⊕⊕	2 ⊕⊕⊕○	2 ⊕⊕○○	2 ⊕○○○

Treatment

- High quality efficacy data from large controlled trials enabled a stronger treatment recommendation for men with organic hypogonadism.
 - We recommend testosterone therapy in hypogonadal men to induce and maintain secondary sex characteristics and correct symptoms of testosterone deficiency. (1 | ⊕⊕⊕○)
- Lack of long-term RCT data on the effects of TRT on MACE and prostate cancer led to a more guarded “suggestion” in older men.
 - We recommend against routinely prescribing testosterone therapy to all men 65 years or older with low T concentrations (1 | ⊕⊕○○). In men >65 years who have symptoms or conditions suggestive of T deficiency (such as low libido or unexplained anemia) and consistently and unequivocally low morning T concentrations, we suggest that clinicians offer T therapy on an individualized basis after explicit discussion of the potential risks and benefits. (2 | ⊕⊕○○)

Adverse Events Associated with TRT in Older Men

Systematic Review and Meta-Analyses

- Erythrocytosis the most frequent AE
- No significant change in LUTS in men with IPSS < 21

Literature Review

- Increased risk of detection of subclinical prostate disease
- The trials not large enough or long enough to evaluate effects on MACE and prostate cancer risk
- No clear evidence that TRT increases the risk of MACE or prostate cancer

Ponce et al, JCEM 2018 in press; Snyder et al, NEJM 2016;374:611-24; Basaria et al, NEJM 2010;363:109-22. Basaria et al, JAMA 2015;314:570-81; Spitzer et al, Nature Endocrinol Metab 2013

Monitoring

- Evaluate the patient at 3-12 months after treatment initiation and then annually to assess whether symptoms have responded to treatment and whether the patient is suffering from any adverse effects.
- Monitor T concentrations 3-6 months after initiation of T therapy: aim to raise serum T into the mid-normal range
- Check hematocrit at baseline, 3-6 months after starting treatment, and then annually.
- Evaluate formulation-specific adverse effects at each visit.
- Measure BMD of lumbar spine and/or femoral neck after 1-2 years of T therapy in hypogonadal men with osteoporosis, consistent with regional standard of care.

Prostate Monitoring

- For men 55-69 years and for men 40-69 years who are at increased risk for prostate cancer who choose prostate monitoring, perform DRE and check PSA before initiating treatment; check PSA and perform DRE 3-12 months after initiating T treatment, and then in accordance with guidelines for prostate cancer screening depending on the age and race of the patient.
- Obtain urological consultation if there is:
 - An increase in serum PSA concentration >1.4 ng/ml within 12-months of initiating T treatment.
 - A confirmed PSA >4 ng/mL at any time
 - Detection of a prostatic abnormality on DRE
 - Substantial worsening of LUTS.

Case 1: Diagnosis of Male Hypogonadism

Case #1: Diagnosis of Male Hypogonadism

A 66-year old man presents with decreased libido and osteopenia. His exam is remarkable for a BMI of 31 and is otherwise normal. Serum total testosterone at 8 AM is 250 and 265 ng/dL (normal: 270-890 ng/dL) on 2 different days. Serum calculated free testosterone is 90 pg/mL (normal: 50-200 pg/mL). Serum FSH and LH are 3 IU/L and 6 IU/L (normal: 1-7 IU/L).

Question: What is the next best step? (*Audience Response*)

- A. Measure free testosterone by equilibrium dialysis
- B. Measure bioavailable testosterone
- C. Confirm that the testosterone assay is accurate and reliable
- D. Initiate testosterone therapy

Audience Note: You may submit questions related to diagnosis now

Case #1: Diagnosis of Male Hypogonadism (cont.)

A 66-year old man presents with decreased libido and osteopenia. His exam is remarkable for a BMI of 31 and is otherwise normal. Serum total testosterone at 8 AM is 250 and 265 ng/dL (normal: 270-890 ng/dL) on 2 different days. Serum calculated free testosterone is 90 pg/mL (normal: 50-200 pg/mL). Serum FSH and LH are 3 IU/L and 6 IU/L (normal: 1-7 IU/L).

Panel:

What would you do now?

Audience Note: You may submit questions related to diagnosis now

Case #1: Diagnosis of Male Hypogonadism (cont.)

A 66-year old man presents with a history of decreased libido and osteopenia. Total testosterone is low, but calculated free testosterone is normal.

You confirm that the blood samples were drawn in the early morning on two different days after fasting for 6 hours. The testosterone assay is certified by the CDC Hormone Standardization program and is accurate and reliable.

Panel:

What would you do now?

Audience Note: You may submit questions related to diagnosis now

Case #1: Diagnosis of Male Hypogonadism (cont.)

