Male Hypogonadism: Caveats of Testosterone Therapy

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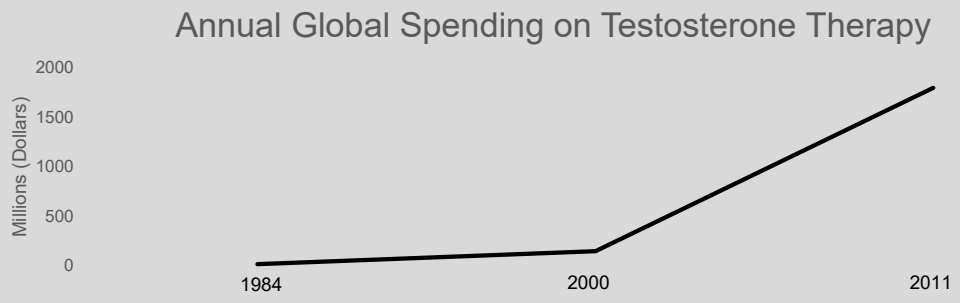
Objectives

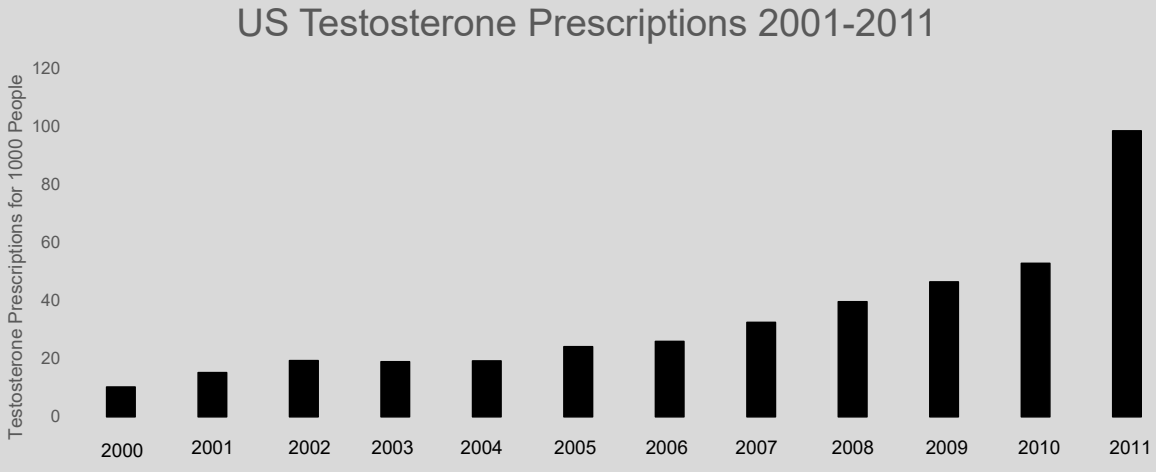
- Review the common presenting symptoms of hypogonadism
- Review the 2018 Endocrine Society Treatment Guidelines for the recommended workup of Male hypogonadism
- Review the limitations of testosterone testing
- Review contraindications to therapy
- Review therapeutic options, costs, side effects, and monitoring recommendations

Testosterone Therapy



MJA 2013; 199: 548–551doi: 10.5694/mja13.10111

Testosterone Therapy



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Symptoms

Specific Signs/Symptoms	• Delayed Sexual Development • Small Testicular Volume • Loss of pubic and/or axillary hair
Suggestive Signs/Symptoms	• Decreased Libido • Erectile Dysfunction • Gynecomastia • Hot Flashes • Low Bone Density, Low-Trauma Fracture
Non-specific Signs/Symptoms	• Decreased Energy, Fatigue • Poor Concentration • Reduced Muscle Strength • Increased BMI, Increased Body Fat

