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Learning Objectives

• At the conclusion of this activity, the participant will be able to:
  – Discuss causes and symptoms of androgen deficiency in the adult male.
  – Explain various hormones that can be used in testosterone replacement therapy.
  – Discuss how to stimulate endogenous production of testosterone.

Reference


Dedication

• This seminar is dedicated in loving memory of Dr. Alicia Stanton whose ground breaking work in hormone replacement therapy lives on in the work of others.
Andropause

- Definition
  - An absolute or relative insufficiency of testosterone or its metabolites in relation to the needs of that individual at that time in his life.
  

Levels of Testosterone

- 30% to 60% of men in their 70s are hypogonadal
  
Levels of Testosterone (cont’d)

• Half of healthy men between the ages of 50-70 years will have a testosterone level below the lowest level seen in healthy men who are 20-40 years of age.


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Men - Testosterone Decline

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Levels of Testosterone (cont’d)

• The Massachusetts Male Aging Study showed a 30-year fall in total testosterone in men averaging 48% and a decline in free testosterone of 85%.

Levels of Testosterone (cont’d)

• There are also seasonal variations in levels of testosterone with peak levels found in the summer and early fall and lower levels in the winter and early spring.


Healthy Male Daily Hormone Production

• Cortisol - 20-30 mgs/day
• Testosterone - 5-6 mgs/day
• Androstenedione - 3 mgs/day
• DHT - 0.300 mgs/day
• Estrone - 0.066 mgs/day
• Estradiol - 0.045 mgs/day
• DHEAS - 50 mgs/day
• DHEA - 15 mgs/day

Testosterone

• Testosterone replacement therapy for men is safe and can provide significant benefits.
• Uncontrolled and controlled trials date back over 70 years.
• There is not a reported age at which hormone replacement in men over the age of 50 should not be considered.
Causes of Androgen Deficiency in the Adult Male

• Causes are multifactorial
  – Cerebral cortex
  – Hypothalamus and pituitary
  – Testes
  – Target organs

Cerebral Cortex

• Aging process
• Stress
  – Testosterone levels rise when a male achieves or defends a dominant position.
  – Testosterone levels fall when a male is dominated.
  – Excessive stress, both physical and mental, has been shown to activate the HPA axis and decrease the amount or activity of androgens.
  – Physical illness
Cerebral Cortex (cont’d)

- Drugs
  - Psychotropics
    - Antidepressant, anxiolytic, antiepileptic, antipsychotic drugs

References


Hypothalamus and Pituitary

- Age
- GnRH decreased
  - One cause is opiates: heroin, morphine, methadone
Hypothalamus and Pituitary (cont’d)

• High prolactin levels
  – Prolactin levels may increase with stress
  – Prolactin levels may increase with prolactinomas
  – Chronic renal failure
  – Hypothyroidism
  – Drugs can raise prolactin levels


Medications That Can Raise Prolactin Levels

• Drugs that are dopamine antagonists
  – Phenothiazines and imipramine
• Drugs that interfere with dopamine synthesis
  – Alpha-methyldopa

Medications That Can Raise Prolactin Levels

• Drugs that deplete dopamine stores
  – Reserpine
• Drugs that directly stimulate prolactin production
  – H2-blockers
  – Estrogens

Testes

- Impaired development
  - Non-descent or late descent
- Heredity and familial influences
  - Diet, physical activity


Testes (cont’d)

- Age

Testes (cont’d)

- Alcohol
  - Short-term low dose ETOH increases testosterone
  - Short-term low dose or high dose ETOH decreases testosterone
  - Physical stress immediately before ETOH use prolongs the reduction in testosterone
  - Alcoholics may have thyroid and adrenal dysfunction which may further lower testosterone
  - Alcoholics may have high estrogen levels

Testes (cont’d)

• Diet
  – Low cholesterol diets may lower testosterone
  – Vegetarian diets, particularly if low in protein, can increase SHBG which lowers free testosterone.
  – Also men on low-fat, high-fiber, vegetarian diets were shown to have lower total and free testosterone which was reversed when they went back on their regular diet.
  – High-protein, low carb eating programs may increase testosterone

Testes (cont’d)

• Diabetes

Testes (cont’d)

• Temperature
  – Varicocele and hydrocele impair the temperature regulation of the scrotum which keeps the testes at the right temperature
  – Scrotal cooling may be improved by wearing boxer shorts, avoiding tight jeans and long periods of driving

• Trauma
  – Injury
  – Surgery
Testes (cont’d)

• Drugs
  – Psychotropic drugs
  – Chemotherapy
  – Aminoglutethimide
  – Cannabinoids
  – Ketoconazole
  – Heroin, methadone
  – Cimetidine
  – Spironolactone
  – Cyproterone acetate
  – Barbiturates
  – Anticonvulsants
  – Digoxin
  – HMG-CoA reductase inhibitors

References


References (Cont.)

Target Organs

• Age
• Receptor anomalies
• Reduction and down-regulation

Target Organs

• Connective-tissue thickening
• Drugs
  – Aromatase inhibitors
  – Alpha1 and alpha2 adrenoceptor blocking agents can increase tissue resistance to androgen action

References

References (cont’d)

References (Cont.)

References (cont’d)
Functions of Testosterone

• Sex hormone
• Receptors all over a male’s body
• Involved in the making of protein and muscle formation
• Helps manufacture bone
• Improves oxygen uptake throughout the body
• Helps control blood sugar
• Needed for normal sperm development
• Regulates acute HPA responses under dominance challenge

Functions of Testosterone (cont’d)

• Helps regulate cholesterol
• Helps maintain a powerful immune system
• Aids in mental concentration
• Improves mood
• Helps protect the brain against Alzheimer’s disease
• Regulates the population of thromboxane A2 receptors on megakaryocytes and platelets and therefore platelet aggregation
References

References (cont’d)

Signs and Symptoms of Andropause
**Signs and Symptoms of Andropause**

- Fatigue, tiredness, or loss of energy
- Depression, low or negative mood
- Irritability, anger, or bad temper
- Anxiety or nervousness
- Loss of memory or concentration
- Loss of sex drive or libido
- Loss of erections or problems during sex
- Decreased intensity of orgasms
- Weight gain

**Signs and Symptoms of Andropause (cont’d)**

- Backache, joint pains, or stiffness
- Loss of fitness
- Feeling over-stressed
- Decrease in job performance
- Decline in physical abilities
- Bone loss
- Elevated cholesterol
- Increased risk of heart disease
- Increased risk of insulin resistance, diabetes and metabolic syndrome

**Testosterone: Target Organs**
Low Testosterone Levels/Related to Increased Risk of CHD

- Trial showed men with coronary heart disease had a significantly lower total testosterone, free testosterone, and bioavailable testosterone.


Low Testosterone Levels/Related to Increased Risk of CHD (cont’d)

- Studies revealed low endogenous testosterone concentrations are related to mortality due to cardiovascular disease and other causes.


