What You Need to Know About Male Hormones

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American Osteopathic Society of Rheumatic Diseases
Objectives:

1. Discuss the concept of andropause and the physiologic role testosterone plays in men’s health.
2. Discuss the functions of testosterone.
3. Discuss the signs and symptoms of andropause.
4. Discuss the global therapeutic benefits of correcting andropause deficiencies.
5. Understand testosterone biosynthesis.
6. Identify types, doses and method of replacing hormone deficiencies in men.
7. Have on hand a list of peer reviewed studies on testosterone replacement.
8. Implement a global therapeutic management of andropause signs and symptoms.
9. Understand the difference between testosterone replacement and stimulating the endogenous production of hormones.
Andropause

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

Healthy Male Daily Production of Hormones

- Cortisol: 20-30 mgs/day
- Testosterone: 5-12 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 is the main male sex hormone

Produced in the testicles (95% in Leydig Cells) and adrenal gland (5%) and secreted in the testes.

Testosterone declines with age beginning in the early 30’s with levels naturally decreasing by 1%/year by age 40. Between age 25 and 75 men experience a 30% decrease in Total Testosterone and a 50% decrease in free Testosterone.

Official estimates are 20% of men over the age of 50 have abnormally low testosterone levels.
Testosterone

The production of testosterone by the testis is controlled by the pituitary gland.

Testosterone causes beard and body hair growth, promotes the growth of the prostate gland, contributes to male sexuality, and causes bone and muscle growth.

Testosterone stimulates cells in the testis to produce sperm.
Gonadotropin Releasing Hormone (GnRH)

- GnRH is released into the pituitary portal circulation from the hypothalamus.
- GnRH is the only releasing factor for LH and FSH.
- The frequency of the GnRH pulses depends on the following:
  - Stimulation from surrounding cells and noradrenergic activity
  - Inhibition from circulating androgens and estrogens
  - Dopaminergic neurons
  - Serotonergic neurons
  - GABAergic neurons
  - Opioid peptides reduce the negative feedback of gonadal steroids

  Carruthers; ibid. 2004
Gonadotropin Releasing Hormone (GnRH)

- T and DHT act as negative feedback on hypothalamus reducing the GnRH pulse frequency.

- Estrogens acts as negative feedback loop reducing the amplitude of LH and FSH peaks at the pituitary.

- LH (Testosterone Production) is more pulsatile than FSH (Spermatogenesis).
  - Low LH + Low T = Secondary Cause of Hypogonadism. Check Pituitary.

  - Carruthers; ibid. 2004
The biosynthesis of testosterone in the Leydig cells is controlled by:

- Availability of cholesterol at the outer membrane of the mitochondria.
- Rate of transfer to the inner membrane under the control of steroidogenesis activator protein (StAR).
- The initial rate-limiting conversion is catalyzed by cytochrome P450.
- Testosterone has a half life of 12 minutes

Testosterone Metabolism

**Testosterone**

- **DHT**
  - Dihydrotestosterone
  - Skin, liver, prostate
- **Estradiol**
  - Brain, fat, liver, testes
  - Bone resorption
  - HDL/atherosclerosis effects
  - Brain effects
  - Breast effects

Facial hair
Body hair
Prostate growth
Acne

Muscle Mass
Bone formation
Spermatogoniesis
Sexual function
Testosterone Metabolism

- Testosterone is unable to be stored in the testis.

- Consequently testosterone is found:
  - 2% in the bioavailable form in the plasma bound to albumin and SHBG
  - 54% is weakly bound to albumin
  - 44% is bound to sex hormone binding globulin (SHBG)
    - The affinity of SHBG for DHT is 1.3x higher than for testosterone.
    - The affinity of SHBG for DHT is 4x higher than for estradiol.

Sex Hormone Binding Globulin (SHBG)

- Protein made in the liver (manly), testes and brain.
- Transports androgens and estradiol.
- Signals heart, brain and adipose tissue.
- Regulates bioavailability and access to target cells.
- SHBG binds more to androgens than estrogens.

Age-related Decline In Testosterone Levels

Free Test (nmol/l)  SHBG ($10^{-3}$ nmol/l)  Total Test (nmol/l)

- 0.775: 8
- 0.5: 7
- 0.375: 6
- 0.25: 5
- 0.15: 4
- 0.1: 3
- 0.05: 2
- 0.0: 1

Years: 18-29  30-49  50-59  60-69  70-79  80-89  90-100  >100

Testo vs. SHBG
• **98 % of Testosterone is bound to Albumin or SHBG.**
  
  

• **Free + and Albumin-bound Testosterone = Bio-available 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 2009; 56(4):209-12.
  
SHBG Lab Values

**Males:** 10 to 57 nanomoles per liter (nmol/L)
**Females (nonpregnant):** 18 to 144 nmol/L

**High SHBG =**
- High Estrogen
- More Severe/Invasive Prostate CA
- Osteoporosis

**Low SHBG =**
- High Testosterone
- Metabolic Syndrome
  - Risk of Death from CV Dx.
  - High Insulin
  - Obesity
  - cRP, Triglycerides, LDL
  - Arterial Calcification
  - Sleep Apnea
SHBG Lab Values

Males: 10 to 57 nanomoles per liter (nmol/L)
Females (nonpregnant): 18 to 144 nmol/L

Raises SHBG =

- Estrogen
- Progesterone (by increasing E receptors)
- Thyroid Hormone (particularly hyperthy)
- C-Roaches of the Liver
- Anorexia, Starvation
- Hypoglycemia (low insulin)
- Anticonvulsants
- GH deficiency
- Androgen insensitivity
- Aging process

Lowers SHBG =

- Insulin (and insulin resistance)
- Testosterone
- Growth Hormone
- DHEA
- Other Androgens
- Obesity
- Hypothyroidism
- Excessive Cortisol (Cushing’s Syndrome or Disease)
- Progestins (such as by blocking progesterone's effects)
Lifestyle Changes

- Exercise
- Coffee!
- Oral Contraceptives
- Increase fiber and decrease sugar
- Lose weight
## By Increasing Prolactin
- Antipsychotics (both typical and atypical)
- Antidepressants (SSRIs, Tricyclics, MAO-IIs)
- Xanax and Buspar
- H2 Antagonists (Cimetidine, Ranitidine)
- Morphine
- Some Antihypertensives

### Supplements
- ECGC
- Whole Foods
- Flax Seed

## Other Drugs
- Raloxifene (Evista)
- Tamoxifen
- Spironolactone
- Anticonvulsants (Phenytoin)
- Oral (but not transdermal) estradiol
- Ethinyl estradiol (oral contraceptives)
- Metformin
- Exogenous insulin in Type 2 DM
- Adequate T3
- **Danazol**
Benefits of Testosterone

- Increased sense of well-being
- Increased muscle mass, strength, endurance, and increased exercise tolerance
- Adequate memory
- Improved skin turgor
- Elevates brain norepinephrine, enhancing memory and cognition
- Increased sexual interest and sexual performance
Benefits of Testosterone