SAME CASE ... A 66-year old man presents with a history of decreased libido and osteopenia. Total testosterone is low (250 and 265 ng/dL)... **BUT his serum calculated free testosterone is 51 and 57 pg/mL (normal: 50-200 pg/mL).**

Question: What would you recommend? (*Audience Response*)

- A. Diagnose male hypogonadism and initiate testosterone therapy
- B. Diagnose hypotestosteronemia due to obesity and initiate weight loss strategies
- C. Repeat serum total and free testosterone measurement in 3 months
- D. Repeat serum total and free testosterone in 12 months
- E. Diagnose eugonadism and recommend couples therapy

Audience Note: You may submit questions related to diagnosis now

Case #1: Diagnosis of Male Hypogonadism (cont.)

SAME CASE... A 66-year old man presents with decreased libido and osteopenia. Total testosterone is low (250 and 265 ng/dL)... **BUT calculated free testosterone is 51 and 56 pg/mL (normal 50-200).**

Panel:

Would you diagnose hypogonadism?

Would you initiate testosterone therapy?

You obtain the following information from the referring physician:

- Patient has a normal ferritin and sella MRI.
- Serum prolactin is 57 ng/dL (normal 5-20).

Panel:

Would you diagnose hypogonadism?

Would you initiate testosterone therapy?

Audience Note: You may submit questions related to diagnosis now

Key New Recommendations for the Diagnosis of Male Hypogonadism

1. Use an accurate and reliable testosterone assay, optimally certified by accuracy-based standardization (e.g. CDC) or quality control (e.g. CAP) program.
2. Important to define etiology of hypogonadism because it has management implications. The etiology of secondary hypogonadism is mostly functional.
3. In men >65 years who have clinical and biochemical hypogonadism, testosterone treatment on an individualized basis after discussion of potential risks and benefits.

Audience Note: You may submit questions related to diagnosis now

Case 2: Treatment of Male Hypogonadism

Case # 2: Treatment of Male Hypogonadism

A 59-year old man presents with a history of decreased libido that is confirmed by his sexual partner (who is interested in having more sex with the patient). The patient has a history of localized prostate cancer (Gleason 7: 3 + 4) that was treated with radical prostatectomy 3 years ago. His exam is normal except for small testes (4 cc). Serum total testosterone at 8 AM is 110 and 140 ng/dL (normal: 270-890 ng/dL) on 2 different days. Serum calculated free testosterone is 22 pg/mL (normal: 50-200 pg/mL). Serum FSH is 47 and LH is 35 (FSH and LH: normal 1-7). Serum PSA is undetectable.

Question: Would you prescribe testosterone replacement therapy?

(Audience Response)

- A. Yes
- B. No
- C. Maybe, it depends

Audience Note: You may submit questions related to treatment now

Case # 2: Treatment of Male Hypogonadism (cont.)

A 59-year old man presents with decreased libido (confirmed by partner). He has a history of prostate cancer treated with radical prostatectomy. The patient's serum total and free testosterone are low and gonadotropins are elevated. Serum PSA is undetectable.

Panel:

What would you do now?

Would you prescribe testosterone?

Audience Note: You may submit questions related to treatment now

Case # 2: Treatment of Male Hypogonadism (cont.)

A 59-year old man presents with a history of decreased libido (confirmed by partner). He has a history of prostate cancer treated with radical prostatectomy. The patient's serum total and free testosterone are low and gonadotropins are elevated. Serum PSA is undetectable. **Further history reveals a history of myocardial infarction 2 years ago and a deep venous thrombosis of the left leg one year ago after ankle surgery in the same leg.**

Question: Would you prescribe testosterone replacement therapy?

(Audience Response)

- A. Yes
- B. No
- C. Maybe, it depends

Audience Note: You may submit questions related to treatment now

Case # 2: Treatment of Male Hypogonadism (cont.)

A 59-year old man presents with a history of decreased libido (confirmed by partner). He has a history of prostate cancer treated with radical prostatectomy. The patient's serum total and free testosterone are low and gonadotropins are elevated. Serum PSA is undetectable. **Further history reveals a history of myocardial infarction 2 years ago and a deep venous thrombosis of the left leg one year ago after ankle surgery in the same leg.**

Panel:

What would you do now?

Would you prescribe testosterone?

Audience Note: You may submit questions related to treatment now

Key New Recommendations for the Treatment of Male Hypogonadism

1. The potential risks and benefits of TRT should be discussed with the patient, and he should share in treatment decisions.
2. New evidence supports the benefits of TRT on the following: sexual function in middle-aged and older men, unexplained and explained anemia, and volumetric bone density and strength of the spine and hip.
3. Clinicians should discuss the benefits and risks of prostate cancer screening and monitoring with patients being considered for TRT, at ages 40-69 (high risk) and 55-69 (normal risk).
4. The potential CV risks or benefits of TRT in hypogonadal men are not known. We recommend not starting TRT within 6 months of MI or stroke.