Low Testosterone Levels/Related to Increased Risk of CHD (cont’d)

- Study showed a possible correlation between lower testosterone levels, erectile dysfunction and conditions associated with higher cardiovascular risk.

Low Testosterone Levels/Related to Increased Risk of CHD (cont'd)

- Study revealed that men with coronary heart disease that were under the age of 45 had total and free testosterone levels significantly lower than controls.
  

Low Testosterone Levels/Related to Increased Risk of CHD (cont’d)

- Serum free testosterone levels were found to be inversely related to carotid intima-media thickness (IMT) and plaque score.
  
  * Bhasin, S., et al., "Serum free testosterone is inversely related to carotid intima-media thickness (IMT) and plaque score," Diabetes Care 2003; 26:1869-73.

Low Testosterone Levels/Related to Increased Risk of CHD (cont’d)

- Low testosterone levels were found to be associated with atherosclerosis in men.
  
Low Testosterone Levels/Related to Increased Risk of Diabetes and Metabolic Syndrome

- Low testosterone levels are associated with an increased risk for the development of type II diabetes and metabolic syndrome.

References


References (cont’d)

Low Testosterone Levels/Related to Increased Risk of Diabetes and Metabolic Syndrome (cont’d)

• Since testosterone has been shown to lower blood sugar levels, the Endocrine Society now recommends measurement of testosterone in all male patients with type II diabetes.


Low Testosterone Levels Related to Increased Risk of Mortality

• Study showed that low testosterone predicts mortality from cardiovascular disease.


Low Testosterone Levels Related to Increased Risk of Mortality (cont’d)

• Study showed that low testosterone levels were associated with an increased risk of all-cause mortality independent of numerous risk factors. Serum testosterone levels were inversely related to mortality due to cardiovascular disease and cancer.

Low Testosterone Levels Related to Increased Risk of Mortality (cont’d)

• Low endogenous testosterone levels are associated with an increased risk of death from all causes and cardiovascular disease.


Low Testosterone Levels and Hypertension

• Study showed that low total testosterone concentrations are predictive of hypertension, suggesting total testosterone as a potential biomarker for increased cardiovascular risk.


Low Testosterone and Congestive Heart Failure

• In males with heart failure, low serum androgens were associated with an adverse prognosis.

Low Testosterone and Congestive Heart Failure (cont’d)

- In men with chronic heart failure, anabolic hormone depletion is common and deficiency of each anabolic hormone is an independent marker of poor prognosis.

Men: Testosterone and Memory

- In an animal trial, the authors suggested that the development of memory loss in males is related to the loss of testosterone that occurs with age in a male.

Men: Testosterone and Memory (cont’d)

- In men, testosterone plays a major role in brain functioning
- Subclinical androgen deficiency has been suggested to increase the expression of amyloid-B-related peptides in vivo.
Men: Testosterone and Memory (cont’d)

• In this study, age-related decline in free testosterone predicted age-related decline in visual and verbal memory.

Men: Testosterone and Memory (cont’d)

• Low levels of bioavailable testosterone are a positive predictor of memory loss in men as they age.

Men: Testosterone and Memory (cont’d)

• In a medical trial done in Hong Kong, in men with low bioavailable testosterone levels there was a strong correlation with memory loss/Alzheimer’s disease.
Men: Testosterone and Memory (cont’d)

- Males that have a higher ratio of total testosterone to SHBG have a lower rate of development of Alzheimer’s disease.

- Patients with Alzheimer’s disease have been shown to have a lower ratio of total testosterone to SHBG when compared with age-matched controls.

- In another medical trial, which was a prospective longitudinal study, revealed that the risk of Alzheimer’s disease was decreased by 26% for each 10-unit (nmol/nmol) increase in free testosterone at 2, 5, and 10 years before the diagnosis of Alzheimer’s disease was made.
Men: Testosterone and Memory (cont’d)

- Low levels of testosterone may occur prior to the diagnosis of Alzheimer’s disease.
  * Ibid., Moffat.

Men: Testosterone and Memory (cont’d)

- Low testosterone levels have also been associated with mild memory loss that is not related to Alzheimer’s disease.

Men: Testosterone and Memory (cont’d)

- Studies have also shown a correlation between testosterone levels and cognitive abilities such as spatial performance and mathematical reasoning.
Men: Testosterone and Memory (cont’d)

- Studies done in animals have shown that depletion of androgens results in increased pathologic conditions that are associated with Alzheimer’s disease.
  - Increased antibody levels
  - Increased neuronal death
  - Hyperphosphorylation


Men: Testosterone and Memory (cont’d)

- Studies in animals also have shown that both testosterone and dihydrotestosterone have an effect on the upregulation of the hippocampal neurogenesis in adult male rats.


Men: Testosterone and Memory (cont’d)

- Higher levels of free concentrations have been associated with better performance in specific aspects of memory and cognitive function.
- Furthermore, optimal processing capacity was found in men between the ages of 35 and 90 even after adjustment for age, education, and CV morbidity.
References


Men: Testosterone and Memory (cont’d)

• The same was not true of total testosterone levels.

Men: Testosterone and Memory (cont’d)

• In men that have undergone hormonal treatments for prostate cancer with suppression of endogenous testosterone synthesis and blockade of the androgen receptor, studies have shown that there is a beneficial effect on verbal memory but an adverse effect on spatial performance.
Men: Testosterone and Memory (cont’d)

• Likewise, in another study on males receiving treatment for prostate cancer, these patients also had visuomotor slowing and slowed reaction times in several attentional domains.

• In the same patients plasma amyloid levels elevated as testosterone levels declined.


Men: Testosterone and Memory (cont’d)

• In this study, when treatment for prostate cancer was discontinued, memory improved but visuospatial abilities did not.


Testosterone Biosynthesis
Androgen Synthesis

Testosterone Biosynthesis
• In the adult male, 95% of the testosterone that is circulating in the blood is made in the Leydig cells of the testes which is 6-7 mg a day of testosterone is made in the healthy adult man.
• The remaining 5% of the circulating testosterone is made in the adrenal glands.

Testosterone Biosynthesis (cont’d)
• The making of testosterone is regulated by biofeedback mechanism which can be influenced by physiological, pharmacological, and lifestyle factors.
Sex Hormone Binding Globulin (SHBG)

- SHBG is a protein that transports androgens and estradiol in men in the blood and regulates the bioavailability and access to target cells.
- SHBG binds more to androgens than estrogens.
- SHBG mediates androgen and estrogen signaling as well.

Free Testosterone vs. SHBG

SHBG

- SHBG is a protein made most by the liver
- It is also made by the testes and brain
- SHBG serves as a transport center to move testosterone and estrogen
- Therefore, it regulates hormone levels throughout the body

SHBG (cont’d)

- SHBG also sends signals to the heart, brain, and adipose tissue to ensure optimal function.
  