- Decreases body fat
- Maintains bone strength
- Protects against osteoporosis
- Reduced LDL cholesterol
- Improves insulin sensitivity
- Protects Against Diabetes
- Involved in the making of protein and muscle formation
- Improves oxygen uptake throughout the body
- Needed for normal sperm development
- Regulates acute HPA responses under dominance challenge
Benefits of Testosterone

- Protects against high blood pressure
- Protects against arthritis
- Reduces excess body fat
- Protects against multiple sclerosis
- Prevention and treatment of depression
- Prevention of Alzheimer's disease and dementia
Benefits of Testosterone

- Helps regulate cholesterol
- Helps maintain a powerful immune system
- Aids in mental concentration
- Improves mood
- Regulates the population of thromboxane A2 receptors on megakaryocytes and platelets and therefore platelet aggregation
Benefits of Testosterone

References


S/S Testosterone Deficiency

- Low libido, inability to maintain an erection
- Anxiety, depression
- Weight gain, decreased fitness level and effectiveness of workout
- Low self esteem
- Thin drying hair, sagging cheeks
- Droopy eyelids, thin lips
S/S Testosterone Deficiency

- Thin, pale, dry skin, with poor turgor
- Muscle wasting
- Memory loss, joint pain
- Loss of drive, competitive edge
- Increased brain aging
- Cardiovascular Aging
- Increased Heart Attacks and Strokes
S/S Testosterone Deficiency

• Hot flashes
• Persistent fatigue
• Irritable, nervous and hesitant
• Increased fat in hips, abdomen, and breasts
• Anemia
Testosterone: Target Organs

Brain
Libido, aggression, cognition

Skin
Male pattern body and facial hair, balding, sebum production

Muscle
Increase in strength and volume

Liver
Synthesis of serum proteins

Kidney
Stimulation of erythropoietin production

Fat
Decrease fat mass

Male sexual organs
Penile growth
Spermatogenesis
Prostate growth and function

Bone Marrow
Stimulation of stem cells

Bone
Accelerated linear growth
Closure of epiphyses
Maintains BMD
Etiology of Testosterone Deficiency

- Slowing Metabolism
- Aging
- Testicular injury or infection
- Chemotherapy
- Adrenal fatigue (burnout), stress, toxins
- Depression, Psychological issues
- Statins, Liver Disease
- Nutritional deficiencies
- Diabetes, Obesity
- Growth hormone deficiency
- Smoking and alcohol intake
- Hyperprolactinemia due to pituitary tumor
Challenges in Recognizing and Diagnosing Androgen Deficiency

- Diagnosis of TD is not straightforward
- Symptoms are vague and many are nonspecific (depression, hypothyroidism, anemia, aging)
- 3 validated screening tools are now available:
  - ADAM, NERI, and Aging Male Survey
- Disagreement over biochemical definition of “normal” and “low” testosterone levels
- No single level of testosterone separates hypogonadism from eugonadism
- Selection of “lower limit” of T is arbitrary, not defined scientifically or via registry of patients

1. Do you have a decrease in libido?
2. Do you have a lack of energy?
3. Do you have a decrease in strength and/or endurance?
4. Have you lost height?
5. Have you decreased an “enjoyment of life?”
6. Are you sad and/or grumpy?
7. Are your erections less strong?
8. Have you noted a decrease in ability to play sports?
9. Are you falling asleep after dinner?
10. Has there been a recent deterioration in work performance?

• Positive screen = YES for # 1-7 or any 3 questions
• *Androgen Deficiency in Aging Males Morley et al. Metabolism 2000.
Age Related Testosterone Decline

MALE Testosterone Decline with Age

ng/dL

Age

20 years 30 years 40 years 50 years 60 years 70 years
Mechanism of Decline

- **GnRH**
- **Estrogens**
  - **Aromatase**
  - **TNFα & other adipokines**
  - **Visceral fat**
  - **Triglyceride uptake**

- **LH**
- **Leptin**
- **Insulin**
  - **SHBG**
  - **Lipoprotein lipase**

- **Testis**
  - **Testosterone production**
  - **Circulating total T**
  - **Circulating free T**

- **Testosterone deficiency**
Age Related Testosterone Decline

• 30% to 60% of men in their 70s are hypogonadal.

• 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.

• 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%.
American Family Physician: Controversies in Family Medicine

“Should FP’s Screen for Testosterone Deficiency in Men?”

Pro’s

- T declines as men age
- TD is a real syndrome with real symptoms and improvable metabolic outcomes
- Studies suggesting CV risk have MAJOR flaws
- TRT has proven benefit in cardiometabolic syndrome

Con’s

- Aging adults are a profitable market; TRT has been promoted as a “youth restoring tonic and disease preventive.”
- “Pharmaceutical companies use nonspecific symptoms to foster disease states.”
- No consistent relationship has been proven between T levels and symptoms associated with low T.


Fugh-Berman A. No: Screening may be harmful, and benefits are unproven. Am Fam Physician 2015;91(4):226-228.
The AMA vs. Testosterone

- Current evidence does not support the use of testosterone in older men with low testosterone levels.

- Evidence of the value of testosterone as an antiaging therapy does not exist.

Testosterone supplements linked to heart attacks in new study

The FDA said today that it was evaluating the cardiovascular safety of testosterone products. The investigation is prompted by two recent published studies that found a significant increase in cardiovascular events in men who received testosterone therapy.

The FDA said it had not concluded that testosterone is unsafe but recommended that “health care professionals should consider whether the benefits of FDA-approved testosterone treatment is likely to exceed the potential risks of treatment.” Testosterone is approved for use only in men who lack or have low testosterone levels in conjunction with an associated medical condition.
Current Evidence does not Support the Use of Testosterone in Older Men with Low Testosterone levels.

- Risk of non-fatal MI greater in the 3 months after testosterone Rx.
- ICD-9 study, patients not seen or interviewed
- No information on preparation, dose or interval of usage or if even used
- No info on fatal MI or cardiovascular mortality or all cause mortality
- No information on testosterone serum levels before or after therapy

No evidence currently suggests that custom CBHT formulations offer clinically relevant benefits.

Facts: Testosterone and Heart Disease

- Low testosterone levels are associated with increased mortality, atherosclerosis, and incident coronary artery disease;

- Mortality is reduced by one half in testosterone-deficient men treated with testosterone therapy compared with untreated men;

Conclusional: Delusional?
A Predetermined Outcome?

With T 10% w Event vs. Without T 21% Events = T Caused Events?

With T 5% Deaths vs. Without T 9% Deaths = T Caused Deaths?

YOU DON'T SAY
Testosterone and Heart Disease—Study Retracted

1. Authors improperly excluded 1132 men from analysis. Corrected to 128 subsequently.
   a. (Error rate 89%)
2. 100 women were identified among the study group.
3. Original group of 1132 individuals, meaning that one out of eleven “men” in the study were actually women.
4. More than 160 leading testosterone researchers and 29 medical societies from around the world joined ASG called for retraction of the study following revelation of the data errors, asserting that the magnitude and quality of the errors rendered the study "no longer credible."
No Consistent Relationship has been Proven Between T Levels and Symptoms Associated with Low T.