Audience Note: You may submit questions related to treatment now

Case 3:
Monitoring During
Testosterone Replacement
Therapy

Case # 3: Monitoring During Testosterone Replacement Therapy

A 50-year old man presents with a history of decreased libido that is confirmed by his sexual partner (who is interested in having more sex with the patient). He has a history of gout. His exam is normal except for small testes (4 cc). Serum total testosterone at 8 AM is 110 and 140 ng/dL (normal: 270-890 ng/dL) on 2 different days. Serum calculated free testosterone is 22 pg/mL (normal: 50-200 pg/mL). Serum FSH is 47 and LH is 35 (FSH and LH: normal 1-7).

Question: What tests would you order before beginning testosterone therapy? (*Audience Response*)

- A. Fasting serum lipids
- B. Fasting serum glucose
- C. Hematocrit
- D. PSA

Audience Note: You may submit questions related to monitoring now

Case # 3: Monitoring During Testosterone Replacement Therapy

A 50-year old man presents with a history of decreased libido (confirmed by partner). The patient's serum total and free testosterone are low and gonadotropins are elevated.

Panel:

What additional clinical information or test results would you require before initiation testosterone of replacement therapy?

Would you do prostate cancer screening before initiating testosterone therapy?

Audience Note: You may submit questions related to monitoring now

Case # 3: Monitoring During Testosterone Replacement Therapy

A 50-year old man presents with a history of decreased libido (confirmed by partner). His laboratory tests are consistent with primary hypogonadism.

Patient declines a digital rectal exam, but he elects to have a serum PSA measured before initiation of testosterone replacement therapy. His serum PSA is 1.1 ng/mL. His hematocrit is 44% (normal 38-48%). He prefers testosterone gel therapy.

Panel:

What follow-up tests would you recommend after initiation of testosterone gel?

Audience Note: You may submit questions related to monitoring now

Case # 3: Monitoring During Testosterone Replacement Therapy

A 50-year old man presents with a history of decreased libido (confirmed by partner). His laboratory tests are consistent with primary hypogonadism. Patient declines a digital rectal examine, but he elects to have a serum PSA measured before initiation of testosterone replacement therapy. His pre-treatment serum PSA is 1.1 ng/mL, and his pretreatment hematocrit is 44% (normal 38-48%). **His serum PSA after 4 months of testosterone therapy is 2.1 ng/mL.**

Panel:

What you would recommend regarding further follow-up for prostate cancer screening?

Audience Note: You may submit questions related to monitoring now

Case # 3: Monitoring during Testosterone Replacement Therapy

This man follows up with his primary care provider after initiation of testosterone gel, and you do not see him until 5 years later (at age 55). He feels well. He applies 61 mg of testosterone gel (1.62%) daily. His pre-treatment serum PSA was 1.1 ng/mL, and his pretreatment hematocrit was 44% (normal 38-48%). His serum PSA after 4 months of testosterone therapy was 2.1. **After 5 years of testosterone therapy, his PSA is 3.1 ng/mL, and his hematocrit is 52%. His serum total testosterone is 775 ng/mL (normal: 270-870).**

Question: What would you recommend now? (Audience Response)

- A. Discontinuation of testosterone until hematocrit is < 50%
- B. Discontinuation of testosterone until hematocrit is < 50% and urologist has evaluated patient for prostate cancer
- C. Reduction in dosage of testosterone gel and reassessment of hematocrit
- D. No change in therapy; annual monitoring of hematocrit and PSA

Audience Note: You may submit questions related to monitoring now

Case # 3: Monitoring during Testosterone Replacement Therapy

This man follows up with his primary care provider after initiation of testosterone gel, and you do not see him until 5 years later (at age 55). He feels well. He applies 61 mg of testosterone gel (1.62%) daily. His pre-treatment serum PSA was 0.8 ng/mL, and his pretreatment hematocrit was 44% (normal 38-48%). His serum total testosterone is 775 ng/mL (normal: 270-870). His serum PSA after 5 years of testosterone therapy is 3.1 ng/mL, and his hematocrit is 52%.

Panel:

What you recommend regarding further follow-up for prostate cancer screening?

What would you recommend regarding his testosterone dosage?

Audience Note: You may submit questions related to monitoring now

Key New Recommendations for Monitoring During Testosterone Replacement Therapy

1. Monitor T levels 3 to 6 months after initiation of T therapy with a goal level in the mid-normal range.
2. Monitor hematocrit levels at baseline, 3 to 6 months after initiation of T therapy, and then yearly.
3. If a patient decides to go forward with prostate cancer screening, proceed with screening at baseline and 3-12 months after initiation of T. After this initial monitoring, follow prostate cancer screening guidelines for the general population.

Audience Note: You may submit questions related to monitoring now

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