  
SHBG (cont’d)

- On cell surfaces there is a SHBG receptor molecule that helps cells communicate with other cells.


SHBG (cont’d)

- SHBG also regulates the bioavailable fraction of sex hormones and access to SHBG receptor cells in sex steroid target organs in the body.
  - Testes
  - Prostate
  - Breast
  - Bone
  - Muscles
  - Brain

SHBG (cont’d)

- SHBG may increase with age

- Consequently as hormone levels decline even lower levels may be available for the body to use since more of the hormones may be bound to SHBG.
- Therefore it is important to measure SHBG
SHBG (cont’d)

- Most of the testosterone in the body is bound to albumin or SHBG.
  
  

SHBG (cont’d)

- The combination of free and albumin-bound testosterone is what determines the bio-available amount of testosterone.
  
  * Pines, C., et al., “Variations in the concentration of the sex hormone binding globulin is a major factor causing a variation in total testosterone values,” Endocrinol Nutr 2000; 56(4):209-12.
  

References


SHBG (cont’d)

• High levels of estrogen increase the body’s production of SHBG in a male. Therefore high levels of estrogen cause more testosterone to be bound in a male. Signs of feminization may occur.
• High levels of testosterone depress production of SHBG in a male.

References


Low SHBG

• Low SHBG levels are associated with an increased risk of metabolic syndrome.
Low SHBG (cont’d)

• In men, low SHBG and low total testosterone levels are associated with an increased risk of metabolic syndrome.
  * Ibid., Saad.
  * Brand, J., et al., “Associations of endogenous testosterone and SHBG with glycated haemoglobin in middle-age and older men,” Clin Endocrinol (Oxf) 2010; Dec 15.

References


Low SHBG

• Low levels of SHBG in men are associated with an increased risk of mortality from cardiovascular disease.
  * Ibid., Kalme.
Low SHBG (cont’d)

• Low SHBG levels in males are associated with obesity.

Low SHBG (cont’d)

• Low levels of SHBG are associated with elevated levels of CRP, triglycerides, and LDL levels.

Low SHBG (cont’d)

• Low levels of SHBG are also associated with arterial calcification.
Low SHBG (cont’d)

• Studies in males have shown a correlation between sleep apnea and decreased SHBG, free testosterone, and total testosterone levels.

Low SHBG (cont’d)

• The lower the levels of SHBG, free testosterone, and total testosterone, the more it is associated with severe sleep apnea.
  * Ibid., Grunstein.
  * Ibid., Meston.

Low SHBG (cont’d)

• In a medical trial, men were treated for 3 months for sleep apnea with CPAP and their SHBG and total testosterone levels rose.
  * Ibid., Grunstein.
SHBG

- Causes of low SHBG in men
  - Hypothyroidism
  - Hyperprolactinemia
  - Excess androgen syndromes
  - Anabolic steroid use
  - Cushing’s syndrome

High SHBG

- High SHBG levels predict more severe and invasive tumor growth in men with prostate cancer.
  
  

High SHBG (cont’d)

- A rise in SHBG with age has a strong association with osteoporosis.
- SHBG may be a useful marker for predicting the severity of osteoporosis.
  
References


SHBG

- **Causes of high SHBG in men**
  - Hyperthyroidism
  - Androgen insensitivity
  - Cirrhosis of the liver
  - Aging process
  - Anticonvulsants
  - GH deficiency


Replacement of Male Hormones
Male Hormones
- Pregnenolone
- DHEA
- Estrone/Estradiol
- Dihydrotestosterone
- Androstenedione
- Testosterone

Lab Work
- Total testosterone, free testosterone vs. salivary testing
- DHT
- Estradiol
- Estrone
- DHEA
- CBC
- Cortisol
- SHBG
- Progesterone
- PSA
- Albumin
- Traditional lab work: SMA

Digital Rectal Examination
- Digital rectal examination should be performed every six months if the patient is on testosterone replacement therapy.
Lab Work (cont’d)

- A PSA of <4.0 but rising by 1.5 ng/ml in one year or 0.75 ng/ml per year over two years should have further evaluation.
- PSA > 4 should have further evaluation

Pregnenolone

Functions of Pregnenolone

- Regulates the balance between excitation and inhibition in the nervous system
- Increases resistance to stress
- Improves energy both physically and mentally
- Enhances nerve transmission and memory
- Reduces pain and inflammation
- Blocks the production of acid-forming compounds
Functions of Pregnenolone (cont’d)

• Modulates the neurotransmitter GABA
• Helps to repair nerve damage
• Promotes mood elevation
• Improves sleep
• Modulates NMDA receptors
  – Regulates pain control, learning, memory, and alertness

Causes of Low Pregnenolone Levels

• Aging process
• Eating too much saturated fat and trans-fats
• Low cholesterol levels
• Hypothyroidism
• Pituitary tumor
• Having a severe illness
  – Pregnenolone will make more cortisol and less of the other hormones to help the body deal with stress.

Symptoms of Pregnenolone Deficiency

• Arthritis
• Depression
• Fatigue
• Inability to deal with stress
• Insomnia
• Lack of focus
• Memory decline

References


References


Pregnenolone Used in Treatment

- Arthritis
- Depression
- Memory loss
- Fatigue
- Moodiness
- Improves delta-wave sleep
- Prevention of memory loss
- Autoimmune diseases such as rheumatoid arthritis, ankylosing spondylitis, and lupus
References

References

New Study: Use of Pregnenolone
- Pregnenolone may protect the brain from cannabis intoxication.
Elevated Pregnenolone Levels Can Cause the Following Symptoms

- Acne
- Drowsiness
- Muscle aches
- Fluid retention
- Headache
- Heart racing
- Insomnia due to overstimulation
- Irritability, anger, anxiety

Dose of Pregnenolone

- Start with 10 mg
- Use SR form since it is more physiologic
DHEA

- Is a hormone made by the adrenal glands.
- A small amount is also made in the brain and skin.
- DHEA production declines with age starting in the late twenties.
- By the age of 70 the body may only make ¼ of the amount of DHEA it made earlier.
- DHEA makes estrogen and testosterone in both women and men.