**Coronary Heart Disease**

- **Men with coronary heart disease have significantly lower total testosterone, free testosterone, and bioavailable testosterone.**
  - English, K., et al., “Men with coronary artery disease have lower levels of androgens than men with normal coronary angiograms,” Eur Heart Jour 2000; 21(11):890-4

- **Low endogenous testosterone concentrations are related to mortality due to cardiovascular disease and other causes.**

- **Men with coronary heart disease under age 45 have total and free testosterone levels significantly lower than controls.**
Myth: Testosterone Causes Prostate Cancer

Based on one report from 1941

• No relationship of T, DHT, E2 to prostate Ca

• No reports of PC in men treated with T after radical prostatectomy

• Benefits from head to toe when hypogonadism treated

• Morgentaler A. Testosterone and Prostate Cancer: An Historical Perspective on a Modern AMA. Eur Urol. 2006 Jul 26
Myth: Testosterone Causes Prostate Cancer

- 3886 men with prostate cancer, 6438 controls

No associations were found between the risk of prostate cancer, Testosterone, calculated free testosterone, dehydroepiandrosterone sulfate, androstenedione, androstanediol, estradiol, calculated free estradiol


• Conclusion- Testosterone therapy in hypogonadal men does not increase the risk of prostate cancer.
Myth: Testosterone Causes Prostate Cancer

• “No compelling evidence at present suggests that men with higher testosterone levels are at greater risk of prostate cancer or that treating men who have hypogonadism with exogenous androgens increases this risk.

• In fact it should be recognized that prostate cancer becomes more prevalent exactly at the time in a man's life when testosterone levels decline.”


Testosterone and Depression

T has Antidepressant effect in Depressed Patients, esp. those w Hypogonadism.


Testosterone and Growth Hormone Improve Body Composition and Muscle Performance in Older Men

Supplemental T produced significant gains in lean mass, strength and aerobic endurance with significant reductions in whole body and trunk fat. GH further enhances outcome

Testosterone Levels Inversely Proportional to Degree of Depression

- Free T in lowest quartile = highest incidence of depression

<table>
<thead>
<tr>
<th></th>
<th>At Risk</th>
<th>Free T</th>
<th>Depression</th>
<th>Dep.-Free T</th>
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<tbody>
<tr>
<td>Male</td>
<td>295 ng/dl</td>
<td>6.0 ng/ml</td>
<td>147.5 ng/dl</td>
<td>3.0 ng/ml</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Median 12-14 ng/ml)</td>
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<td></td>
</tr>
<tr>
<td>Female</td>
<td>22 ng/dl (Median 44 ng/dl)</td>
<td>1.0 ng/dl (Median 2-4 ng/dl)</td>
<td>11 ng/dl</td>
<td>0.5 ng/dl</td>
</tr>
</tbody>
</table>
No Consistent Relationship has been Proven Between T Levels and Symptoms Associated with Low T.

ED Predicts Coronary Events: 10-Year Follow-up

- 2115 men from Olmstead County Study of Urinary Symptoms and Health Status Among Men
  - 1402 (66%) aged 40 to ≥70 y with sexual partner and no known CAD at study entry
  - 156 CAD events
- ED and CAD may share common underlying vascular pathology
- In younger men, ED related to marked increase in risk of cardiac events
- In older men, ED of little prognostic importance

![Graph showing incidence per 1000 person-years by age group: 40-49, 50-59, and 70+.

Legend: *No ED*; *ED*]

AD, coronary artery disease; ED, erectile dysfunction.
No Consistent Relationship has been Proven Between T Levels and Symptoms Associated with Low T.

Carotid Artery Disease

- 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 is associated with atherosclerosis in men.
No Consistent Relationship has been Proven Between Testosterone Levels and Symptoms Associated with Low T.
No Consistent Relationship has been Proven Between T Levels and Symptoms Associated with Low T.

Incident CVD in Men With ED and No Prior Cardiovascular Event

- 7-y estimate of cardiovascular events approaching 15%

- Of 8063 men without CVD at study entry, 3816 (mean age, 62 y) had ED
- Of 4247 men without ED at study entry, 2420 reported incident ED after 5 yrs

CVD, cardiovascular disease; ED, erectile dysfunction.
# Prevalence of Concomitant Cardiometabolic Conditions in Men With Total Testosterone < 300 ng/dL

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Hypogonadism* Prevalence (95% CI)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>52.4 (47.9-56.9)</td>
<td>2.38 (1.93-2.93)</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>50.0 (45.5-54.5)</td>
<td>2.09 (1.70-2.58)</td>
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<tr>
<td>Hypertension</td>
<td>42.4 (39.6-45.2)</td>
<td>1.84 (1.53-2.22)</td>
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<tr>
<td>Hyperlipidemia</td>
<td>40.4 (37.6-43.3)</td>
<td>1.47 (1.23-1.76)</td>
</tr>
<tr>
<td>Asthma or COPD</td>
<td>43.5 (36.8-50.3)</td>
<td>1.40 (1.04-1.86)</td>
</tr>
<tr>
<td>Prostate disease</td>
<td>41.3 (36.4-46.2)</td>
<td>1.29 (1.03-1.62)</td>
</tr>
</tbody>
</table>

*Men with total testosterone < 300 ng/dL.

No Consistent Relationship has been Proven Between T Levels and Symptoms Associated with Low T.

**TD and Metabolic Syndrome: A Bidirectional Association**

Of 803 patients with sexual dysfunction, 236 (29.4%) were diagnosed as having metabolic syndrome.

*P < .0001 vs no metabolic syndrome components. CI = confidence interval.

No Consistent Relationship has been Proven Between T Levels and Symptoms Associated with Low T.

Metabolic Syndrome-Diabetes

Endocrine Society recommends measurement of testosterone in all male patients with T2DM


Hypogonadal T levels yield 2X risk of Insulin Resistance.

No Consistent Relationship has been Proven Between T Levels and Symptoms Associated with Low T.

Metabolic Syndrome-Diabetes References

Google Scholar-68,900 Articles; 8630 Since 1/1/2017

Google - 1.23 million references

No Consistent Relationship has been Proven Between T Levels and Symptoms Associated with Low T.

- **Low TT is predictive of hypertension**
- **TT is a biomarker for increased cardiovascular risk.**

- **Low TT = ↑ Mortality in CHF**

- **Low TT = Memory Loss**
No Consistent Relationship has been Proven Between T Levels and Symptoms Associated with Low T.

- **Memory**

- Testosterone plays a major role in brain function.

- Even subclinical androgen deficiency increases expression of amyloid-B-related peptides in vivo.

- Age-related decline in free T predicts decline in visual/verbal memory.

- Low bioavailable T is a positive predictor of memory loss in men as they age.