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Classifying Hypogonadism

Primary	Secondary
• Kleinfelter Syndrome • Cryptorchidism • Testicular Trauma/Torsion • Orchitis • Radiation to the Testes • Certain Chemotherapies • Androgen Synthesis Inhibitors	• Pituitary or Hypothalamic Tumor • Iron Overload/Hemochromatosis • Infiltrative Hypothalamic/Pituitary Disease • Hyperprolactinemia • Idiopathic Hypogonadotropic Hypogonadism • Opiod, Glucocorticoid, or Anabolic Steroid Use • Systemic Illness • History of Pituitary Surgery or Radiation Therapy

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Case 1

A 47 year old man presents with decreased libido and fatigue. He was seen by his primary care physician and had labs drawn. Serum total testosterone at 4 PM was 175 ng/dL. His exam is remarkable for a BMI of 43, Tanner 5 Development, and a symmetrical testicular exam of 25 cc each. He has heard wonderful things about testosterone and asks to be started on replacement today.

What should we do next?

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. Yialamas[10]

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https://www.endocrine.org/clinical-practice-guidelines/testosterone-therapy

Recommended Workup

History and Physical: Focusing on Signs, Symptoms, and Medications

↓

Measure Morning, Fasting Testosterone

Measure Free Testosterone if concerned for abnormal SHBG

↓ → If normal consider alternative causes

Confirm With Repeat Morning, Fasting Level

↓

Measure FSH and LH

← **Low and/or Normal (Secondary)**

- Prolactin
- Iron Studies
- Pituitary MRI (if clinically indicated)

→ **High (Primary)**

- Karyotype testing if history does not point to a primary cause

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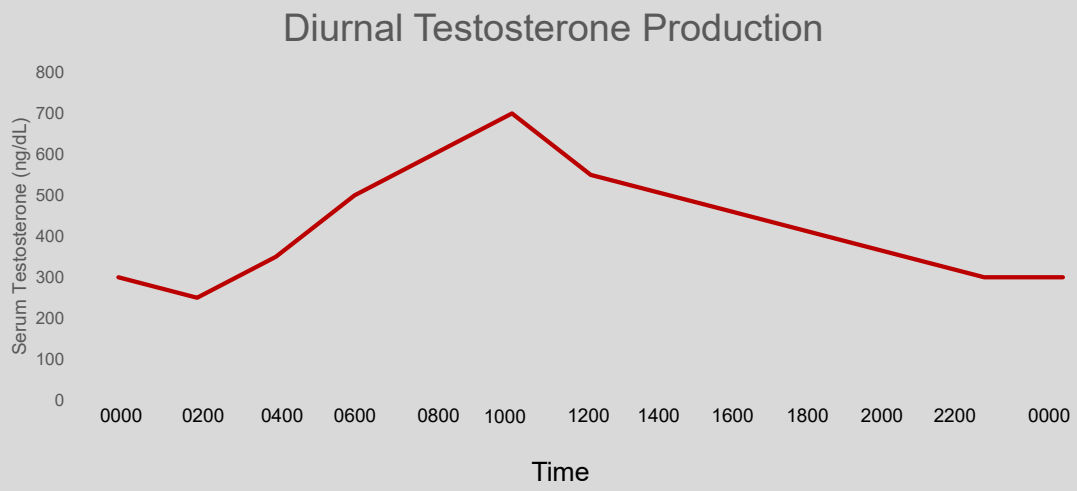
Testosterone Testing Caveats



