Male Hypogonadism

More than just a low testosterone?

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Endocrinology

Cleveland Clinic
Conflicts of Interest

None to declare
Case 1

• A 54 year old man is referred for evaluation of low testosterone
• The patient had presented to his PCP with the complaints of diminished libido and erectile dysfunction for the past year
• He noted fatigue that has been ongoing for the past few years, worsening over time
• He has not been formally diagnosed with any medical conditions at the present time
Case 1 continued.....

• On physical exam he is obese (BMI 31)
• No evidence of gynecomastia
• Normal appearing male body habitus
• Normal testicular and prostate exam
• Laboratory evaluation noted a serum testosterone level of **180 ng/dL**
  – reference range: 249-836 ng/dL
How should this patient be evaluated?

- A) Order a testicular ultrasound
- B) Obtain MRI of the brain
- C) Testosterone is low, treat with testosterone replacement therapy
- D) Obtain a semen analysis
- E) Obtain repeat testosterone, LH/FSH
Low Testosterone

• Confronted with the finding of a low serum testosterone level, physicians should not jump to the diagnosis of hypogonadism and treat with testosterone supplementation

• Confirmation and thorough evaluation is warranted prior to making a diagnosis and/or starting therapy
Objectives

• Review signs/symptoms of low testosterone
• Review the hypothalamic-pituitary-gonadal axis
• Discuss how to evaluate the finding of low serum testosterone
• Realize the importance of determining if the etiology is 1° (testicular) or 2° (hypothalamic/pituitary)
• Review the differential diagnosis of male hypogonadism
• Review the risks and benefits of testosterone replacement therapy (TRT)
• Review the various modes of TRT
Definition

• Male hypogonadism is defined as the failure of the testes to produce adequate amounts of androgen and/or sperm
Symptoms of low testosterone

Table 1

<table>
<thead>
<tr>
<th>Symptoms of Hypogonadism</th>
<th>Sexual</th>
<th>Emotional/Psychiatric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical</td>
<td>Sexual</td>
<td>Emotional/Psychiatric</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Decreased libido</td>
<td>Depression</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>Erectile dysfunction</td>
<td>Anxiety</td>
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<tr>
<td>Sparse body hair</td>
<td>Oligospermia</td>
<td>Irritability</td>
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<tr>
<td>Decreased bone mineral density</td>
<td></td>
<td>Insomnia</td>
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<tr>
<td>Fat distribution</td>
<td></td>
<td>Memory Impairment</td>
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<tr>
<td>Impaired hematopoiesis</td>
<td></td>
<td>Cognitive dysfunction</td>
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<tr>
<td>Osteoporosis</td>
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</tbody>
</table>

Symptoms of Low Testosterone

Chances are, if you are overweight, physically inactive, have chronic medical problems, or married (with children) you will fail this test........

Symptoms of low T are vague and non-specific

Hypothalamic-Pituitary-Gonadal Axis

Faiman C. Cleveland Clinic Current Clinical Medicine, 2nd edition
Diurnal Rhythm

• Testosterone is highest near 8 am
  – check for deficiency when level should be highest

• Confirm the finding
  • At least one confirmatory measurement
    – early morning specimens should be obtained near 8 am
  • Acute effect of stressful illness may result in a transient lowering of testosterone levels

Beware of the night-shift worker!
Total vs. Free vs. Bioavailable Testosterone (male)

Affinity for SHBG is at least 4X higher vs. albumin
What to measure?
Total-T vs. Bioavailable-T vs. Free-T

• The level of total testosterone is affected by alterations in the levels of its binding protein
  – mainly SHBG and albumin

• Free testosterone is the biologically active hormone
  – considered to be a more accurate representation of the “true” testosterone status

• Bioavailable testosterone is felt by some clinicians to be a better reflection of the true level of active hormone vs. that of the level of free testosterone alone
Reduction in SHBG level
Sex Hormone Binding Globulin

• Results in low total serum testosterone levels
• Seen in patients with obesity and/or DM-2
  – states of insulin resistance
• Also seen in other conditions such as
  – Acromegaly
  – Hypothyroidism
  – Nephrotic syndrome
  – Therapy with glucocorticoids, progestins, and androgenic steroids

Reduction in SHBG level

Sex Hormone Binding Globulin

• In these settings checking the level of free testosterone and/or bioavailable testosterone may be more appropriate