Functions of DHEA

- Decreases cholesterol
- Decreases formation of fatty deposits
- Prevents blood clots
- Increases bone growth
- Promotes weight loss
- Increases brain function
- Increases lean body mass

Functions of DHEA (cont’d)

- Increases sense of well-being
- Helps one deal with stress
- Supports the immune system
- Helps the body repair itself and maintain tissues
- Decreases allergic reactions
- Lowers triglycerides
References


Etiologies of Low DHEA

- Andropause
- Decreased production
- Stress
- Aging
- Smoking (nicotine inhibits the production of 11-beta-hydroxylase which is needed to make DHEA)

Replacement of DHEA

- Increases muscle strength and lean body mass
- Activates immune function
- Increases quality of life
- Improves sleep
- Increases feeling of wellness
Replacement of DHEA

- Decreases joint soreness
- Increases sensitivity of insulin
- Decreases triglycerides
- Stops the damaging effects of stress
- Elevates growth hormone levels

References


References (cont’d)

References (cont’d)

References (cont’d)

Symptoms of DHEA Excess
- Fatigue
- Anger
- Depression
- Deepening of voice
- Insomnia
- Mood changes
- Weight gain
- Facial hair
- Acne
- Sugar cravings
- Restless sleep
- Irritability
Dose of DHEA

- Higher doses can be used in males vs. females
- Male dose: 5 mg to 50 mg
- Use SR since it is more physiologic

Estrogens

Estrogen Levels in Males

- Men make estrone, estradiol, and estriol
- It is important to measure both estrone and estradiol
- Estriol is still experimental
- Males need a small amount of estrogen to help maintain memory and maintain bone structure
Estrogen: Men and Memory

• Estradiol has a protective effect on the brain structures in older males.


Estrogen: Men and Memory (cont’d)

• Serum estradiol and testosterone levels have been shown to be lower in men with Alzheimer’s disease compared with age-matched controls.


Estrogen Levels in Males

• Medications may lower estrogen levels in men and cause estrogen levels to be too low.
  – Phenobarbital
  – Chlordiazepoxide
  – Carbamepazine
  – Trazodone
  – Sulcrafate

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Estriol Replacement in Males

- It is experimental at this time but for autoimmune encephalitis and multiple sclerosis, estriol replacement is being used in males.


Estrogen Levels in Males

- Estrogen levels may elevate as men age due to
  - Increased aromatase activity
  - Alteration in liver function
  - Zinc deficiency
  - Obesity
  - Overuse of alcohol
  - Ingestion of estrogen-containing food or environmental estrogens
  - High doses of testosterone

Estrogen Levels in Males (cont’d)

- Estrogen levels may elevate as men age due to
  (cont’d)
  - Environmental estrogens, endocrine disrupters, plastics
  - Foods that may increase estrogen levels (see handout)
  - Medications (see handout)
Elevated levels of estrogen in males are associated with:
- Gynecomastia
- Decreased sex drive/erectile dysfunction
- Doubled risk of stroke
- Higher rates of heart attack, peripheral artery disease, and coronary atherosclerosis

Estrogen Levels in Males (cont’d)

Elevated levels of estrogen in males are associated with (cont’d)
- Insulin resistance
- Rheumatoid arthritis
- BPH
- Prostate cancer


Elevated Estrogen Levels in Males

Study showed that high estradiol in males was associated with an increased risk of stroke.

Elevated Estrogen Levels in Males (cont’d)

• High estradiol levels in men were associated with acute myocardial infarctions

Elevated Estrogen Levels in Males (cont’d)

• High estrone and low testosterone levels were associated with promoting the development of atherogenic lipid milieu in men with coronary heart disease

Elevated Estrogen Levels in Males (cont’d)

• Low testosterone and elevated estradiol was associated in this study with lower extremity peripheral artery disease in older men.
Elevated Estrogen Levels in Males (cont’d)

- Men with myocardial infarction had high estradiol and low testosterone levels
  

Elevated Estrogen Levels in Males (cont’d)

- Elevated levels of estradiol in men were associated with an increase incidence of strokes, peripheral vascular disease, and carotid artery stenosis compared to subjects with lower estradiol levels.
  

Elevated Estrogen Levels in Males (cont’d)

- Elevated levels of estrogen in men are associated with an increased risk of heart disease.
  
Estrogen Levels in Males (cont’d)

• Ways to lower high estrogen levels in males
  – Decrease dose of testosterone
  – Zinc
  – Chrysin
  – Anastrazole and other aromatase inhibitors
  – Maca

Estrogen Levels in Males (cont’d)

• Ways to lower high estrogen levels in males (cont’d)
  – Grape seed extract
  – Wild nettle root
  – Decrease intake of estrogen containing foods (see handout)
  – Eat foods that decrease estrogen (see handout)

Estrogen Levels in Males (cont’d)

• Ways to lower high estrogen levels in males (cont’d)
  – Decrease alcohol intake
  – Lose weight
  – Eat organic foods and avoid environmental estrogens
  – High dose vitamin C (also increases testosterone production)
  – Vitamin K
  – Niacin
Dihydrotestosterone

Dihydrotestosterone (DHT)

- Most potent naturally occurring androgen
  - 3 times more potent than testosterone
- Synthesized from the conversion of testosterone through 5-alpha reductase

Dihydrotestosterone (DHT)

- Responsible for formation of male sex-specific characteristics and development of male genitalia and prostate
  - Low levels can affect sexual function and libido, muscle tone
- Elevated levels may cause
  - Hirsuitism
  - Male pattern baldness
  - BPH
Treatment with Transdermal DHT Gel

• Transdermal DHT as a gel has been used in two trials for hormone replacement therapy in men.


References

Treatment with Transdermal DHT Gel

• Second trial was a double-blind, placebo controlled, randomized trial also using DHT gel to evaluate muscle strength.
• Study showed limited improvement in muscle strength but no physical or cognitive function change.


Treatment with Transdermal DHT Gel

• In the Prostate Cancer Prevention Trial (PCPT), finasteride reduced prostate cancer risk by 25%. More studies need to be done to determine if DHT plays a role in the development of prostate cancer.


• Therefore, further trials need to be done before transdermal DHT replacement should be considered.

DHT

• DHT has growth promoting effect on prostate cells that is greater than that of testosterone---2.4-10 times greater

DHT (cont’d)

• High DHT levels stimulate the androgen receptors to produce greater amounts of PSA
• DHT interacts with extracellular tissues to elevate prostate cancer cell mobility

DHT (cont’d)

• High DHT levels have been shown to enhance early atherosclerosis

5-Alpa-Reductase

• 5-alpha-reductase converts testosterone to dihydrotestosterone (DHT)
• DHT binds to androgen receptors in prostate cell nuclei and promotes proliferation of the cells
• There are three subtypes of isoenzymes of 5-alpha-reductase
5-Alpha-Reductase Inhibitors (5ARIs)

- A reduction of DHT should inhibit prostate growth and lead instead to apoptosis and a decrease in the size of the prostate.
- Therefore by decreasing DHT production, 5ARIs can decrease the size of the prostate and subsequently help with the symptoms of LUTS.
- 5ARIs help to stop the disease as opposed to just treating the symptoms.


5-Alpha-Reductase Inhibitors

- Two 5ARIs are available that both have been shown to have a similar clinical effect.
  - Finasteride
    - Inhibits type II 5-alpha-reductase

5-Alpha-Reductase Inhibitors

- Two 5ARIs are available that both have been shown to have a similar clinical effect
  - Dutasteride
    - Inhibits type I and type II 5-alpha-reductase

* Ibid., AUA Practice Guidelines.
* Ibid., Paolone.
Reference


Dutasteride

• Inhibits DHT-induced secretion of PSA
• Inhibits cancer cell proliferation
• Higher doses results in cancer cell death in both androgen-dependent (LNCaP) and androgen-independent (PC-3) cell lines.