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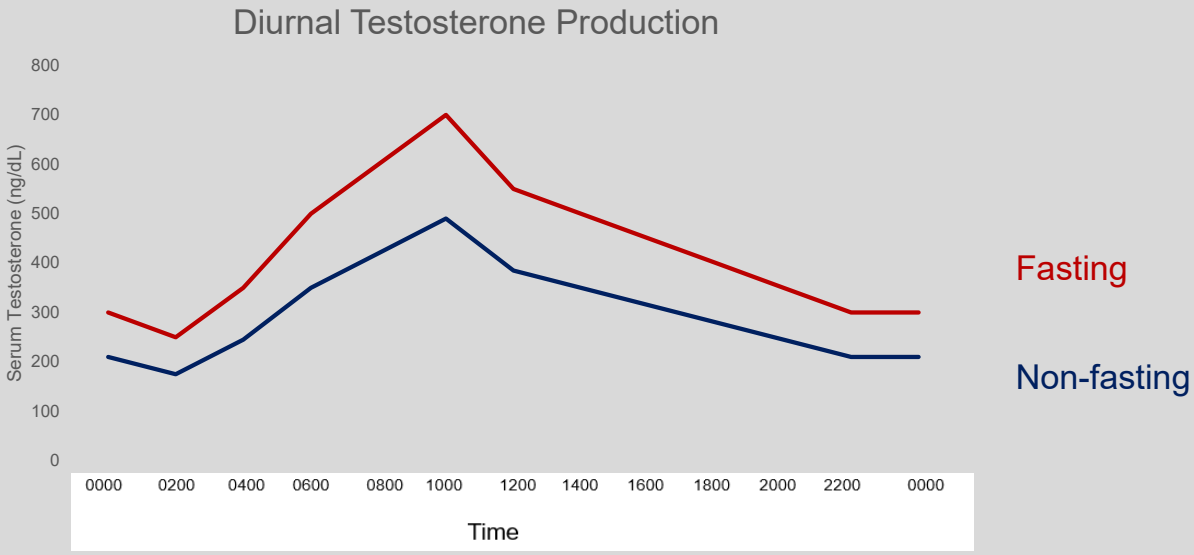

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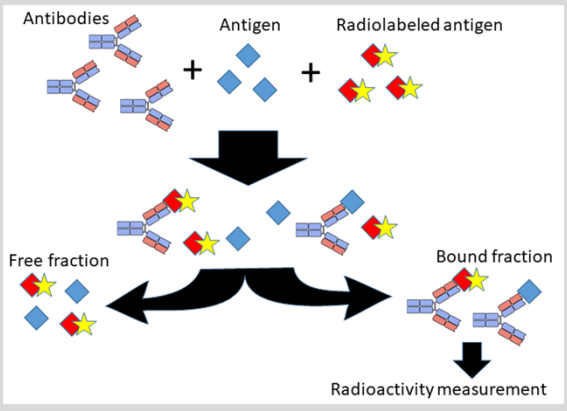
Measuring Testosterone



Radioimmunoassay

Liquid Chromatography
Tandem Mass Spectrometry

https://upload.wikimedia.org/wikipedia/commons/d/d6/Radioimmunoassay_process.png

https://commons.wikimedia.org/wiki/File:Liquid_chromatograph_with_mass_spectrometer,_in_CAFIA_laboratory,_Czech_Republic.png#filelinks

Testosterone Testing Caveats

- At their first appointment we discuss the free hormone hypothesis.
- The free hormone hypothesis states that intracellular concentrations and biologic activity of a hormone are dependent upon the concentrations of the free rather than protein-bound hormone in plasma.
- Support for this comes from an analysis of the European Male Aging Study data, which showed that men with low free Testosterone concentrations had sexual and physical symptoms consistent with Testosterone deficiency, regardless of their total Testosterone concentrations (compared to middle-aged and older men who had normal total Testosterone and free Testosterone concentrations)
- We also discuss that total testosterone represents testosterone bound to carrier proteins including SHBG (Sex Hormone Binding Globulin).
- We discuss that a variety of conditions can affect SHBG and in turn can affect total testosterone levels in a direct manner. If they are present or suspicion is high, free testosterone should be checked
  - Particularly if SHBG is low then total testosterone can be falsely low and unreliable to make a diagnosis of a low testosterone

Free Testosterone Testing

When to Check Free Testosterone levels		
Condition associated with low SHBG level	Condition associated with high SHBG level	• Total testosterone at a borderline range near the low end of normal for the assay you are using
• Obesity • Diabetes Mellitus • Hypothyroidism • Nephrotic Syndrome • Progestin, Androgen, and/or Glucocorticoid use	• HIV • Aging • Cirrhosis and hepatitis • Anorexia • Hyperthyroidism • Anticonvulsant use • Estrogen use	

