Risks Associated with Testosterone Replacement Therapy: A Safety Review

Dr. Kenneth Orbeck

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CE Credits: 1.25 contact hours

Target Audience: Pharmacists & Nurses

Program Overview:
The program is designed to assist pharmacists, nurses and nurse practitioners better understand the potential risks associated with testosterone replacement therapy. These health care professionals will also be updated on available testosterone treatment therapies. The program includes information on pharmacologic treatments, drug interactions, patient counseling, safety risks and a question/answer period.

Objectives:
- Identify the prevalence, epidemiology and pathophysiology of testosterone deficiency
- Interpret the signs and symptoms related to low testosterone and hypogonadism
- Outline pharmacologic therapies available for testosterone deficient patients based upon patient variables comorbidities
- Review recent findings on safety related issues regarding testosterone replacement therapy

Speaker:
Dr. Kenneth Orbeck practices integrative and functional medicine at his South Carolina-based bioidentical hormones practice, BodyLogicMD of Myrtle Beach. Dr. Orbeck dedicates his practice to helping women and men find relief from hormonal imbalances such as menopause, andropause (the male menopause), adrenal fatigue and thyroid disorders, using a three-tiered approach to wellness, combining customized nutrition and fitness regimens with bioidentical hormone therapy. Dr. Orbeck believes that proper diet, regular exercise and balanced hormones are the cornerstones of longevity. Dr. Kenneth Orbeck Orbeck received his undergraduate degree from Calvin College in 1983 and completed his Doctorate of Osteopathic Medicine at the University of Osteopathic Medicine and Health Sciences in 1987. Furthermore, Dr. Orbeck is currently an active member of the Fellowship for Anti-Aging, Regenerative and Functional Medicine (FARMM), and the Age Management Medical Group (AMMG).

Speaker Disclosure:
Dr. Orbeck has no actual or potential conflicts of interest in relation to this program.

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Low Testosterone

- Due to a decrease in bioavailable testosterone
- Less sudden in onset than female menopause
- May have serious long-term consequences
Low Testosterone Symptoms

- Loss of drive and competitive edge
- Decreased level of fitness and effectiveness of workouts
- Joint pain and muscle stiffness
- Increased brain aging
  - Decreased memory
- Increased heart/circulation aging
  - Increased MI’s and CVA’s
  - Decreased hemodynamic function

Sexual Function with Low Testosterone

- Reduced libido (desire) and fantasies
- Reduced morning erections
- Longer recovery time between orgasms
- Reduced erectile tension
- Decreased intensity of orgasms

Testosterone

- Secreted by the Leydig cells of the testes
- Under the influence of LH
- Young males normally produce 7mg/day
- Normally highest production in the morning

- "Life force hormone"; primary source of libido, associated with aggression
- Produced mainly in testes in men, secondarily in adrenals; produced in both adrenals and ovaries in women
- Protects against osteoporosis, helps maintain lean muscle mass, inhibits estrogen-induced proliferation of breast tissue
- "Androgynous de-differentiation of the sexes" in old age (relative estrogen decline in women, relative testosterone decline in men) (Hays B 2005)
**Testosterone Reduction**

- Low levels in both sexes associated with reduced bone density, libido, lean muscle mass
- Low testosterone can result from:
  - DM
  - Liver disease
  - Hemochromatosis
  - Obesity
  - Smoking
  - Chronic ETOH
  - Ketoconazole
  - Cimetidine
  - Glucocorticoids

**Dihydrotestosterone (DHT)**

- ~25% secreted by testes, 75% from bioconversion in liver, kidney, muscle, prostate, and skin
- Blood concentration of DHT is 10% that of T, but at least twice as potent due to increased affinity for androgen receptor; cannot be aromatized to estrogen
- Produced in utero, is responsible for development of male sex characteristics
- Primary contributing factor in androgenic alopecia, benign prostatic hypertrophy, hirsutism in women

**Enzymes That Produce DHT**

**Actions of DHEA – Anabolic**

- Prohormone for sex steroids
- Anti-glucocorticoid
- Immune supporting
- Anti-atherogenic, lowers serum triglycerides
- Enhances insulin sensitivity; anti-obesity effect
- Maintains tissue strength and repair, supports bone density
- Neuroprotective; enhances memory
- Promotes sense of well-being
Testosterone Decline

- "...recent years have seen a substantial, and yet unrecognized, age-independent population-level decrease in Testosterone in American men."
- "The population-level declines are greater in magnitude than the cross sectional declines in Testosterone typically associated with age."