• Bioavailable testosterone
  – T loosely bound to albumin + free T

• Recall total serum testosterone is the sum of
  • SHBG-T (60%)
  • Loosely bound to albumin (38%)
  • Free testosterone (2%)
Testosterone Measurements

• Commercially available testosterone assays are not standardized well, and some are frankly unreliable

• Repeat, confirmatory measurements, especially for bioavailable/free testosterone, should always be performed by a reliable reference laboratory

• Efforts to standardize the assays are underway

Approach to Low Serum Testosterone

Verify low testosterone near 8 am \(^1\)^ \(^2\)

Check LH/FSH \(^3\)

Low or normal range LH/FSH (Hypogonadotropic)

- Secondary Hypogonadism
  - Evaluate for Gonadotroph Suppression or Deficiency (Hypothalamic/Pituitary Process)

Elevated LH/FSH (Hypergonadotropic)

- Primary Hypogonadism
  - Evaluate for Testicular Disorder

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1- Repeat confirmatory level should always be performed at a reliable reference laboratory
2- On occasion, total testosterone levels may be low but bioavailable and/or free testosterone levels may be normal
3- Initial evaluation should also include serum prolactin, TSH, free T4, and ferritin
Etiology

• Correct identification of the underlying etiology can have considerable implications in terms of the patients overall health

• It will also assist the clinician in determining when (and if) the initiation of testosterone therapy is appropriate
Primary Hypogonadism

• ↑LH/FSH in the setting of ↓testosterone  
  – suggests a testicular etiology

• Age of the patient at presentation, and careful questioning regarding pubertal development and fertility must be undertaken
Primary Hypogonadism

- Toxin exposure (chemotherapy)
- Congenital defects
  - Anorchia, cryptorchidism
- Karyotype abnormalities
  - Klinefelter Syndrome
- Orchitis (mumps, autoimmune)
- Testicular trauma or infarction
- Hemochromatosis
- Increase in temperature of testicular environment
  - Varicocele, large panniculus
- Medications which inhibit androgen synthesis
  - Ketoconazole

Secondary Hypogonadism

• ↓ or normal LH/FSH in the setting of ↓ testosterone
  • suggests a hypothalamic/pituitary etiology

• Congenital Disorders
  – Inherited/Genetic defect

• Acquired
  – Damage to gonadotrophs
  – Suppression of gonadotrophs
Congenital Disorders

• Kallmann syndrome
  – Anosmia and GnRH deficiency

• Mutation/Deficiency of GnRH receptors

• Genetic mutations associated with pituitary hormone deficiencies
  – PROP-1 mutation
Acquired Damage to Gonadotrophs

- Sellar mass/cysts
  - pituitary adenomas, craniopharyngioma, rathke cleft cyst, meningioma

- Infiltrative lesions
  - lymphocytic hypophysitis, Langerhans cell hystiocytosis, sarcoidosis, hemochromatosis, infection

- Metastatic lesions (breast, renal cell, lung)

- Trauma (head injury)

- Radiation exposure/Surgery to sellar region

- Pituitary apoplexy

- Stalk severance
Acquired
Suppression of Gonadotrophs

Numerous Causes!!!!!!!!!!!
Medications

• Chronic therapy with common medications such as opioids and/or corticosteroids can result in secondary hypogonadism

• GnRH analogues (leuprolide)
  – used in the treatment of prostate cancer

Obesity

- Obesity and the related conditions are independently associated with decreased plasma testosterone
  - Obstructive sleep apnea
  - Insulin resistance and/or type 2 diabetes mellitus

Obstructive Sleep Apnea

• Disturbances in the sleep cycle, regardless of the underlying cause, can result in decreases in the serum testosterone levels
  • likely by disruption of the normal diurnal rhythm

• Often, correction of the underlying sleep disturbance can result in normalization of the serum testosterone levels

• Caution must be used, and a thorough evaluation for sleep apnea should take place in high risk individuals (obese)

• Testosterone replacement therapy can adversely affect ventilatory drive and induce or worsen obstructive sleep apnea!