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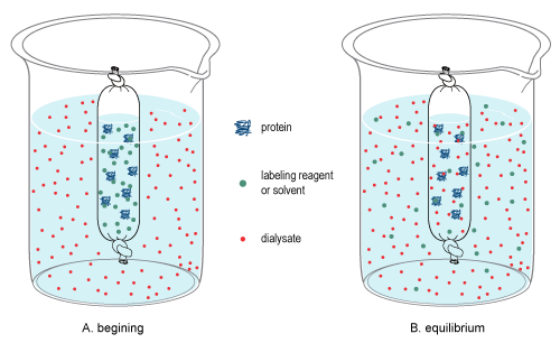
Measuring Free Testosterone



Equilibrium Diaylsis

Liquid Chromatography
Tandem Mass Spectrometry

https://commons.wikimedia.org/wiki/File:Dialysis_Figure.png

https://commons.wikimedia.org/wiki/File:Liquid_chromatograph_with_mass_spectrometer,_in_CAFIA_laboratory,_Czech_Republic.png#filelinks

Testosterone Testing

- Total testosterone should be measured as a fasting level between 8-10 in the morning to minimize false lows and fits with the diurnal fluctuations of testosterone
- If there is a concern for potential changes to SHBG to impact testosterone testing, then free testosterone levels should be checked (ideally by equilibrium dialysis)
- Two measurements are required to establish a diagnosis of a low testosterone level
- If potential medications or substances are suspected as a secondary cause of a low testosterone these should be stopped for at least 4 weeks prior to repeat testing

Classifying Hypogonadism

Primary	Secondary
• Kleinfelter Syndrome • Cryptorchidism • Testicular Trauma/Torsion • Orchitis • Radiation to the Testes • Certain Chemotherapies • Androgen Synthesis Inhibitors	• Pituitary or Hypothalamic Tumor • Iron Overload/Hemochromatosis • Infiltrative Hypothalamic/Pituitary Disease • Hyperprolactinemia • Idiopathic Hypogonadotropic Hypogonadism • Opiod, Glucocorticoid, or Anabolic Steroid Use • Systemic Illness • History of Pituitary Surgery or Radiation Therapy

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Contraindications to Testosterone Therapy

Conditions Which Preclude Testosterone Replacement Therapy
• Breast Cancer • Metastatic Prostate Cancer • Unevaluated Prostate Nodule • Baseline PSA greater than 4 (or 3 if high risk) • Obstructive Sleep Apnea (Untreated) • Baseline Hematocrit Greater than 48% • Poorly Controlled Congestive Heart Failure • Desire for Fertility • BPH associated with Severe LUTS

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Obstructive Sleep Apnea Screening

OSA Screening Questionnaire	
S	Does the patient **S**nore?
T	Does the patient feel **T**ired or fatigued during the day?
O	Have they been **O**bserved to stop breathing during their sleep?
P	Do they have high blood **P**ressure?
B	Is their **B**MI more than 35?
A	Is their **A**ge greater than 50?
N	Is their **N**eck circumference greater than 40 cm?
G	Male **G**ender?

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A Score Equal or Greater than 3 indicates high risk for OSA

Return to the Case 1

A 47 year old man presents with decreased libido and fatigue. He was seen by his primary care physician and had labs drawn. Serum total testosterone at 4 PM was 175 ng/dL. His exam is remarkable for a BMI of 43, Tanner 5 Development, and symmetrical testicular exam of 25 cc. He has heard wonderful things about testosterone and asks to be started on replacement today.

What should we do next?

Return to the Case 1

- We first discussed the caveats/limitations of testosterone testing
- We discussed that his test was not done in the morning or in a fasting state so it could represent a false low (in addition to his obesity potentially effecting his SHBG)
- Ultimately we repeated fasting testosterone testing
- His AM total testosterone returned normal at 400 ng/dL and his free testosterone was also normal at 11 ng/dL

Case 2

- A 65 year old man presents with decreased libido and fatigue.
- He was seen by his primary care physician and had labs drawn.
- Serum total testosterone at 8 AM was 100 ng/dL. His free testosterone was also low at 0.5 ng/dL His exam is remarkable for Tanner 5 Development, and a symmetrical testicular exam of 25 cc each.