Dutasteride (cont’d)

• Study of 4,325 men with BPH were selected randomly to receive dutasteride or placebo.
• 52% reduction in prostate cancer in the dutasteride group.

5-Alpha-Reductase Inhibitors (cont’d)

• Possible side effects of 5ARIs
  – Decreased libido
  – Erectile dysfunction
  – Ejaculatory disorder
  – Breast tenderness (rare)

5-Alpha-Reductase Inhibitors (cont’d)

• C/I in children and women that are pregnant
• After 6 months on 5ARIs the PSA level may go down up to 50% therefore if the patient is on these medications and their PSA doubles (no matter what the level is) the patient must have a urological evaluation.

References

5-Alpha-Reductase Inhibitors (cont’d)

• Chemoprevention of prostate cancer is currently being looked at by using 5ARIs.
  – Study showed a 24.8% relative risk reduction of developing prostate cancer after 7 years in patients taking finasteride.

5-Alpha-Reductase Inhibitors (cont’d)

• Chemoprevention of prostate cancer is currently being looked at by using 5ARIs.
  – Another study is currently evaluating dutasteride for the potential of decreasing the risk of prostate cancer.

Androstenedione
Androstenedione

• Made by the adrenal glands
• Common precursor of male and female sex hormones
  – Production of adrenal androstenedione is regulated by ACTH
  – Production of gonadal androstenedione is regulated by gonadotropins

Androstenedione (cont’d)

• Possible side effects of androstenedione
  – Breast development
  – Behavioral changes including mood swings and depression
  – Increase risk of heart disease
  – Male pattern baldness


Androstenedione (cont’d)

• Androstenedione is banned for use in the United States and many other countries.
Studies on Testosterone Replacement

Testosterone Cognitive Function

• Testosterone replacement improves cognitive function.

Testosterone and Alzheimer’s

• Testosterone replacement prevents the production of beta amyloid precursor protein in men.
Testosterone and Memory

• Study showed that testosterone therapy in elderly men showed some reversal of cognitive dysfunction.

Testosterone and Memory (cont’d)

• Testosterone therapy has been shown to help with mild cognitive impairment.

Testosterone and Memory (cont’d)

• Animal studies have shown that testosterone replacement can improve memory possibly by reducing amyloid-B peptide production.
Testosterone and Memory (cont’d)

- Testosterone therapy in older hypogonadal men improved spatial cognition and verbal fluency.
  
  

Testosterone and Memory (cont’d)

- In older men without dementia testosterone replacement reduced working memory errors.
  

Testosterone and Memory (cont’d)

- In this trial testosterone improved verbal and spatial memory and constructional abilities in nonhypogonadal men with mild memory loss and early Alzheimer’s disease.
  
Testosterone and CAD

- “Short-term administration of testosterone induces a beneficial effect on exercise-induced myocardial ischemia in men with coronary artery disease. This effect may be related to a direct coronary-relaxing effect.”
  

Testosterone and CAD (cont’d)

- Study revealed that testosterone replacement was associated with a decrease in HDL-C and lipoprotein a.
  

Testosterone and CAD (cont’d)

- The mechanism of testosterone replacement decreasing lipids may be due to testosterone’s positive effects on abdominal fat and insulin resistance.
  
Testosterone and CAD (cont’d)

- Short-term administration of testosterone induces a beneficial effect on exercise-induced myocardial ischemia in men with coronary heart disease. This effect may be related to a direct coronary-relaxing effect of testosterone.


Testosterone and CAD (cont’d)

- Short-term intracoronary administration of testosterone, at physiological concentrations, induces coronary artery dilatation and an increase in coronary blood flow in men with established coronary heart disease.


Testosterone and CAD (cont’d)

- Low-dose supplementation with testosterone in men with chronic stable angina reduced exercise-induced myocardial ischemia.

Testosterone and CAD (cont’d)

- Testosterone replacement has been shown to increase coronary blood flow in patients with coronary heart disease.
  
  

Testosterone and CAD (cont’d)

- Transdermal testosterone replacement has been shown to improve chronic stable angina by increasing the angina-free exercise tolerance vs. controls that were getting placebos.
  

Testosterone and CAD (cont’d)

- Another study showed that testosterone replacement reduced exercise induced myocardial ischemia.
  
### Testosterone and CAD (cont’d)

- Testosterone is a coronary vasodilator by functioning as a calcium antagonistic agent
  

### Testosterone and CAD (cont’d)

- Testosterone replacement therapy in hypogonadism moderates metabolic components associated with cardiovascular risk.


### Testosterone and CAD (cont’d)

- Testosterone replacement has been shown to decrease inflammation and lower total cholesterol.

Testosterone and CAD (cont’d)

- Testosterone replacement in patients with congestive heart failure has been shown to improve exercise capacity, improve insulin resistance, and improve muscle performance.
  

Testosterone and Prostate Cancer

- “There is no clinical evidence that the risk of either prostate cancer or BPH increases with transdermal testosterone replacement.”
  

Testosterone and CAD (cont’d)

- Interestingly, men that are older with the highest risk of prostate cancer have the lowest levels of testosterone.
  
Testosterone and Insulin Resistance

• Testosterone replacement decreases insulin resistance
• Supraphysiologic doses of testosterone increase insulin resistance
• Hyperinsulinemia decreases testosterone and replacement decreases hyperinsulinemia

References

Treatment

- Transdermal
- Use compounding pharmacy
  - Less expensive than commercial available forms
  - Can titrate to the individual needs of the patient

Testosterone and Erectile Function

- Transdermal 81% effective
- Oral 51% effective
- IM 53% effective

TRT: Transdermal Patches

- Testosterone transdermal system
  - Available in 2.5-mg and 5-mg preparations
    - Typical starting dose is 5-mg/day; can increase to 7.5-mg or decrease to 2.5-mg as needed
  - Applied at night to a clean, dry area of skin on the back, stomach, upper arms, or thighs
TRT: Transdermal Patches (cont’d)

- Testosterone transdermal system (cont’d)
  - Sites should be rotated daily, allowing 7 days before re-applying to the same site
  - Side effects:
    * Skin irritation, vesicle formation, contact dermatitis, headache, and depression

TRT: Gel Formulations

- Testosterone gel
  - Applied in the morning to the shoulders, abdomen, or upper arm; preferably at the same location every day
    - Use gloves or wash hands after application
    - Allow gel to dry (10-15 min) before covering with clothing
    - Wait 4 hours prior to showering or swimming
    - Wash with soap and water if skin-to-skin contact with another person anticipated

TRT: Gel Formulations (cont’d)

- Testosterone gel (cont’d)
  - Dosing: 5 grams (50 mg testosterone) daily, can be increased to 7.5 – 10 grams as needed
  - Side effects: acne, headaches, emotional lability, nervousness, gynecomastia, mastodynia, insomnia, hypertension, hot flashes, polycythemia, and increased PSA
  - Local skin irritation occurs much less frequently than with patches
TRT: Transbuccal Tablet