- Low bioavailable testosterone = Correlation b memory loss/Alzheimer’s disease.
Testosterone and the Brain

• Attenuates inflammatory cytokines
  • Increases IL-10 (which inhibits pro-inflammatory cytokines IFN-gamma, IL3, TNF alpha, GM-CSF)

• Protects against mitochondrial dysfunction

• Controls neuronal excitability
  • Improves Seizure Control

• Testosterone decreases pain, anxiety and improves cognitive function by converting to DHT

  • Reddy DS. Testosterone modulation of seizure susceptibility is mediated by neurosteroids 3 alpha androstanediol and 17 beta estradiol. Neuroscience.: 2004
No Consistent Relationship has been Proven Between T Levels and Symptoms Associated with Low T.

• Alzheimer’s Dx. And Dementia

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

• Low plasma T is significantly associated with ↑ risk of Alzheimer’s Dx. in elderly men (random RR = 1.48, 95% CI 1.12-1.96, P = 0.006).

• Alzheimer’s Dx. risk is ↓ by 26% for each 10-unit (nmoL/nmoL) ↑ in free T at 2, 5, and 10 years before the diagnosis of Alzheimer’s disease was made.
Low Testosterone Predicts Mortality from Cardiovascular Disease


EPIC-Norfolk: Testosterone Concentrations Related to All-Cause and CVD Mortality*

*N=2314 men aged 42-78 yrs

CVD = cardiovascular disease; EPIC-Norfolk = european prospective investigation of cancer.
Endocrine Society Guidelines
Testicular Hypogonadism

History and physical (symptoms and signs)

Morning Total T
< 300 ng/dL

Low T

Exclude reversible illness, drugs, nutritional deficiency
Repeat T [use free or bio T, if suspect altered SHBG]
LH+FSH
SFA [if fertility issue]

Confirmed low T [e.g., Total T < 300ng/dL; or free or bio T < normal [e.g., free T < 5ng/dL]]

Low T, low or normal LH+FSH (2.°)

Low T, high LH+FSH (1.°)

Karyotype
[Klinefelter syndrome]

Normal T, LH+FSH

Positive T, LH+FSH

Follow up

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SHBG = sex hormone-binding globulin; LH = luteinizing hormone; FSH = follicle stimulating hormone; SFA = sperm functional assessment.
Hormone ranges are based upon pooled data.

Usually a two standard deviations a randomized mean defines the range.
Ranges may be narrow; i.e.
- Post-menopausal Progesterone (0.1-0.8 ng/ml)

Ranges may be broad; Total Testosterone: 264 to 916 ng/ml.
  (New Lab Corp. Value)
Hormone levels should be centered around the median level of its acceptable range.

The ideal net effect is that the levels are close to the median of the range.
Laboratory Evaluation in TBI
“The Optimal Physiological Level”

Major National Lab

Total Testosterone  Range (264-916)=1180/2 = 590 Median

(Prior to July 17, 2017 Range (348-1197)= 772.5 Median

Range lowered due to obesity crisis showing improvement w low testosterone levels
Laboratory Evaluation in TBI
“The Optimal Physiological Level”

50% and above

Optimal Physiological Levels
Lab Testing

- Total testosterone, free testosterone vs. salivary testing
- DHT
- Estradiol, Estrone
- DHEA
- CBC, CMP
- Fasting Insulin, Hb A1C
- A.M. Cortisol
- SHBG
- Progesterone
- Prolactin
- Pregnenolone
- PSA
- C-Reactive Protein
- 25 OH Vitamin D
- IGF-1, GH, IGFBP3
- TSH, free T3, free T4, reverse T3, TPO, antithyroglobulin
- Lipid Panel
- LH, FSH
- Zinc
Male Hormone Testing | Results | Range
--- | --- | ---
Growth Hormone | 5ng/ml* | 
Somatomedin C (IGF-1) | > 200 ng/ml | 
IGFBP-3 | >4000 ng/ml | 
DHEA-S | 245 ug/dl* | 
Estrone (E1) | < 60 pg/ml* | 
Estradiol (E2) | <25 pg/ml* | 
Progesterone | 0.8 ng/ml* | 
Pregnenolone | 110 ng/dl* | 
EP Ratio | < 250 | 
DHT | < 55 ng/dl | 
SHBG | < 75 pg/ml | 
FSH | 7 mIU/ml* | 
LH | 5.1 mIU/ml | 
Prolactin | 14 ng/ml* | 
Zinc | 95mcg/dL | 
Insulin | <30 mIU/L | 
Vitamin D3 | >60 ng/dl* | 
ACTH | 35 pg/ml | 
Cortisol | < 15 ug/dl | 
SHBG | < 75 pg/ml | 
Testosterone Free | 12-14 pg/ml* | 
Testosterone Total | 690 ng/ml* | 
TSH | <2.5 mcg/ml* | 
T3, Free | > 2.5 pg/ml | 
T4, Free | > 1.5 ng/ml | 
rT3 | 80-250 pg/ml | 
T3/rT3 Ratio | >1.06 | 
TPO | <35 |
<table>
<thead>
<tr>
<th>Male Hormone Testing</th>
<th>Results</th>
<th>Range</th>
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<tbody>
<tr>
<td>Growth Hormone</td>
<td>1.7</td>
<td>5ng/ml*</td>
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<tr>
<td>Somatomedin C (IGF-1)</td>
<td>122</td>
<td>&gt; 200 ng/ml</td>
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<tr>
<td>IGFBP-3</td>
<td>3128</td>
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<td>DHEA-S</td>
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<td>Estrone (E1)</td>
<td>&lt;5</td>
<td>&lt; 60 pg/ml*</td>
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<tr>
<td>Estradiol (E2)</td>
<td>68</td>
<td>&lt;25 pg/ml*</td>
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<td>Progesterone</td>
<td>0.96</td>
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<td>Pregnenolone</td>
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<td>DHT</td>
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<td>&lt; 55 ng/Dl</td>
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<td>SHBG</td>
<td>58</td>
<td>&lt; 75 pg/ml</td>
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<td>FSH</td>
<td>5.8</td>
<td>7 mIU/ml*</td>
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<tr>
<td>LH</td>
<td>8.9</td>
<td>5.1mIU/ml</td>
</tr>
<tr>
<td>Prolactin&lt;5</td>
<td>1.3</td>
<td>14 ng/ml*</td>
</tr>
<tr>
<td>Zinc</td>
<td>68</td>
<td>95mcg/dL</td>
</tr>
<tr>
<td>Insulin</td>
<td>19</td>
<td>&lt;30mIU/L</td>
</tr>
<tr>
<td>Vitamin D3</td>
<td>99</td>
<td>&gt;60 ng/dl*</td>
</tr>
<tr>
<td>ACTH</td>
<td>42</td>
<td>35 pg/ml *</td>
</tr>
<tr>
<td>Cortisol</td>
<td>22</td>
<td>&lt; 15 ug/dl</td>
</tr>
<tr>
<td>TSH</td>
<td>0.99</td>
<td>&lt;2.5 mcu/ml*</td>
</tr>
<tr>
<td>T3, Free</td>
<td>3.1</td>
<td>&gt; 2.5 pg/ml</td>
</tr>
<tr>
<td>T4, Free</td>
<td>1.8</td>
<td>&gt; 1.5 ng/ml</td>
</tr>
<tr>
<td>rT3</td>
<td>326</td>
<td>80-250 pg/ml</td>
</tr>
<tr>
<td>T3/rT3 Ratio</td>
<td>0.99</td>
<td>&gt;1.06</td>
</tr>
<tr>
<td>TPO</td>
<td>199</td>
<td>&lt;35</td>
</tr>
</tbody>
</table>
## 6. Total Testosterone/SHBG

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal</th>
<th>T Deficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Serum tot. Testo/SHBG (free Testo index in mmol)</td>
<td>20 90-100</td>
</tr>
<tr>
<td>Female</td>
<td>Serum tot. Testo/SHBG (free Testo index in mmol)</td>
<td>8 8</td>
</tr>
</tbody>
</table>
What Test(s) to Use?