What should we do next?

Treatment Options

Injectable Testosterone			
Formulation	Dosing Range	Advantages	Disadvantages
Testosterone Enanthate	50 -100 mg once weekly or 100 - 200 mg every 2 weeks	Flexible dosing Inexpensive	Injection Required Peak/Trough Effect
Testosterone Cypionate	50 - 100 mg once weekly or 100 - 200 mg every 2 weeks	Flexible dosing Inexpensive	Injection Required Peak/Trough Effect
Testosterone Undecanoate	750 mg followed by a repeat 750 mg dose after 4 weeks, and then 750 mg every 10 weeks	Less Frequent Dosing	Restricted through REMS

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Treatment Options

Topical Testosterone			
Formulation	Dosing Range	Advantages	Disadvantages
1% Gel	50-100 mg applied once daily to the shoulders and/or upper arms	Flexible Dosing No injections	Contact Safety Precautions Higher Cost
1.62% Gel	20.25-81 mg applied once daily to the shoulders and upper arms	Flexible Dosing No injections	Contact Safety Precautions Higher Cost
2% Gel	10-70 mg applied once daily to the thighs	Flexible Dosing No injections	Contact Safety Precautions Higher Cost
Transdermal Solution	30-120 mg applied once daily to the axillae	Flexible Dosing No injections	Contact Safety Precautions Higher Cost

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Treatment Options

Subcutaneous Testosterone			
Formulation	Dosing Range	Advantages	Disadvantages
Solution (Xyosted)	50-100 mg once weekly	Flexible Dosing Needle not visualized	Requires Injection Higher Cost
Pellets	150 to 450 mg every 3 to 6 months	Infrequent Administration	Requires In Office Procedure Higher Cost

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Treatment Options

Oral Testosterone			
Formulation	Dosing Range	Advantages	Disadvantages
Capsule	Three brands are available in the US: • Jatenzo: 158-396 mg twice daily • Kyzatrex: 100-400 mg twice daily • Tlando: 225 mg twice daily	Ease of Administration No injections	Very Expensive Twice Daily Dosing Required

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Cost

Cost of Testosterone Therapy	
Formulation	Cost
Injectable Testosterone	40-100 Dollars per month
Topical Testosterone	200-500 Dollars per month
Testosterone Pellets	500 Dollars per cycle
Oral Testosterone	800-1000 Dollars per month

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Side Effects

- Erythrocytosis
- Increase in Acne and/or oily skin
- Reduced sperm count/decreased fertility
- Scalp Hair Loss
- Worsening/Unmasking of Obstructive Sleep Apnea
- Detection of subclinical prostate cancer
- Worsening of metastatic prostate cancer

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Formulation Specific Side Effects

Formulation	Specific Side Effects
Injectable Testosterone	Injection site reactions
Topical Testosterone	Skin irritation Contact Safety Precautions
Testosterone Pellets	Expulsion of the pellet

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Monitoring

Testosterone Levels	• Should be checked every 3-6 months after starting testosterone therapy (typically every 3 months for the first year) • Goal testosterone level is 300-700 ng/dL for testosterone collected at an appropriate time based on the formulation used
Hematocrit	• Check hematocrit at baseline, 3–6 months after starting treatment, and then annually. • If hematocrit is 54%, stop therapy until hematocrit decreases to a safe level (and evaluate the patient for hypoxia and sleep apnea and underlying iron abnormalities)
PSA	• For men 55–69 years of age and for men 40–69 years of age who are at increased risk for prostate cancer, perform digital rectal examination and check PSA level before initiating treatment. • Check PSA and perform digital rectal examination 3–12 months after initiating T treatment (and then in accordance with guidelines for prostate cancer screening)