- Testosterone buccal system
  - Sustained release formulation of 30 mg unmodified testosterone given every 12 hours
    - Absorption unaffected by food and beverage intake
    - Avoids first-pass metabolism by absorption into buccal mucosa

TRT: Transbuccal Tablet

- Testosterone buccal system
  - Side effects: gingivitis, edema, or blistering at application site, bitter taste, xerostomia, toothache, stomatitis, anxiety, and stinging of the lips
    - Generally well tolerated
    - Cannot use saliva testing to evaluate


TRT: Testosterone Esters

- Testosterone enanthate:
  - 200 – 400 mg IM every 2 – 4 weeks
- Testosterone cypionate:
  - 50 – 400 mg IM every 2 – 4 weeks
- Testosterone propionate:
  - 10 – 25 mg IM 2 – 3 x/week (not for long-term use)
TRT: Testosterone Esters

- Esterification of testosterone
  - More hydrophobic, longer duration of action
- Supraphysiologic concentrations reached 24 hours after a 200-mg injection (of enanthate or cypionate), followed by gradual decline to hypogonadal levels
- Adverse effects:
  - Mood swings and variability in libido, sexual function, and energy levels due to varying PK; injection site reactions, polycythemia, acne, nonproductive cough, and gynecomastia

TRT: Testosterone Esters

- Testosterone undecanoate
  - 1,000 mg every 12 weeks following a 6-week loading dose
- Longer half life and duration of action than that of other testosterone esters
  - Due to longer hydrophobic side chain & castor oil carrier
  - Maintains testosterone levels consistently within normal physiologic range
  - Minimizes side effects due to varying PK of shorter acting esters

Testosterone Undecanoate

- Possible adverse effects
  - Injection site reactions
  - Increase in hemoglobin and erythrocyte count
  - Gynecomastia and breast tenderness
  - Increased PSA and prostate size in the elderly
Compounded Sterile Testosterone Injections

- May compound testosterone cypionate IM and propionate IM in one syringe with sesame seed oil
- May compound testosterone, anastrozole, and HCG into one syringe IM
- May compound testosterone IM with zinc IM
- May compound testosterone IM with anastrozole IM.
  - Dose of anastrozole is usually 0.05 mg/ml to 1mg/ml
  - Dose of testosterone is according to lab results

Testosterone Injections

- DO NOT HAVE PATIENT USE TESTOSTERONE SQ. IT IS FOR IM USE ONLY.
- OTHERWISE THE PATIENT MAY DEVELOP AN ABSCESS AT THE SITE OF INJECTION!

<table>
<thead>
<tr>
<th>Testosterone Options</th>
<th>Doses</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone transdermal</td>
<td>5-mg and 2.5-mg patches,</td>
<td>Recreation of normal circadian rhythm</td>
<td>Skin irritation</td>
</tr>
<tr>
<td>patch</td>
<td>replaced nightly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testosterone topical gel</td>
<td>1-10 g/day</td>
<td>Skin irritation less common than with patch</td>
<td>Concern of transfer to others</td>
</tr>
<tr>
<td>Testosterone Transbuccal</td>
<td>50-mg tablet twice daily</td>
<td>Avoids first pass metabolism</td>
<td>Unpleasant taste, tolerability</td>
</tr>
<tr>
<td>tablet</td>
<td>(every 12 hours)</td>
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<tr>
<td>IM Testosterone:</td>
<td>200 mg q 2-4 wks</td>
<td>Inexpensive</td>
<td>Invasive, painful, injection site reactions</td>
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<tr>
<td>cypionate -enanthate</td>
<td>100 mg q 2-4 wks</td>
<td>Frequence</td>
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<tr>
<td>propionate</td>
<td>10-25 mg q 2-3x/wk</td>
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</tr>
<tr>
<td>IM Testosterone undecanoate</td>
<td>1,000 mg every 12 wks</td>
<td>Consistent levels; 4 injections/yr</td>
<td>Concern for effects on prostate</td>
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<tr>
<td></td>
<td>following a 6-wk loading</td>
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<tr>
<td></td>
<td>dose</td>
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</tbody>
</table>

* Adapted from Pfiel, E. "Current and future testosterone delivery systems for the treatment of the hypogonadal male."
Testosterone Topical Solution

- 30mg/pump=1.5mL
- Recommend 30mg under each arm pit
- Has application cup
- Cover under arms with clothes after the solution dries~
  3 minutes
- Flammable until dry. Let dry before smoking or going
  near an open flame.

Dosing of Compounded Testosterone Cream or Gel

- Dose of testosterone is 5-50 mg cream or gel according to lab
  results
- May compound Chrysin in the same syringe with testosterone.
  Chrysin is a natural aromatase inhibitor to lower estrogen levels.
  Male skin has a higher concentration of aromatase enzyme on the
  surface. Chrysin has natural yellow color, it does not stain skin.
  Dose of Chrysin depends on the level of estrone or estradiol:
  usually 5-50 mg cream. Cannot put Chrysin in a gel base.
- May compound progesterone in the same syringe as testosterone
  and Chrysin

Contraindications to Testosterone Use

- Prostate cancer
- Breast cancer
- Prolactinoma
- Prostate nodules or indurations
- Unexplained PSA increase
- Severe BPH
- Severe untreated sleep apnea
Stimulating Endogenous Production of Testosterone

Clomiphene Citrate

- Clomiphene is a SERM (selective estrogen receptor modulator)
- Clomiphene is NOT FDA approved for use in males
- Does not work in men over age 55
- Does not work if the patient has a chronic illness
- Clomiphene increases gonadotropins by inhibiting negative feedback on the hypothalamus: increases LH and FSH

Reference

Clomiphene Citrate (cont’d)

• Studies showed that clomiphene citrate for hypogonadism was safe and effective in patients wishing to preserve fertility.

Clomiphene Citrate (cont’d)

• Study showed that low dose clomiphene (25 mg) citrate was effective for hypogonadal males.

Clomiphene Citrate (cont’d)

• Study used clomiphene citrate and testosterone gel with good results for hypogonadal males.
Clomiphene Citrate (cont’d)

• Yet another study showed that clomiphene citrate was safe and effective as a treatment for hypogonadism.

Clomiphene Citrate (cont’d)

• Medical trial used clomiphene citrate 25 mg a day then increased to 50 mg with successful outcomes.

Clomiphene Citrate (cont’d)

• Some possible side effects
  – Gynecomastia
  – Leydig cell tumor or testis
Clomiphene Citrate (cont’d)

• Some possible side effects (cont’d)
  – Pulmonary embolus


HCG

• HCG is a hormone with both alpha and beta sub-units. The alpha sub-unit is almost identical to the alpha sub-units of LH and FSH.
• Many males under the age of 40 have low testosterone levels.
• In younger males HCG is the preferred treatment for hypogonadism.
• Testosterone should not be used unless there is Leydig cell failure in younger men.