Testosterone Decline

- Testosterone declines with age beginning in the early 30's
- By age 40, levels naturally decline by 1% per year
- Testosterone production declines due to
  - Increasing SHBG
  - Decreasing LH
  - Decreased Leydig cell activity
- During the time between 25 to 75 years old:
  - 30% decrease in Total Testosterone
  - 50% decrease in Bioavailable Testosterone

Testosterone Decline

- "Half of healthy men between the ages of 50-70 years will have a bioavailable testosterone level below the lowest level seen in healthy men who are 20-40 years of age."
- Diet and insulin resistance
- Stress levels/cortisol demand
- Toxic exposure


Insulin Increase

- High carbohydrate diet
- Increased Stress
- Decreased estrogens
- Increased testosterone
- Insomnia
- Increased DHEA
- Decreased Thyroid
- Excessive progesterone
- Lack of exercise

Insulin and Sex Hormones

Elevated insulin levels can decrease the synthesis of DHEA, the precursor to the other sex hormones

- Insulin decreases the adrenal enzyme 17,20-lyase which makes DHEA

Smith, P. "HRT: The Answers", 2003
What Constitutes “Stress”?

- “Fight or flight” responses
- Fear, anxiety, worry
- Depression, feelings of defeat or helplessness
- Pain syndromes
- Infection, inflammation
- Hypoglycemia
- Inadequate sleep
- Disrupted sleep wake cycles
- Toxic exposure

“CORTISOL STEAL” or PREGNENOLONE SHUNT

Toxins

- Esters of phthalic acid and are mainly used as plasticizers
- Environmental Toxins
  - Jet fuels
  - Pesticides / Insecticides
  - Organic solvents

**Toxins - Phthalate Sources**

- Personal care items
  - Make-up, shampoo, moisturizer, liquid soap, hair spray, cologne
- Detergents
- Cleaning materials

**Phthalate Syndrome**

- "A variety of effects on the development of the reproductive system can be observed in males at much lower doses than previously observed after exposure to various phthalates."

- Phthalate syndrome
  - Infertility
  - Decreased sperm count
  - Cryptorchidism
  - Hypospadias
  - Other reproductive tract malformations.

- Those effects are characteristic more generally of disturbance of androgen action.


**Bisphenol A**

- Primarily used to make plastics
- Polycarbonate bottles (clear, flexible plastic)
- BPA is an endocrine disruptor and can mimic the body's own hormones


- Early development appears to be the time of greatest sensitivity to its effects

- In 2007, a consensus statement by 38 experts on bisphenol A concluded that average levels in people are above those that cause harm to animals in laboratory experiments


**BPA and Obesity**

- A 2008 review has concluded that obesity may be increased as a function of BPA exposure
  
  Elobeid et al, Current opinion in endocrinology, diabetes, and obesity 15 (5): 403–408

- A 2009 review of available studies has concluded that "perinatal BPA exposure acts to exert persistent effects on body weight and adiposity".
  

- A 2009 review has concluded that "Eliminating exposures to (BPA) and improving nutrition during development offer the potential for reducing obesity and associated diseases".
  

**Low Testosterone and Mortality**

- 800 men over 50 years old followed 18 years
- Compared mortality in the lower 1/3 level of testosterone with the upper 1/3
- The group of men in the lower 1/3 testosterone level group had a 33% increased rate of death from all causes than the upper 1/3
- In men with Metabolic syndrome:
  - Testosterone 22% lower
  - Testosterone levels inversely related to IL-6 and CRP

Risks Associated with Testosterone Replacement Therapy: A Safety Review

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**Testosterone and Erectile Dysfunction**

- "Visceral obesity, a component of metabolic syndrome, adversely affects endothelial function and testosterone levels, contributing to hypogonadism and erectile dysfunction."
- Clinical screening for the risk of erectile dysfunction in obese patients should include:
  - Waist circumference
  - Testosterone levels
  - Body mass index
  - Physical inactivity


**Testosterone and Cognitive Function**

- Testosterone correlated with cognitive function and
- TRT improves it:
  - High free testosterone was associated with better performance on tests of memory, executive function and spatial ability
  - Reduced risk for Alzheimer's
  - Improved cerebral blood flow
- Androgen supplementation in elderly hypogonadal men improves spatial cognition and verbal fluency
- In elderly men without dementia, it may reduce working memory errors
- Testosterone or DHT therapy in men aged 34 to 70 years improved verbal memory and spatial memory respectively


**Testosterone and Alzheimer’s**

- TRT prevents the production of beta amyloid precursor protein in men
- Testosterone reduces neuronal secretion of Alzheimer’s beta-amyloid peptides.
  Proc Natl Acad Sci USA 2000 Feb 1;97(3):1202-5
- Alzheimer's male patients TRT treated improved over 1 year; control group deteriorated