Insulin Resistance/DM-2

• Insulin resistance
  • Low total testosterone but normal free testosterone
    – Reduction in SHBG
  • Low levels of free testosterone can also be observed, particularly in morbid obesity, but the cause remains unclear
  • Decrement is proportional to the degree of obesity

• Testosterone levels have been reported to be lower in obese men with diabetes than in those with obesity alone
  • Decrement comparable in magnitude to the effects of other chronic diseases
  • Suggests that low testosterone may simply be a marker of poor health

# Obesity and Children

Obesity and Children


<table>
<thead>
<tr>
<th>Table 1</th>
<th>Lean</th>
<th>Obese</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>25</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>16.5±1.4</td>
<td>16.0±1.5</td>
<td>0.17</td>
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<tr>
<td>BMI</td>
<td>20.9±2.2</td>
<td>36.0±5.3</td>
<td>&lt;0.001</td>
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<tr>
<td>BMI Z Score</td>
<td>-0.1±0.9</td>
<td>2.4±0.4</td>
<td>&lt;0.001</td>
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<tr>
<td>BMI percentile</td>
<td>49±25</td>
<td>99±1</td>
<td>&lt;0.001</td>
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<tr>
<td>Race: Caucasians</td>
<td>17 (68%)</td>
<td>15 (60%)</td>
<td>0.21</td>
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<tr>
<td>African Americans</td>
<td>7 (28%)</td>
<td>5 (20%)</td>
<td></td>
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<tr>
<td>Others</td>
<td>1 (4%)</td>
<td>5 (20%)</td>
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<tr>
<td>Sys BP</td>
<td>120±11</td>
<td>130±10</td>
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<tr>
<td>Dia BP</td>
<td>68±9</td>
<td>74±11</td>
<td>0.06</td>
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<tr>
<td>Heart Rate</td>
<td>67±13</td>
<td>75±15</td>
<td>0.05</td>
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<tr>
<td>Tanner stage</td>
<td>4.7±0.5</td>
<td>4.7±0.5</td>
<td>0.9</td>
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<tr>
<td>TT (nmol/l)</td>
<td>616.7 ng/dL</td>
<td>302.6 ng/dL</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>cFT (nmol/l)</td>
<td>0.44±0.18</td>
<td>0.26±0.11</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Testosterone concentrations (fasting, 8-10am) of young obese pubertal and post pubertal males are 40-50% lower than those with normal BMI

Hemochromatosis

• Hereditary Hemochromatosis
  – A common autosomal recessive disease characterized by an increase in iron absorption
  – Both 1° and 2° hypogonadism can occur with long-standing iron overload
    • 2° is much more common

• Iron overload, regardless of the cause, can result in hypogonadism

Elevated Prolactin (Hyperprolactinemia)

• Medications
  – Dopamine antagonists (antipsychotics, metoclopramide)

• Pituitary adenomas
  – microadenomas < 10 mm
  – macroadenomas ≥ 10 mm
  – lactotroph hyperfunction
    • stalk compression interrupting/reducing the tonic suppression of prolactin secretion by dopamine

• Hypothyroidism

• Stress (seizure), Chronic renal failure, Cirrhosis

• Chest wall injury (trauma, active herpes zoster)
Excess Estrogen

• Exogenous
  – Exposure to estrogen containing contraceptives/creams

• Endogenous
  – Testicular or adrenal estrogen-secreting tumors
  – Rare syndrome of aromatase excess

Anabolic Steroids

• Exposure to anabolic steroids can result in secondary hypogonadism and testicular atrophy
  – Deliberate or inadvertent exposure
  – May persist for years after cessation of the anabolic agents

• If clinical suspicion exists, a urine anabolic steroid screen can be obtained
Anorexia

- Anorexia nervosa is certainly far less common in males than in females
  - Excessive exercise, Low BMI

- Chronic malnutrition and cachexia, regardless of the cause, can result in secondary hypogonadism
  - Malabsorptive conditions: Crohn’s and celiac disease
  - Advanced cancer
  - Renal Failure (ESRD)

Acute Illness

• Gonadotroph Sick Syndrome
  – Hypogonadism is a relatively common finding in any critical illness
  – Analogous to euthyroid sick syndrome with respect to the hypothalamic-pituitary-thyroid axis
  – It is transient, and resolves with resolution of the underlying medical condition
    • sepsis, myocardial infarction, etc.