HCG (cont’d)

• HCG does not cause loss of testicle volume and no decrease in sperm count that may occur with testosterone replacement treatment.
• HCG needs functioning Leydig cells to work
• Measure LH and FSH levels.
• LH levels
  – If LH > 5 mIU/ml then HCG may not work
  – If LH <3 mIU/ml then HCG usually gives good results
  – If LH is 3-5 mIU/ml then the results are usually variable
**HCG Dosing**

- The following are guidelines that should be used when using HCG for low testosterone levels in men.
  - The most commonly used dose is 2,000-5,000 units per week SQ in divided doses with the most common dose being 1,000 units twice a week.
  - Antibodies can develop with use so most protocols suggest using HCG two months on and one month off or six weeks on and two weeks off.
  - Total, free, and bio-available testosterone usually increases about 25% and symptoms are improved.

**References**


**HCG (cont’d)**

- Side effects and precautions
  - Anaphylaxis
  - May cause water retention/edema
  - VTE has been reported
  - Intracranial lesions
  - May get redness at injection site
  - Acne
  - Hypertension
  - Do NOT use in patients with prostate cancer or other androgen-dependent neoplasm
  - Do not use orally, contains benzyl alcohol

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HCG

• May use HCG and testosterone together to try and help preserve spermatogenesis.
• Advise the patient that there is no guarantee that spermatogenesis will be preserved.
  

Natural Therapies to Increase Testosterone and Suppress Estrogen

<table>
<thead>
<tr>
<th>Food</th>
<th>How play a role in testosterone synthesis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinc</td>
<td>Natural aromatase inhibitor; extracted from various plants, found in high concentrations in honey.</td>
</tr>
<tr>
<td>Chrysin</td>
<td>Amino acid derivative; may be more active than testosterone in aging men with sexual dysfunction and depression caused by androgen deficiency.</td>
</tr>
<tr>
<td>Carnitine</td>
<td>Derived from Phytophagium occidentale shrub in Brazil. Considered an aphrodisiac and effective treatment of impotence.</td>
</tr>
<tr>
<td>Cruciferous</td>
<td>Certain Isothiocyanates and glucosinolates, which act as antioxidants and inducers of proteins that may suppress prostate cancer.</td>
</tr>
<tr>
<td>Quercetin</td>
<td>Found in wine, inhibits synthesis of estrogen by inhibiting aromatase.</td>
</tr>
<tr>
<td>Saw palmetto</td>
<td>Reduce symptoms of BPH. Saw palmetto reduces nocturnal urinary urgency, increased urinary flow rate, decreased residual urine volume in the bladder, and reduced discomfort from urination symptoms. Nettle root may increase free testosterone levels by binding to SHBG.</td>
</tr>
<tr>
<td>Muira puama</td>
<td>Extracted from Ptchopetalum olacoides shrub in Brazil. Considered an aphrodisiac and effective treatment of impotence.</td>
</tr>
<tr>
<td>Nettle</td>
<td>Support testosterone production by decreasing oxidative damage to tissues synthesizing testosterone.</td>
</tr>
</tbody>
</table>

Case #1
Case #2
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Testosterone and Heart Disease

By Pamela W. Smith, M.D., MPH, MS

Introduction

Two recent trials suggest that testosterone replacement therapy may increase the risk of heart disease and/or stroke. 1, 2

These were poorly designed studies which conflict with numerous previous medical trials that show the beneficial effects of testosterone on the heart and that low testosterone levels in males are associated with an increased risk in the development of heart disease.

The following is a comprehensive review of the medical literature on low testosterone being associated with an increased risk in the development of cardiovascular disease and that testosterone replacement at appropriate levels not only decreases the risk of heart disease but can also be used to treat coronary disease.

Low Testosterone Levels and Increased Risk of Heart Disease

Men with coronary heart disease had a significantly lower total testosterone, free testosterone, and bioavailable testosterone. 3

Low endogenous testosterone concentrations are related to mortality due to cardiovascular disease and other causes. 4, 5

Study showed a possible correlation between lower testosterone levels, erectile dysfunction and conditions associated with higher cardiovascular risk. 6

Study showed that men with coronary heart disease that were under the age of 45 had total and free testosterone levels significantly lower than controls. 7

Serum free testosterone levels were found to be inversely related to carotid intima-media thickness (IMT) and plaque score. 8

Low testosterone levels have been found to be associated with atherosclerosis in men. 9

Low Testosterone Levels and Increase Risk of Diabetes Type II and Metabolic Syndrome

Low testosterone levels are associated with an increased risk for the development of type II diabetes and metabolic syndrome. 10, 11, 12, 13, 14
Since testosterone has been shown to lower blood sugar levels, the Endocrine Society now recommends measurement of testosterone in all male patients with type II diabetes mellitus.  

**Low Testosterone Levels Are Associated with an Increased Risk of Mortality**

Study showed that low testosterone predicts mortality from cardiovascular disease.  

Study showed that low testosterone levels were associated with an increased risk of all-cause mortality independent of numerous risk factors. Serum testosterone levels were inversely related to mortality due to cardiovascular disease and cancer.  

Low endogenous testosterone levels are associated with an increased risk of death from all causes and cardiovascular death.  

**Low Testosterone Levels and Increased Risk of Hypertension**

Study showed that low total testosterone concentrations are predictive of hypertension, suggesting total testosterone as a potential biomarker for increased cardiovascular risk.  

**Low Testosterone and Congestive Heart Failure**

In males with heart failure, low serum androgens were associated with an adverse prognosis.  

In men with chronic heart failure, anabolic hormone depletion is common and deficiency of each anabolic hormone is an independent marker of poor prognosis.  

**Testosterone Replacement and Heart Disease**

Study showed that for all-cause mortality, for each increase of six nanomoles of testosterone per liter of serum was associated with an almost fourteen percent drop in the risk of death.  

Study revealed that testosterone replacement was associated with a decrease in HDL-C and lipoprotein a.  

The mechanism of testosterone replacement decreasing lipids may be due to testosterone’s positive effects on abdominal fat and insulin resistance.  