- Total T vs. Free T vs. Bioavailable T vs. Salivary T...
- Best test is morning Total T (+/- fasting)
- If abnormal, repeat [ NL ~300 - ~1000ng/dL ]
- Check LH to exclude primary secondary causes
  - If low, evaluate pituitary axis function
- Perform semen analysis & FSH if to R/O infertility
- DEXA scan in cases of chronic hypogonadism
- If TT < 150ng/dL, check prolactin and pituitary MRI
- Chromosomal studies indicated in prepubertal males to R/O Klinefelter’s Syndrome if:
  - Low Total T, elevated FSH and LH: suggesting primary
## Laboratory Evaluation in TBI

### “The Optimal Physiological Level”

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Median Male</th>
<th>Median Female</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHEA-S</td>
<td>200 ug/dL</td>
<td>277 ug/dL</td>
<td>M (88-487)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>F (30-260)</td>
</tr>
<tr>
<td>Total Testosterone</td>
<td>690 ng/ml</td>
<td>44 ng/ml</td>
<td>M (280-1100)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>F (15-70)</td>
</tr>
<tr>
<td>Free Testosterone</td>
<td>14 ng/ml</td>
<td>2-4 ng/m</td>
<td>M (1.9-27)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>F (0.2-2.6)</td>
</tr>
<tr>
<td>DHT</td>
<td>&lt;52 ng/dL</td>
<td>&lt;15 ng/dL</td>
<td>M (11.2-95)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>F (&lt;30)</td>
</tr>
<tr>
<td>SHBG</td>
<td>45 pg/ml</td>
<td>&lt;75 ng/dL</td>
<td>M (10-80)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>F (20-130)</td>
</tr>
</tbody>
</table>
25 y/o Daily Testosterone production rates: 4 to 11.8 mg per day.

Ave = 28 mg - 80 mg/week.

Testosterone Replacement Clinic Rx.: 200 mg IM/week

With Supraphysiologic doses we get elevated Estrogen/DHT

<table>
<thead>
<tr>
<th>Product</th>
<th>Dose</th>
<th>Lab Level</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clomid**</td>
<td>50mg 3-5x a week</td>
<td>2-3 months</td>
<td>Less than 40 years of age and prophylaxis. Apply to shoulder and upper</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>arms only.</td>
</tr>
<tr>
<td>AndroGel 1%</td>
<td>1-4 pumps/day</td>
<td>T(T)&gt;350-750ng/dL</td>
<td>High DHT levels and Estradiol.</td>
</tr>
<tr>
<td>AndroGel 1.62%</td>
<td>1 x day</td>
<td>T(T)&gt;350-750ng/dL</td>
<td>High DHT levels and Estradiol.</td>
</tr>
<tr>
<td>Testim 1% Gel</td>
<td>5-10g/day</td>
<td>T(T) 300-1000ng/dL</td>
<td></td>
</tr>
<tr>
<td>TestoCream 10%</td>
<td>½ - 1 gram/day</td>
<td>F(T)&gt; 10-14ng/dL</td>
<td>Apply to flank if not in contact with other people.</td>
</tr>
<tr>
<td>Testosterone</td>
<td>40-100mg/week-Male</td>
<td>F(T)&gt; 10-14ng/dL</td>
<td>Once weekly subcutaneous or IM injection.</td>
</tr>
<tr>
<td>Cypionate IM</td>
<td>10-30mg/week - Female</td>
<td>T(T)&gt;300-1000ng/dL</td>
<td></td>
</tr>
<tr>
<td>Testosterone</td>
<td>Based upon weight.</td>
<td></td>
<td>Initially high levels dropping over 4-6 months. Once implanted cannot</td>
</tr>
<tr>
<td>Pellets</td>
<td></td>
<td></td>
<td>remove.</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Males: 25-50mg BID3x/wk</td>
<td>F(T)&gt;10-14ng/dL</td>
<td>Short half-life needing frequent dosing.</td>
</tr>
<tr>
<td>Lozenge (Troche)</td>
<td>Female: 12.5-25mg BID3x/wk</td>
<td>T(T)&gt;300-1000ng/dL</td>
<td></td>
</tr>
<tr>
<td>Testosome®</td>
<td>Males: 1cc Oral AM, Daily</td>
<td>F(T)&gt; 10-14ng/dL</td>
<td>Short half-life with excellent absorption. CNS benefits include improved</td>
</tr>
<tr>
<td></td>
<td>Females: 1 cc Oral, TIW</td>
<td>Female: F(T)&gt; 2-4ng/dL</td>
<td>focus, concentration, decrease anxiety, improved depression, rise in</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>libido and mental energy. ¥</td>
</tr>
</tbody>
</table>

¥ - Based upon 3 months of testing with 10mg dose sampling.
Testosterone Replacement Therapy

Onset of Action (On Average)

Crèams and Gels:  4-8 Weeks
Injectables:        4 Weeks
Pellets:            4-7 Days
Testosterone Replacement Therapy

- **Oral-Never! (Methyltestosterone)-Hepatotoxic**
- **Sublingual (50-200 mg 2/3x/d)-Wears Off Quickly**
- **Transdermal**
  - Commercial Products
    - 1-2% Concentrations
    - Expensive
  - Compounded
    - 10-20% Concentrations
    - Reliability of Compounder is Key
Testosterone Replacement Therapy

- **Injectables**-
  - Q 2 weeks-Hormone is depleted. Like starting over each time
  - Weekly-
  - Bi-weekly
    - Lessens conversion to Estrogen
    - Needle phobia must be overcome
Testosterone Replacement Therapy

• Injectables-
  • Testosterone Undecanoate
    – 12 week half life
    – Has 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
    – Pt Must Be Observed Post Injection for Pulmonary Oil Microembolism
    – Very Expensive
  • Testosterone Cypionate
    » 12 day half life
  • Testosterone Ethanate
    – 10.5 day half life
  • Testosterone Proprionate
    – 36 hour half life
Combining Therapies

- Testosterone cypionate IM +:
  - Propionate IM in one syringe
  - Anastrozole + HCG into one syringe IM
  - Zinc IM (Natural Aromatase Inhibitor)
  - Anastrozole IM.
    - Anastrozole dose is usually 0.05 mg/ml to 1mg/ml
Testosterone Replacement Therapy