• Testosterone levels are invariably low
  – Checking is not recommended in this setting

HIV

• HIV can cause primary or secondary hypogonadism
• Can occur with active HIV infection, in patients whom control of viral replication has been obtained with HAART, and even in patients who have normalized CD4+ cell counts

• Development of hypogonadism in HIV patients is multifactorial
  – Weight loss
  – Opportunistic infections (pituitary/hypothalamus or testes)
  – Illicit drugs (heroin)
  – Medications
    • opioids, ganciclovir, ketoconazole, megestrol [appetite stimulant], cytoxan [malignancy]

Aging (? Andropause)

• Most reports have suggested an age-related decrease in testosterone levels  
  – Particularly in those > 65 years of age

• There also appears to be a loss of circadian rhythm in some, but not all, reports

• It appears that factors such as functional status and overall health may play a more important role in the pathophysiology of hypogonadism in males of advanced age rather than age alone

Chronic Medical Conditions

• Liver cirrhosis, renal failure (ESRD), and rheumatoid arthritis, etc., can play a role in the development of secondary hypogonadism
  – The pathogenesis may involve dysfunction in all components of the hypothalamic-pituitary-gonadal axis

• Multifactorial
  – Metabolic disturbances
  – High frequency of acute illness and hospitalization
  – Medications (corticosteroids, etc.)

Alcohol Abuse

• Alcohol can have adverse effects at all levels of the hypothalamic-pituitary-gonadal axis

• Resulting in low serum testosterone and reduced spermatogenesis

Severe Primary Hypothyroidism

• Can result in hypopituitarism

• Pituitary function usually recovers with restoration of euthyroidism

Pubertal Delay

• Depending on the age of presentation, differentiating pubertal delay vs. permanent hypogonadotrophic hypogonadism can be challenging.
Fertility

• In the male presenting with low serum testosterone, semen analysis is not routine

• Usually reserved for patients presenting with the primary complaint of infertility
Case Concluded

• The patient’s low serum testosterone was confirmed on subsequent measurements near 8 am
  – 128 and 182 ng/dL (reference range 249-836)

• LH 1.4 mIU/mL (reference range 1.2-8.6)
• FSH 2.7 mIU/mL (reference range 1.3-9.9)
  – Both inappropriately normal in the setting of the low serum testosterone

• Further evaluation noted a TSH of 248 µIU/mL (reference range 0.4-5.5) and a slight elevation of prolactin 24.6 ng/mL (reference range 1.6-18.8)
Case Concluded

- The patient was started on levothyroxine therapy and after 3 months was noted to be euthyroid (TSH 1.8 µIU/mL) and with normalization of the serum prolactin.

- Testosterone levels at that time were found to be 350 and 420 ng/dL (near 8 am).

- The cause of this patient’s secondary hypogonadism was severe hypothyroidism and secondary mild hyperprolactinemia.

- This case serves to illustrate that thorough evaluation is warranted prior to initiating testosterone therapy.
Case 2

- 41 year old male reports low testosterone noted on blood tests. His PCP ordered the test after the patient reported the inability to obtain an erection.
- He has been on Zoloft for ten years, he thought it was just the Zoloft.
- Reports zero sex drive.
- His wife initially accepted this thinking it was related to his depression and medications.
- Physical exam BMI 39, no gynecomastia, no testicular mass, no abnormal striae.
Labs

- Testosterone, Serum **20 ng/dL** (249-836)
- Testosterone, Free **0.59 ng/dL** (5.00-21.00)
- LH and FSH undetectable
- TSH 1.05 µIU/mL (0.34-5.60)
- Free T4 0.76 ng/dL (0.58-1.64)
- IGF-1 75 ng/mL (70-307)
- ACTH stim test normal
- Prolactin **276.4 ng/mL** (1.60-18.80)
MRI
Damage vs. Suppression

Levels of LH/FSH are often much lower, or even undetectable with gonadotroph damage vs. Levels of LH/FSH seen in the setting of gonadotroph suppression

The degree of testosterone lowering is often more profound with gonadotroph damage vs. gonadotroph suppression

Time of onset/duration has profound influence as well
Key Points

• Testosterone measurements should occur near 8 am
• A low serum testosterone value should always be confirmed by a reliable reference laboratory
• The definition of a low testosterone level varies from lab-to-lab
  – In general, values <200-250 ng/dL are clearly low in most laboratories, and values between 250-350 ng/dL may be considered borderline low
• Determine if the etiology is primary (testicular) or secondary (hypothalamic/pituitary)
• Acute illness and treatment with opioids, anabolic steroids, or corticosteroids can cause hypogonadism
My Suggested Approach