**Testosterone and Cardiovascular Risk**

- Testosterone improves exercise induced ST depression
- Lower testosterone associated with coronary artery disease & atherosclerosis
- Low testosterone associated with dyslipidemia
- Testosterone dilates coronary arteries
- Testosterone reduces angina
  - Exercise induced ischemia reduced
  - Improvements in pain perception and limitations

Testosterone and Inflammation

- anti-inflammatory profile
- Fewer inflammatory cytokines, TNF, IL-1 beta
- More anti-inflammatory cytokines - IL-10
- Lower total cholesterol
- Pathogenic role in the initiation and progression of coronary atheroma
- Cytokines are the mediators of cellular inflammation


Testosterone and BPH

"Multiple studies have failed to demonstrate the exacerbation of voiding symptoms attributable to benign prostatic hypertrophy during testosterone supplementation"

- "Testosterone replacement therapy appears to have little effect on prostate tissue androgen levels and cellular function and causes no significant adverse effects on the prostate."
- "At the present time, there is no conclusive evidence that testosterone therapy increases the risk of prostate cancer or benign prostatic hyperplasia (BPH)"


Proprietary Information of BodyLogicMD, Inc.

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Testosterone and Prostate Cancer

Risk of testosterone therapy inducing prostate cancer:
- Review of 16 studies – some placebo controlled
- No increased risk over background prevalence
- Up to 15 years following patients


Morgentaler A Testosterone and Prostate Cancer: An Historical Perspective on a Modern Myth. Eur Urol. 2006 Jul 26; - 1941: Huggins and Hodges reported that reductions in testosterone via castration or estrogen treatment caused metastatic prostate CA to regress
- Administration of exogenous testosterone caused a PC to grow (one patient)
- Multiple reports revealed no PC progression with testosterone administration

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**Conclusions regarding TRT and Prostate Cancer**

- Low levels of testosterone do not protect against prostate cancer.
- High levels of testosterone do not increase the risk of prostate cancer.
- Treatment with testosterone does not increase the risk of prostate cancer.
- Men with history of metastatic prostate cancer that have had treatment to reduce testosterone level to near zero, may have increased risk with testosterone supplementation.

**Testosterone, DHEA and Alopecia**

**Complaints of Testosterone Deficiency**

- Decreased muscle mass and strength
- Decreased sex drive
- Reduced frequency and firmness of erections; reduced ejaculate volume
- Hot flushes
- Excessive emotions/sensitivity to difficulty
- Unnecessary worry, anxiety, fear
- Depression
- Loss of self confidence
- Joint pains
- Persistent fatigue that increases with activity


**Physical Signs of Testosterone Deficiency**

- Dry eyes
- Reduced muscle tone
- Depressed attitude
- Nervous, irritable, hesitant
- Poor concentration and memory
- Decreased axillary and pubic hair
- Pale skin
- Increased fat in breasts, abdomen and hips
- Anemia

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Testing for Testosterone Deficiency

• Blood testing (serum)
  – Total/free testosterone
  – SHBG
  – DHT
  – DHEA
  – Estrone and Estradiol
  – LH/FSH
• 24 hour urine testing
• Saliva testing
• Blood spot testing

Caveats for Optimal Testing

Avoid for 24 – 72 hours prior to testing:

– Sexual intercourse
– Vigorous exercise
– Emotional stress

Serum vs. Saliva testing


Interim Conclusions

• Increased insulin resistance has lead to an obesity epidemic
• Increased environmental toxins has created endocrine disruption leading to inflammation and imbalance
• Increased stress/cortisol demand has contributed to the obesity epidemic and enhanced hormonal imbalances
  – Decreased availability of progesterone for testosterone production and estrogen balance
  – Decreased availability of DHEA
  – Increased aromatization of testosterone to estrogen resulting in a pro-inflammatory environment

Interim Conclusions

• The environment for increased inflammation and its disease consequences has been created:
  – Increased adiposity and testosterone conversion to estrogen
  – Decreased testosterone, progesterone and DHEA production
• Limit toxin exposure.
• Focus on hormone balance for all hormones; testosterone, estrogen, progesterone, DHEA, insulin, cortisol and thyroid.
General Treatment Plan

- Increase insulin sensitivity:
  - Low glycemic index diet to reduce glucose load and need for insulin
  - As need for insulin remains low over time, receptors begin to upregulate and insulin sensitivity increases
- Increase exercise and build lean muscle mass
- Reduce stress/cortisol demand
  - Yoga, Tai chi, exercise
  - Recognizing sources of stress and setting boundaries
  - Investigating other possible sources (Gluten intolerance)

Testosterone Replacement

- Considerations:
  - Will patient use gels, injections, SL, etc?
  - Does the patient wish to maintain his fertility?
  - What is the testicular function?
  - What lifestyle changes does the patient need to make?
  - Does the patient have a history of elevated PSA or prostate disease/cancer?