Injectables

- Adverse effects:
  - Mood swings
  - Variability in libido, sexual function, and energy levels
  - Injection site reactions
  - Erythrocytosis-No change in Platelet Levels from T Rx
  - Acne
  - nonproductive cough
  - Estrogen Excess
    - Gynecomastia
    - CV Issues
Testosterone Replacement Therapy

Pellet Dosing

- **Average: 900-1200 mg testosterone pellets**
  - 1400-1800 mg larger men, chronic disease
    - 100 or 75 mg pellet implants with smaller trocar
    - No difference in release rate between 2 (100 mg) pellets and a 200 mg pellet

- **Most studies look at 600-1200 mg doses**
  - 100 and 200 mg pellets
Testosterone Replacement Therapy

Pellet “Failures”

- QUALITY CONTROL ISSUE W PELLET
- DOSING ERRORS
- STRESS
- DIET: Refined foods, processed carbohydrates, low fat=Pellet Failure
- LACK OF EXERCISE
- LACK OF SUNLIGHT: Low levels of Vitamin D
- ESTROGEN DOMINANCE
- OPERATOR ISSUE
- MEDICATIONS
Testosterone Replacement Therapy

Medications Leading to Pellet “Failures”

- BP Meds
  - Diuretics
  - ACE Inhibitors, ARBS, Alpha Blockers, Beta Blockers, Calcium Channel Blockers
- Statins
- Antidepressants/Antianxiety Agents
  - SSRI, MAOI
  - Benzodiazepines
- NSAIDS
- Antihistamines
- Anti Parkinson’s Medications
- PPI’s, H-2 Antagonists
- Muscle Relaxants
- Chemotherapy Drugs
## Formulation-Specific Adverse Effects

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Injectable</strong></td>
<td></td>
</tr>
<tr>
<td>Testosterone cypionate/enanthate</td>
<td>Mood fluctuations or changes in libido  Pain at injection site  Erythrocytosis</td>
</tr>
<tr>
<td>TU (in development in the United States)</td>
<td>Pain at injection site</td>
</tr>
<tr>
<td><strong>Implants</strong></td>
<td></td>
</tr>
<tr>
<td>Testosterone pellets</td>
<td>Potential infections or expulsion</td>
</tr>
<tr>
<td><strong>Topical</strong></td>
<td></td>
</tr>
<tr>
<td>Topical gel and solution</td>
<td>Skin-to-skin transference (less risk with newer, high-potency, low-volume formulations)</td>
</tr>
<tr>
<td>Patch system</td>
<td>Skin irritation</td>
</tr>
<tr>
<td><strong>Buccal</strong></td>
<td></td>
</tr>
<tr>
<td>Buccal system</td>
<td>Alterations in taste and irritation of gums and oral mucosa</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oily skin, acne, skin reactions</td>
<td>Skin irritation more common with scrotal patches</td>
</tr>
<tr>
<td>Breast enlargement or tenderness</td>
<td>Often transient; abates over time</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>Not reported as a consequence of treatment, but consider COPD in heavy smokers or men who are overweight</td>
</tr>
<tr>
<td>Polycythemia</td>
<td>Uncommon, but associated with age, sleep apnea, smoking history, and COPD</td>
</tr>
<tr>
<td>Liver function abnormalities or tumors</td>
<td>Rare with injectable esters and transdermal formulations</td>
</tr>
<tr>
<td>Lower extremity edema</td>
<td></td>
</tr>
<tr>
<td>Symptomatic BPH and prostate cancer</td>
<td>Modest and inconsistent increases in prostate volume</td>
</tr>
<tr>
<td>COPD</td>
<td>potential worsening of hypoxemia</td>
</tr>
</tbody>
</table>

COPD = chronic obstructive pulmonary disease; BPH = benign prostatic hyperplasia.
Testosterone Replacement Therapy

Contraindications

• Active Prostate Cancer
• Prostate nodules or indurations
• Breast Cancer
• Unexplained PSA elevation
• Hematocrit > 50 (55 at higher elevations)
• Unstable Congestive Heart Failure
• Sleep apnea
• Fertility—HCG, Clomiphene Citrate
**Clomiphene Citrate**

- Inhibits negative feedback on the hypothalamus:
  - Increases LH and FSH.
- On Average 50 mg 2x/wk. Doubles Total Testosterone Levels in 4 weeks
- Improves osteopenia/osteoporosis and ADAM S/S


---

telephone conversation

I reviewed test results.

Pituitary MRI is normal. Thyroid ultrasound is consistent with Hashimoto's thyroiditis without nodules.

We discussed treatment options for testosterone. I indicated that the clomiphene that he has used and has had success with it is not FDA approved for this purpose and we do not know the long-term effects. However it is available to him and maybe the most convenient thing to use. Also will likely preserve his fertility if that is currently intact. Exogenous testosterone will suppress his testosterone and spermatogenesis which doesn't mean it cannot recover in the future and be stimulated by hCG. These are all unknowns. Also is not a good idea for a young man his age to go without testosterone. Feels chronic fatigue and complete loss of libido.

I offered to get him another opinion with another endocrinologist or at another Medical Center. I also offered to send him to a urologist for subcutaneous testosterone implants and also consultation. He will consider his options and let me know.
Outcomes of Clomiphene Citrate Treatment in Young Hypogonadal Men.

Long-term follow-up of CC treatment for HG shows that it is an effective and safe alternative to testosterone supplementation in men wishing to preserve their fertility.

- Katz DJ, Nabulsi O, Tal R, Mulhall JP.

**Dose:** 25-50 mg 2-5x/wk.

**Side Effects: Same as testosterone side effects**
- Pulmonary Embolism
- Leydig Cell Tumor
T Enhancement Without T

**HCG**

- Is a Pro-hormone
- Creates an anabolic state
- Balances Catabolism
- Increase T
- Preserves testicular size and sperm count
- Promotes weight loss

- Decreases
  - Triglycerides
  - Body fat waist to hip ratio
  - HOMA-IR Score

- Increases
  - Fat free mass

- Unchanged
  - CRP, Homocysteine
  - Lipid profile
Testosterone Enhancement Without Testosterone

HCG

• Preserves testicular volume
• Preserves sperm count
• Needs functioning Leydig cells.
• 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
Treatment Considerations

- **Human Chorionic Gonadotropin (HCG)**
  - Dose to Preserve Size or Semen Volume:
    - 250 IU SQ days 6 and 7 of weekly IM injection
    - 250 IU SQ every 3rd day for Transdermal Gel
  - Dose as Stand Alone Therapy:
    - 3000 IU SQ q 2 wks (increases free T by 25%)
      - Or
    - 1000 IU SQ 2x/wk

Can develop antibody
- RX should be 2 months on, 1 month off.
Testosterone Enhancement Without Testosterone

**HCG Side Effects**

- 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
Other Considerations - Estrogen Excess

Optimal Levels 20-30 pg/ml

- Breast Enlargement
- Prostate Enlargement
- Difficulty Urinating
- Increased Emotional Lability
- Tearfulness
- Decreased sex drive
- ED

Doubled risk of stroke
Higher rates of heart attack, peripheral artery disease, and coronary atherosclerosis
Insulin resistance
Rheumatoid arthritis
BPH
Prostate cancer

Estrogen Excess

• Etiology
  – Increases in aromatase activity
  – Obesity
  – Alcohol excess
  – Environmental estrogens
  – Estrogen containing food
  – Zinc deficiency
  – Liver dysfunction
  – Supraphysiologic Testosterone Therapy
  – Calcium deficiency
  – Diabetes
Avoid Estrogen Excess

E is Neuroprotective

Maintains cerebral blood flow, lactate production

Lowers risk of PTSD after trauma.
Modulates pain.
Strongest predictor of acute mortality and poor long-term outcome.