• Verify low Testosterone near 8 am
  – at least 1 confirmatory measurement
• Check LH/FSH, Prolactin, TSH/FT4, Ferritin
  • High yield
• Review medications and take detailed history and physical
• Further evaluation may include MRI brain, testicular US, and complete anterior pituitary hormone assessment
  – age, history, and testosterone level usually determine degree of further evaluation
  – refer to endocrinology at this stage if unsure
MRI
Secondary Hypogonadism

- The yield of pituitary-hypothalamic imaging in older men is fairly low in the absence of other pituitary hormone abnormalities/deficiencies
- There are limited data regarding appropriate criteria for performing pituitary imaging studies
- Many experts recommend imaging in patients with secondary hypogonadism when:
  - the total testosterone level is very low (e.g. <100-150 ng/dL)
  - there are abnormalities of multiple hypothalamic-pituitary axes
  - no clear identifiable etiology
  - if clinical symptoms warrant further testing with imaging
    - visual field deficits, cranial nerve palsy, etc.

Who should undergo assessment of testosterone status?

- Screening for androgen deficiency in the asymptomatic general population is not recommended

- The non-specific nature of many of the signs and symptoms of androgen deficiency makes it difficult to give concrete recommendations as to who should have testosterone levels measured

- Those with the complaint of ED should have their testosterone level assessed

Who should NOT undergo assessment of testosterone status?

• Those who are acutely ill and hospitalized
• Those who are severely obese and are complaining of fatigue
• Testosterone levels should be assessed only after the acute illness has resolved and, in a severely obese patient with fatigue, only after a thorough evaluation for sleep apnea has been undertaken
Treatment

• Discuss the R/B/A of treatment
  – This conversation between the physician and patient should include dialogue regarding the uncertainty of the risks and benefits of testosterone supplementation in the older male population
  – Treatment is only recommended in patients with clinically significant symptoms of androgen deficiency
  – Simply treating low T values is not recommended
  – Treat the underlying cause, if one can be found
    • May require referral to specialist

Treatment

• Make decision on individual basis

• You prescribe the testosterone, you do the f/u testing and monitoring!
  – PSA
  – HCT
  – DRE
  – Baseline, at 3 and 6 months, and then annually
Treatment Options

• Available modalities of testosterone replacement therapy (TRT) in the United States include:
  – Depot-testosterone –IM cypionate or enanthate
  – Topical solutions-Axiron
  – Gels-Testim, Androgel, or Fortesta
  – Patches-Androderm
  – Subcutaneous testosterone pellets-Testopel
  – Buccal-Striant SR
Oral Testosterone

• NOT approved for use in the United States
• Testosterone undecanoate has been used
  – available only in Canada and Europe
• Methyltestosterone, still available in the United States, should not be used since hepatotoxicity can be fatal
  – Prolonged use of the oral methyltestosterone formulation is associated with hepatocellular carcinoma, peliosis hepatitis, and other types of hepatotoxicities
  – Not seen with the other replacement preparations
Transdermal vs. IM

Started 5 mg via Androderm patch Q evening

Started 200 mg IM T enanthate Q 2 weeks

Dosage adjustments were allowed for both groups if adverse events occurred or morning T levels were outside the normal range of 306-1031 ng/dL.

Treatment Goals
Serum Testosterone Levels

- Transdermal preparations
  - mid-normal range
  - approximately 400-600 ng/dL
- IM testosterone cypionate or enanthate
  - approximately 400-700 ng/dL midway between injections
  - some advocate trough of 300-350 ng/dL
- Subcutaneous pellets
  - within the normal range at the end of the dosing interval

Role of anti-estrogen therapy in the treatment of low serum testosterone

• Although the use of anti-estrogen therapy (Clomiphene) or aromatase inhibitors for the sole purpose of raising serum testosterone is endorsed by some, this is not a common practice in the United States and it is generally discouraged by most specialists.

• However, these medications may be warranted in the setting of infertility where their utility is beyond that of merely increasing the levels of serum testosterone.
Contraindications

- According to the most recent Endocrine Society Guidelines, testosterone therapy is not recommended in patients with:
  - Breast or prostate cancer
  - Palpable prostate nodule or induration or PSA > 4 ng/ml without further urological evaluation
    - PSA > 3 ng/ml in individuals at high risk for prostate cancer
      - African Americans
      - Men with 1st degree relatives who have prostate cancer
  - Erythrocytosis (hematocrit > 50%)
  - Hyperviscosity
  - Untreated obstructive sleep apnea
  - Severe lower urinary tract symptoms with American Urology Association (AUA)/International Prostate Symptom Score (IPSS) greater than 19
  - Class III or IV heart failure (uncontrolled or poorly controlled)
  - Those desiring fertility