Injectable Testosterone

- Testosterone esters in oil are slowly absorbed from the lipid phase
- Different esters absorb at various rates giving them different half lives:
  - T cypionate 12 days
  - T enanthate 10.5 days
  - T propionate 4.5 days
- The longer acting esters may convert more readily to estrogen
Testosterone Replacement: Testosterone cypionate Injections

- Commercially available or compounded
- Q2 weeks 200mg IM (Older method)
  - Supraphysiologic levels followed by low levels
  - More aromatization to estradiol
  - Less DHT than transdermal
- Weekly dose 60 - 100mg IM
  - Better physiologic, stable levels
  - Less aromatization to estradiol
- Bi-weekly dose 40-60mg IM or SQ
  - SQ may have more consistent levels (Shippen)

Testosterone Replacement: Transdermal (Gel versus Cream)

- Well absorbed in most men
- Serum levels may not be as useful for creams
  - saliva may reflect levels better
- Higher conversion to DHT since hair follicles contain 5 alpha reductase
  - 5 alpha reductase inhibitors
- Saw palmetto, metformin, spironolactone, finasteride
- Steady state after 24 hours

Testosterone Replacement: Transdermal

- Commercially Available:
  - Androderm patches: 5mg per day
  - Androgel, Testim
    - 1% transdermal gel
    - 50, 75 and 100mg packages
- Compounded testosterone
  - Dose between 5-50mg/day
    - Physiological doses: 5-10mg/day
    - Can custom produce transdermal gel or cream
    - Can titrate serum levels by varying percentage (1-10%) and dose

Testosterone Replacement: hCG

- Human chorionic gonadotropin
- Polypeptide hormone produced by the human placenta
  - Alpha and beta subunit
    - Alpha subunit is essentially identical to the alpha subunits of LH and FSH
- Stimulates testes to produce more testosterone
- Avoids the testosterone replacement side effects of lower sperm count and loss of testicular volume
- If FSH and LH already high, it probably won’t work
- hCG alone (no exogenous testosterone) is the preferred therapy for men under 40 with adequate testicular function
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Testosterone Replacement: hCG
John Crisler, DO Method

- Augments testosterone production for those on exogenous testosterone therapy as well
- Testosterone replacement depresses LH due to HPA axis suppression/feedback
  - hCG is an LH analog
- 250IU SQ hCG on days 5 and 6 of weekly testosterone cypionate IM injections
- 250IU SQ every 3rd day for transdermal T
- No need to ever go over 500IU on any given day
  - Too much stimulation of testicular aromatase
  - Induces Leydig cell desensitization

Contraindications for Testosterone Therapy

- Active Prostatic carcinoma
- Breast cancer
- Prostate nodules or indurations
- Unexplained prostate-specific antigen (PSA) elevation
- Erythrocytosis (hematocrit >50)
- Unstable congestive heart failure
- Severe untreated sleep apnea

Clinical Care with Testosterone Replacement Therapy

- Prior to starting therapy:
  - Physical exam with DRE (digital rectal exam)
  - Essential labwork: total/free T, PSA, SHBG, FSH, LH, E2, DHT, CBC, prolactin, lipids, LFT's
  - Additional lab work: Thyroid panel, fasting insulin, hemoglobin A1C, cardiac risk factors, bone density
- Every 3-6 months until stable:
  - Total/free T, CBC, PSA, E1, E2, lipids, LFT's, DHT and SHBG
  - Titrate T and E2 to stay in physiologic range minimize E1
  - DRE every 6 months

Urological Consult

- Verified serum PSA is >4.0 ng/ml
- Increase in serum PSA concentration more than 1.4 ng/ml within any 12 month period of testosterone therapy
- PSA velocity of >0.4 ng/ml/year using PSA after first 6 months as a reference
- Detection of prostate abnormality on DRE
- An American Urological Association Prostate Symptom Score of >19

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Dangers of Unsupervised Testosterone Use

- TRT Controversial
- Complications
  - Active drug
  - Byproducts
- Disease states
  - Prostatic Inflammatory disease
  - Prostate cancer

Summary

- Testosterone is safe and effective if used under medical supervision
- Variety of products and delivery systems
- Optimize quality of life