Decreases risk, onset and progression of neurological deterioration
Alzheimer’s Disease, schizophrenia
Aids in recovering from stroke and TBI.
RX

- Zinc Citrate (30-90 mg/d)
- Quercetin (250 - 500 mg/d)
- Glycyrrhiza – licorice
- Grape seed extracts composed mainly of proanthocyanins
- Resveratrol
- DIM (1-3 gm/d p.o.)

Chrysin (250 mg bid p.o., topical 50 mg/d)

- Progesterone Cream 2-5%, Caps 10-15 mg/d
- Myomin
- Berberine
- Vitamin K
- Anastrozole (0.5-1.0 mg 1-3x/wk.)
Protocol includes adding in upstream hormones shut down by T:

- **Pregnenolone** stimulates progesterone production = neuroprotective

- **DHEA** improves myelin sheath
Pregnenolone

- Precursor to DHEA, Estrogen, Progesterone, and Testo
  - Made from cholesterol
- When cholesterol is below 140 cannot make P effectively
- Decreases with age
  - At age 75, most people have a 65% decline compared to age 35
**Pregnenolone sulfate** regulates neurotransmission in the hippocampus-
Learning and memory.


**Pregnenolone** improves cognitive performance and is improved with replacement

**Pregnenolone** is neuroprotective

Pregnenolone sulfate and aging of cognitive functions: behavioral, neurochemical, and morphological investigations. Horm Behav 2001 Sep;40(2):215-7 Mayo W; INSERM U259, Institut Francois Magendie, Rue Camille Saint-Saens, 33077 Bordeaux Cedex, France.
Pregnenolone

Reduces neurotransmission with reduced:

- Anxiety
- Panic attacks
- Agitation and aggression,
- Insomnia.
- Social Phobias

Deficient in Chronic Fatigue and Adrenal Insufficiency

Dose: 25-60 mg/daily (Comes combined w DHEA)

A Presynaptic Action of the Neurosteroid Pregnenolone Sulfate on GABAergic Synaptic Transmission. *Mol Pharmacol* 64:857–864, 2003 Zakaria MT, CHEDLISH, VI, and Jaideep: Kapur, Department of Neurology, University of Virginia Health Sciences Center, Charlottesville, Virginia
• Decreases cholesterol
• Decreases formation of fatty deposits
• Prevents blood clots
• Increases bone growth
• Promotes weight loss
• Increases brain function
• Increases lean body mass
- 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
- Regenerates myelin
- Antidepressant
- Regulates mood, inflammatory cytokines and interleukins
- High Cortisol/DHEA Ratio=Active Depression
- Low Cortisol/DHEA Ratio=Depression Lessens
REPLACING DHEA

• Increase muscle strength and lean body mass
• Activate immune function
• Increase quality of life
• Improve sleep
• Increase feeling of wellness
• Decrease joint soreness
• Increase sensitivity of insulin
• Decrease triglycerides
• Stop the damaging effects of stress
• Elevate growth hormone levels
<table>
<thead>
<tr>
<th>Symptoms of DHEA Excess</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Anger</td>
</tr>
<tr>
<td>Depression</td>
</tr>
<tr>
<td>Deepening of voice</td>
</tr>
<tr>
<td>Insomnia</td>
</tr>
<tr>
<td>Mood changes</td>
</tr>
<tr>
<td>Weight gain</td>
</tr>
<tr>
<td>Facial hair</td>
</tr>
<tr>
<td>Acne</td>
</tr>
<tr>
<td>Sugar cravings</td>
</tr>
<tr>
<td>Restless sleep</td>
</tr>
<tr>
<td>Irritability</td>
</tr>
</tbody>
</table>
DHEA DOSING

“The Mother of All Sex Hormones”

Male: 25mg SL/PO BID and ↑
   excess converts to Estrogen

Female: 5mg SL/PO BID and ↑
   excess converts to Testosterone

Evening dose will ↑ GH
Dihydrotestosterone (DHT)

Testosterone

- DHT
  - Dihydrotestosterone
    - Skin, liver, prostate

- Estradiol
  - Brain, fat, liver, testes
  - Bone resorption
  - HDL/atherosclerosis effects
  - Brain effects
  - Breast effects

Facial hair
Body hair
Prostate growth
Acne

Muscle Mass
Bone formation
Spermatogenesis
Sexual function
Dihydrotestosterone (DHT)

• Most potent naturally occurring androgen
  – 3 times more potent than testosterone
• Synthesized from the conversion of testosterone through 5-alpha reductase
• 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
  – Hirsutism
  – Male pattern baldness
  – BPH
- DHT stimulates prostate cells 2.5-10 X testosterone
- High DHT levels stimulate the androgen receptors to produce \( \uparrow \) amounts of PSA.
- DHT interacts with extracellular tissues to prostate increase cancer cell mobility.
- High DHT levels have been shown to enhance early atherosclerosis.
- \textit{High T converts to DHT in the CNS. Precipitates Panic and Anxiety.}
  
DHT makes androgens (testosterone) more potent •

Activity:

▶ Metabolizes progesterone into a-Pregnanediol
▶ Metabolizes cortisol into a-THF (β-metabolites of both through 5β activity)

Upregulated leads to high androgen symptoms:

▶ Men (thinning hair, prostate issues)
▶ Women (PCOS, thinning hair, acne, facial hair growth)

Increased enzyme activity:

▶ High insulin and obesity

Edinger, KL; Frye, CA, Testosterone’s analgesic, anxiolytic and cognitive-enhancing effect may be due in part to actions of its’ 5 alpha-reduced metabolites in the hippocampus; Behav Neurosci; 2004 Dec;118(6):1352-64. Albany, NY
Finasteride and Dutasteride block conversion centrally

Cross BBB resulting in depression, fatigue, and sexual dysfunction, ED, Cognitive Impairment, CV Disease

Symptoms frequently do not resolve when Rx. Is discontinued.