Stop therapy

• If HCT should rise to greater than 54%
  – Cessation of testosterone therapy should occur until HCT decreases to a safe level
  – Evaluate the patient for hypoxia and sleep apnea
  – If indicated, therapy should be reinitiated at a reduced dose

Stop Therapy and Consult Urology

- Verified serum or plasma PSA concentration greater than 4.0 ng/ml

- An increase in serum or plasma PSA concentration greater than 1.4 ng/ml within any 12-month period of testosterone treatment

- A PSA velocity of more than 0.4 ng/ml·yr using the PSA level after 6 months of testosterone administration as the reference
  - PSA velocity should be used only if there are longitudinal PSA data for more than 2 yr

- Detection of a prostatic abnormality on digital rectal examination

- An AUA/IPSS of more than 19

PSA Measurement

• The whole issue regarding PSA measurements has recently come under scrutiny and updated guidelines in the future may deemphasize this practice in men receiving testosterone supplementation

Testosterone Replacement Therapy and Prostate Cancer

• Since androgen deprivation leads to the regression of prostate cancer, there has been concern that TRT may lead to growth or de novo development of prostate cancer

• Historically, TRT has been strongly prohibited in patients with prostate cancer

• However, recent data has challenged this paradigm

Coward RM et al. BJU Int. 2009 May;103(9):1179-83.
Low Testosterone and Cardiovascular Risk

- Low testosterone levels are associated with an increase in the incidence of cardiovascular events and mortality
  - Independent of multiple risk factors and several pre-existing medical conditions
  - Mean/Median age >70 years

Low Testosterone and Cardiovascular Risk

• This does not mean treating the low testosterone ameliorates this risk
  – Analogous to problems seen with HRT in women

• Health status and age at initiation of supplementation may be important
  – The low T may simply be a marker of overall poor health
Testosterone supplementation in older men with a poor functional status and high prevalence of chronic disease may result in an increase in adverse cardiovascular outcomes.
Benefits of Testosterone Supplementation

• Feeling better/Improved quality of life
• Increase in lumbar spine bone mineral density
• Increase in lean body weight, reduction in fat mass
• Improvement in muscle strength
• Improved sexual function
• ? Effect on depression
• ? Improved cognition

Effects of TRT

• Systematic review and Meta-analysis of 30 trials included 1642 men, 808 of whom were treated with testosterone

• Negligible change in major lipid fractions:
  – LDL
  – HDL
  – Tg

• Inconsequential changes in blood pressure and glycemia

Effects of TRT

• In the aging, overweight male with type 2 diabetes and subnormal testosterone levels, treatment should be the implementation of lifestyle measures such as weight loss and exercise
  • May raise testosterone and provide multiple health benefits
• Simply providing testosterone supplementation may alter body composition in a metabolically favorable manner, but changes are modest and have not consistently translated into reductions in insulin resistance or improvements in glucose metabolism
  • May actually cause more harm than good
  • Jury is still out

Treatment

• At the present time, the clinical benefits and long-term risks of testosterone replacement therapy for patients with low testosterone secondary to type 2 diabetes, obesity, chronic medical conditions, or an age-related decline are unclear
  – The etiologies in older men

• Need clinical trials of long enough duration to clearly establish the benefits and risks of testosterone replacement in these populations

What to do?

• Despite the uncertainties, a 3 month trial in patients in whom the risks and benefits are unclear is not unreasonable.
• May be worthwhile in terms of improving quality of life.
• In the majority of patients, a positive response is usually delayed.
  – Physicians should be suspect when dramatic improvements are reported very soon after the initiation of supplementation.
What to do?

• Remember, TRT should **NOT** replace healthy lifestyle changes
  – Regular exercise, weight loss, diet modifications
  – May also provide the patient with symptom resolution

• There has been a dramatic increase in TRT initiation for non-specific symptoms of low testosterone in older androgen-deficient men
  – Significant risk of “overtreating”
  – Much remains unknown about the overall long-term risks and benefits of TRT

Everybody wants to feel better……

Testosterone therapy is not for everyone, nor is testosterone deficiency the explanation for everyone’s fatigue, erectile dysfunction, and lack of libido.
Etiology of fatigue in older men is likely multifactorial......
Testosterone Therapy