Timing of Testosterone Testing On Therapy

Formulation	Timing of Testosterone Testing
Injectable Testosterone	Should be measured mid way through the injection cycle (day 3-4 for weekly cycles and day 7-8 for every 14 day cycles)
Topical Testosterone	Should be measured 2-8 hours after application
Testosterone Pellets	Pellet levels take 1 month to reach steady state and can last 3-6 months. Levels should be measured at the end of the dosing interval
Oral Testosterone	Should be measured 3-5 hours after ingestion

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Return to Case 2

- A 65 year old man presents with decreased libido and fatigue.
- He was seen by his primary care physician and had labs drawn.
- Serum total testosterone at 8 AM was 100 ng/dL. His free testosterone was also low at 0.5 ng/dL His exam is remarkable for Tanner 5 Development, and a symmetrical testicular exam of 25 cc each.

What should we do next?

Return to Case 2

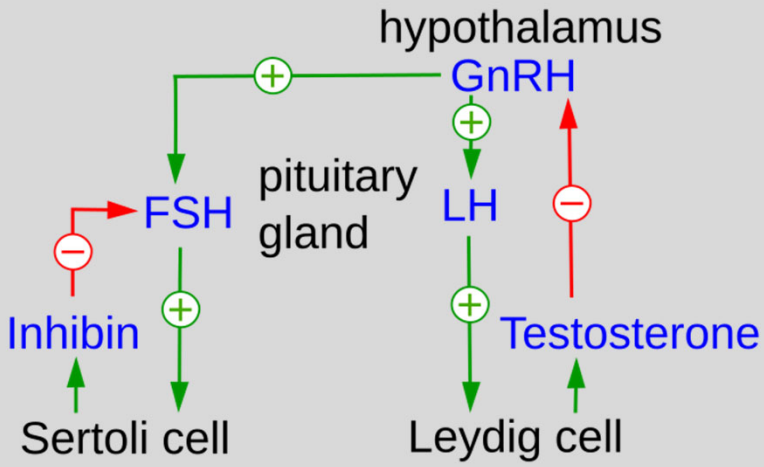
- After a discussion of the risks and benefits of therapy it is decided to start on IM testosterone cypionate 100 mg weekly
- Ultimately he required IM testosterone cypionate 150 mg weekly to maintain goal mid peak testosterone levels

Case 3

- A 75 year old man has been admitted to the hospital for pneumonia. He was complaining of fatigue so testosterone levels were checked inpatient.
- Fasting total testosterone at 8 AM was 100 ng/dL. His exam is remarkable for Tanner 5 Development, and a symmetrical testicular exam of 25 cc each.

What should we do next?

Case 3 Discussion



https://commons.wikimedia.org/wiki/File:Hypothalamus-Hypophysis-Testicle-Hormone-Axis_(engl.).svg

Returning to Case 3

- Repeat fasting total testosterone 8 weeks later revealed a total testosterone of 326 ng/dL. His free testosterone was at 10 ng/dL

Take Home Points

- Total testosterone should be measured as a fasting level between 8-10 in the morning
- If there are risk factors for low SHBG then free testosterone levels should be checked by equilibrium dialysis to avoid false lows
- Two measurements are required to establish a diagnosis of a low testosterone level
- If potential medications or substances are suspected as a secondary cause of a low testosterone these should be stopped for at least 4 weeks prior to repeat testing
- Testosterone therapy may increase the risk of serious adverse effects in men with some conditions and therefore therapy is not recommended with patients with these disorders. This includes those with a history of prostate and breast cancer, baseline testing of PSA above 4 or 3 for those that are high risk, a hematocrit above 48% at baseline, or untreated or undiagnosed/risk for sleep apnea

Take Home Points

- Monitor Testosterone concentrations 3–6 months after initiation of T therapy
- Check hematocrit at baseline, 3–6 months after starting treatment, and then annually.
- Timing of checking testosterone levels for those on therapy is predicated on the therapeutic modality
- Discussion of cost of therapy should be a part of the evaluation