Recommend Progesterone 2-15 mg transdermal, Zinc, Nettles, ECGC Saw Palmetto, Pygeum, Pumpkin Seeds, Pomegranate Juice to control conversion of T to DHT

Edinger KI: Testosterone’s Analgesic, Anxiolytic and Cognitive Enhancing Effects May Be Due to action of 5 Alpha reductase metabolites in Hippocampus. Behavioral Science 2004 Dec;118(6):1352-64

Gordon, M.; Traumatic Brain Injury; 2016 Millennium Health Centers Inc.. p.258
@ 1-3 months then every 6 months there after

- Total T, Free T
- LH/FSH
- SHBG
- Estradiol
- H/H
- PSA q mo.
- DRE q 6 mo.
Testosterone Quiz

1. My face has gotten slack and more wrinkled. 0 1 2 3 4
2. I’ve lost muscle tone. 0 1 2 3 4
3. My belly tends to get fat. 0 1 2 3 4
4. I’m constantly tired. 0 1 2 3 4
5. I feel like making love less often than I used to. 0 1 2 3 4
6. I am forgetting things and less mentally sharp 0 1 2 3 4
7. I feel less self-confident and more hesitant. 0 1 2 3 4
8. My sexual performance is poorer than it used to be. 0 1 2 3 4
9. My muscle tone is poor 0 1 2 3 4
10. I tire easily with physical activity. 0 1 2 3 4

Add up your Overall Score ____________:

Women: 5 or less: Satisfactory level. Between 6 and 10: Possible Testosterone deficiency. 11 or more: Probable Testosterone deficiency. Men: 10 or less: Satisfactory level. Between 11 and 20: Possible Testosterone deficiency. 21 or more: Probable Testosterone deficiency.
"AND IN CONCLUSION"
- Low T inversely linked to CAD after adjusting for age/body fat.
- Men with (+)angiography for CAD had lower T than controls
- Administration of T led to coronary dilatation
- Intima media thickness is increased in men with low T
- Rotterdam study: low T levels correlated ASVD
• Androgen deprivation Tx of prostatic cancer led to increased central pressure, hypertension and arterial stiffness.

• Testosterone levels are inversely correlated with blood pressure

• LIPIDS - Testosterone + correlation with HDL; inverse with: LDL, Trigs, and total cholesterol.
• INFLAM - T has inverse relationship with inflammatory cytokines and T replacement reduces cytokines
• CLOTTING - T has inverse relationship with plasminogen activator inhibitor 1, fibrinogen and factor VII
• PLAQUE - T shown to reduce plaque development
Testo and Metabolic Syndrome

• Insulin resistance develops within months of androgen deprivation therapy
• Low T predicts occurrence of Metabolic Syndrome
• Low T is an independently associated with onset DMT2
• Testosterone < 250 ng/dl in men over 40 years of age overall mortality rate increases by 88%

• Dementia risk with ADT is 4.4% at 5 years
  • Nead, Gaskin, et al. JAMA Oncol. Published online October 13, 2016
### Testosterone Summary

#### S/S of Testosterone Deficiency
- Weak, flabby muscles
- Low Self Esteem
- Loss of Muscle Mass
- Lack of Energy/Stamina
- Loss of Coordination and Balance
- Loss of Confidence
- Mental Fatigue
- Decreased Libido
- Lack of Sex Drive/Orgasm
- Weight Gain
- Depression
- Thinned Hair
- Fatigue
- Dry Skin-Poor Elasticity

#### S/S of Testosterone Excess
- Aggressiveness
- Agitated/Irritable
- Oily Skin/Oily Hair
- Overconfidence
- Acne
- Increased Facial Hair
- Decreased HDL
Case History # 1

CC: 36 y/o male presents w 3 year history of fatigue and poor libido.
PH: Overweight, HBP, GERD,
Meds: Omeprazole, HCTZ
Allergies: None
FH: F-CAD w acute MI age 62; M-DMT2 age 58, Sister PCOS
Social Hx: Former smoker (none in 6 years.), occ. ETOH, - drugs but did “stacking” in early twenties. Got drugs from gym.
ROS: ADAM 8 positives
Case History

# 1

PE: BMI 44.6, BP 142/92
Exam: Negative except for abdominal obesity. WC 48”
DRE: WNL
Lab: Hct. 44.3, FBS 107, Fasting Insulin 18.9, IR=4.99, Hb A1c 6.5%
Testo. 126, free T. 1.0%, Estradiol 84 PSA 0.4
TSH: 3.95, free T3 2.1, TPO 312
IGF-1 82
cRP 4.12, Homocysteine 8.45
DHEA 112

How Would You Proceed?
Testosterone Replacement? What else needs to be addressed?
What are the benefits, risks and CI’s to testosterone replacement?
68 y/o male presents from “Men’s Clinic.”
cc: “My libido is no good and I have a new lady friend. They don’t know what they are doing. I’m on 1 ml (200 mg) of testosterone injections weekly and I’m no better. I wanted them to give me 2 cc but they won’t. Oh, and my feet are swollen, I have to wear sneakers, I don’t fit in my shoes.”

PH: Pulmonary embolism, atrial fibrillation, Insomnia, Peripheral neuropathy, HBP, Chronic sinusitis, Erectile dysfunction, Nocturia x 1
Allergy: Grass, mold
• Meds:
  – Anastrozole 0.5 MG Oral Tablet 2 x/wk., Chromium picolinate,
  – Gabapentin 300 mg @ hs,
  – Melatonin 1 mg @ hs
  – Hydrocodone-Acetaminophen (Norco) 10-325 MG Oral Tablet
  – Lisinopril 10 MG Oral Tablet
  – Prasterone (DHEA) 25 MG Oral Capsule
  – Pravastatin Sodium (Pravachol) 40 MG Oral Tablet
  – Tadalafil (Cialis) 20 MG Oral Tablet
  – Testosterone Cypionate 200 MG/ML Intramuscular Solution q week
  – Zolpidem Tartrate 10 MG Oral Tablet
Case History # 2

PE: BMI 23, BP 122/68, R 14, P72, PO2 97
HEENT, Red in Face, Neck, Heart, Lungs, Abd: + Fluid Bilat: LE +2/4 pitting edema
Genitalia WNL, DRE: Smooth + ¼ slight enlargement
ADAM: +9

Lab: 1/22/2018 : (Pt 1st seen by Us)
- Testo 1392
- E2  53
- DHEA 658
- PSA 2.55
- Insulin 22
- FBS  98, IR 5.32
- IGF-1 189
- cRP 0.6
- Vit D3 55
- TSH 2.3
- freeT3 3.1
- TPO 0.9

Lab: 8/9/2017 Beginning Men’s Clinic)
- Testo 214, free 0.9%
- E2 Did not Check
- DHEA 142.3
- PSA 2.37
- Insulin 26
- FBS 91, IR 5.84
- TSH 2.1

How Would You Proceed?
Testosterone Replacement? What else needs to be addressed?
What are the benefits, risks and CI’s to testosterone replacement?
Case History # 2

- January 2011
  - Total T - 1600
  - Bio T - 736
  - Free T - 36.9
- May 2011
  - Total T - 112
  - Bio T - 16
- June 2011
  - Total T - 2300
  - Bio T - 1081
- December 2011
  - Total T - 1090
  - Bio T - 407
Acupuncture for Libido Enhancement

Sexual Desire (Bosch Point)

Sexual Suppression (Jerome Point)

Sexual Desire (Bosch Point)

Sexual Suppression (Jerome Point)