Short-term administration of testosterone induces a beneficial effect on exercise-induced myocardial ischemia in men with coronary heart disease. This effect may be related to a direct coronary-relaxing effect of testosterone.
Short-term intracoronary administration of testosterone, at physiological concentrations, induces coronary artery dilatation and an increase in coronary blood flow in men with established coronary heart disease. 26

Low-dose supplementation with testosterone in men with chronic stable angina reduced exercise-induced myocardial ischemia. 27

Testosterone replacement has been shown to increase coronary blood flow in patients with coronary heart disease. 28, 29

Transdermal testosterone replacement has been shown to improve chronic stable angina by increasing the angina-free exercise tolerance vs. controls that were getting placebos. 30

Another study showed that testosterone replacement reduced exercise induced myocardial ischemia. 31

Testosterone is a coronary vasodilator by functioning as a calcium antagonistic agent. 32

Testosterone replacement therapy in hypogonadism moderates metabolic components associated with cardiovascular risk. 33

Testosterone replacement has been shown to decrease inflammation and lower total cholesterol. 34

Testosterone replacement in patients with congestive heart failure has been shown to improve exercise capacity, improve insulin resistance, and improve muscle performance. 35

Testosterone replacement has been shown to be helpful in patients with severe heart failure. 37

In this review of the medical literature one can see that numerous studies have shown that low testosterone levels are associated with an increased risk of heart disease and that testosterone replacement therapy is associated with a decreased risk of developing heart disease and is even beneficial in patients that already have coronary vascular disease.

So why did the two recent studies show that there was an increased risk of developing heart disease in male patients that were prescribed testosterone replacement therapy?

There are five serious flows associated with the two recent trials.

Firstly, estrone and estradiol levels were not measure in the subjects in the studies. High estrogen levels in males have been found to be associated with an increase risk in the development of heart disease and stroke. Estrogen levels may elevate due to an increase in
aromatase activity, alteration in liver function, zinc deficiency, obesity, abuse of alcohol, drug-induced estrogen imbalance, and ingestion of estrogen-containing foods or environmental estrogens.

**High Estrogens are Associated with an Increased Risk of Heart Disease and Stroke**

Study showed that high estradiol in males was associated with an increased risk of stroke. 38

Study showed that elevated circulating estradiol is a predictor of progression of carotid artery intima media thickness in middle age men. 39

High estradiol levels in men were associated with acute myocardial infarctions. 40

High estrone and low testosterone levels were associated with promoting the development of atherogenic lipid milieu in men with coronary heart disease. 41

Low testosterone and elevated estradiol was associated in this study with lower extremity peripheral artery disease in older men. 42

Men with myocardial infarction had high estradiol and low testosterone levels. 43

Elevated levels of estradiol in men were associated with an increase incidence of strokes, peripheral vascular disease, and carotid artery stenosis compared to subjects with lower estradiol levels. 44

Elevated levels of estrogen in men are associated with an increased risk of heart disease. 45

**Secondly,** having erythrocytosis is associated with an increased risk in the development of heart disease and thrombosis. 46 A major study on the risk and benefits of testosterone replacement suggests that a baseline hematocrit should be checked at three and six months and then every six to twelve months. If the hematocrit is more than fifty-four percent then testosterone therapy should be stopped until the hematocrit is at a safe level. 47 Hematocrit levels were not measure in these two trials.

**Thirdly,** in both studies not all patients had follow-up testing of testosterone levels. Therefore, dosages of testosterone may have been higher than needed. Supraphysiologic levels of testosterone can induce nitric oxide production and cause oxidative stress which induces endothelial dysfunction. 48

**Fourthly,** some of the men in these trials were using testosterone injections, which are nonphysiologic since they have peak and trough levels over the weekly or biweekly dosing. This issue was wonderfully discussed by Cappola in her review of Vigen’s study. 49
Lastly, testosterone can convert to dihydrotestosterone (DHT) which has been shown to enhance early atherosclerosis. 50 The conclusion of the author of this trial was that the findings highlighted a new androgen receptor/nuclear factor-kappaB mediated mechanism for vascular cell adhesion molecule-1 expression and monocyte adhesion operating in male endothelial cells that may represent an important unrecognized mechanism for the male predisposition to atherosclerosis. The higher the dose of testosterone that is prescribed the more it is converted by 5 alpha-reductase into DHT. In these two recent trials that suggest that testosterone replacement increases the risk of heart disease in men, DHT levels were not measured.

Conclusion

Given the plethora of medical studies indicating the beneficial effects of properly prescribed testosterone, one would have to conclude that these two recent medical trails are poorly designed and their conclusion is flawed. Some of the patients did not have repeat testosterone levels measured. Consequently, the patients may have had supraphysiological levels of testosterone. In addition DHT, estrone, estradiol, and HCT levels were not addressed. Furthermore, the medical literature has shown that hormones in the body are a symphony and this web of interconnection was not considered.

References


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# Foods That Increase Your Estrogen Level

<table>
<thead>
<tr>
<th><strong>Vegetables</strong></th>
<th><strong>Fruits</strong></th>
<th><strong>Cereals and Grains</strong></th>
<th><strong>Legumes (Beans)</strong></th>
<th><strong>Seeds and Nuts</strong></th>
<th><strong>Most Common Oils</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Artichoke</td>
<td>Apple</td>
<td>Barley</td>
<td>Chickpea</td>
<td>Almond</td>
<td>Coconut</td>
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<tr>
<td>Asparagus</td>
<td>Apricot</td>
<td>Corn</td>
<td>Kidney</td>
<td>Cashew</td>
<td>Corn</td>
</tr>
<tr>
<td>Bamboo shoot</td>
<td>Banana</td>
<td>Rice</td>
<td>Pea</td>
<td>Coconut</td>
<td>Linseed (flaxseed)</td>
</tr>
<tr>
<td>Beet</td>
<td>Cherry</td>
<td>Rye</td>
<td>Peanut</td>
<td>Pecan</td>
<td>Olive</td>
</tr>
<tr>
<td>Brussels sprout</td>
<td>Date</td>
<td>Wheat (bran, flour, whole)</td>
<td>Peanut</td>
<td>Pine nut</td>
<td>Peanut</td>
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<tr>
<td>Cabbage</td>
<td>Grape</td>
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<td>Soybean</td>
<td>Pistachio</td>
<td>Rice bran</td>
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<td>Carrot</td>
<td>Grapefruit</td>
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<td>Sesame seed</td>
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<td>Cauliflower</td>
<td>Lemon</td>
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<td>Eggplant</td>
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<td>Garlic</td>
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<td>Green beans</td>
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<td>Lettuce</td>
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<td>Mustard greens</td>
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<td>Okra</td>
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<td>Onion</td>
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<td>Parsley</td>
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<td>Pea seedling</td>
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<tr>
<td>Pepper (red, green, yellow, orange)</td>
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<tr>
<td>Potato (all kinds)</td>
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<td>Pumpkin</td>
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<td>Radish</td>
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<td>Seaweed</td>
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<td>Shallot</td>
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<td>Spinach</td>
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<td>Tomato</td>
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<td>Turnip</td>
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<td>Yam</td>
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FOODS THAT DECREASE ESTROGEN LEVELS

Cruciferous vegetables
   Broccoli
   Cauliflower
   Cabbage
   Brussels sprouts
   Bok choy
   Kale
   Collard greens
   Turnips
   Rutabagas

Mushrooms
   Shiitake
   Portabello
   Baby button
   Crimini

Red grapes

Seeds that contain polyphenols
   Chia
   Flax
   Sesame

Green tea

Pomegranates