## Chapter 2

## Take Control of Your Man Health Now (What is Low T)

So where does this man juice come from exactly? Well testosterone is synthesized from cholesterol, which is an essential biochemical precursor for many hormones. It is the hormone responsible for normal growth, development and maintenance of male sex characteristics and its effects are body wide. It also directly affects lean body mass, strength, bone density, mood, cognitive skills, and sexual function. It is the primary androgenic and anabolic hormone in men and plays an important role in women as well.

Testosterone is produced by the testes in males and by the ovaries in females, with small amounts also produced by the adrenal glands in both men and women. Other hormones in an intricate and delicate dance of cascading hormones regulate the production and secretion of testosterone.

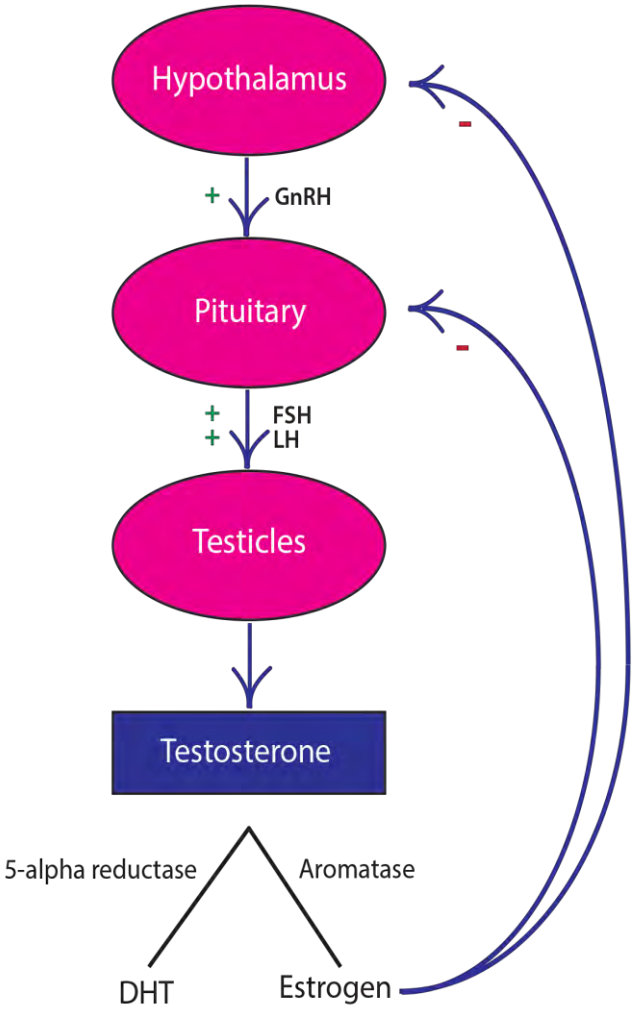
The hormonal and reproductive function of the testicles is regulated through interactions between the hypothalamus, the pituitary gland, and the gonads and is referred to as the Hypothalamic-Pituitary-Testicular Axis or H-P-T-A. The three glands communicate with each other through a cascade of hormones and a negative feedback loop to help maintain homeostatic levels. Altered cellular communication can disrupt this delicate balance.

Causes of Altered Cellular Communication:

- Stress
- Toxins
- Trauma
- Drugs
- Acute & Chronic Disease
- Lifestyle
- Nutrition
- Food Sensitivities
- Intracellular nutrient deficiencies

The release of gonadotropin-releasing hormone, GnRH, via the portal circulation from the hypothalamus to the pituitary stimulates the secretion of the two gonadotropin hormones called luteinizing hormone, LH, and follicle-stimulating hormone, called FSH from the anterior pituitary. Luteinizing hormone facilitates the production and secretion of testosterone from the leydig cells of the testes, while FSH stimulates the production of sperm.

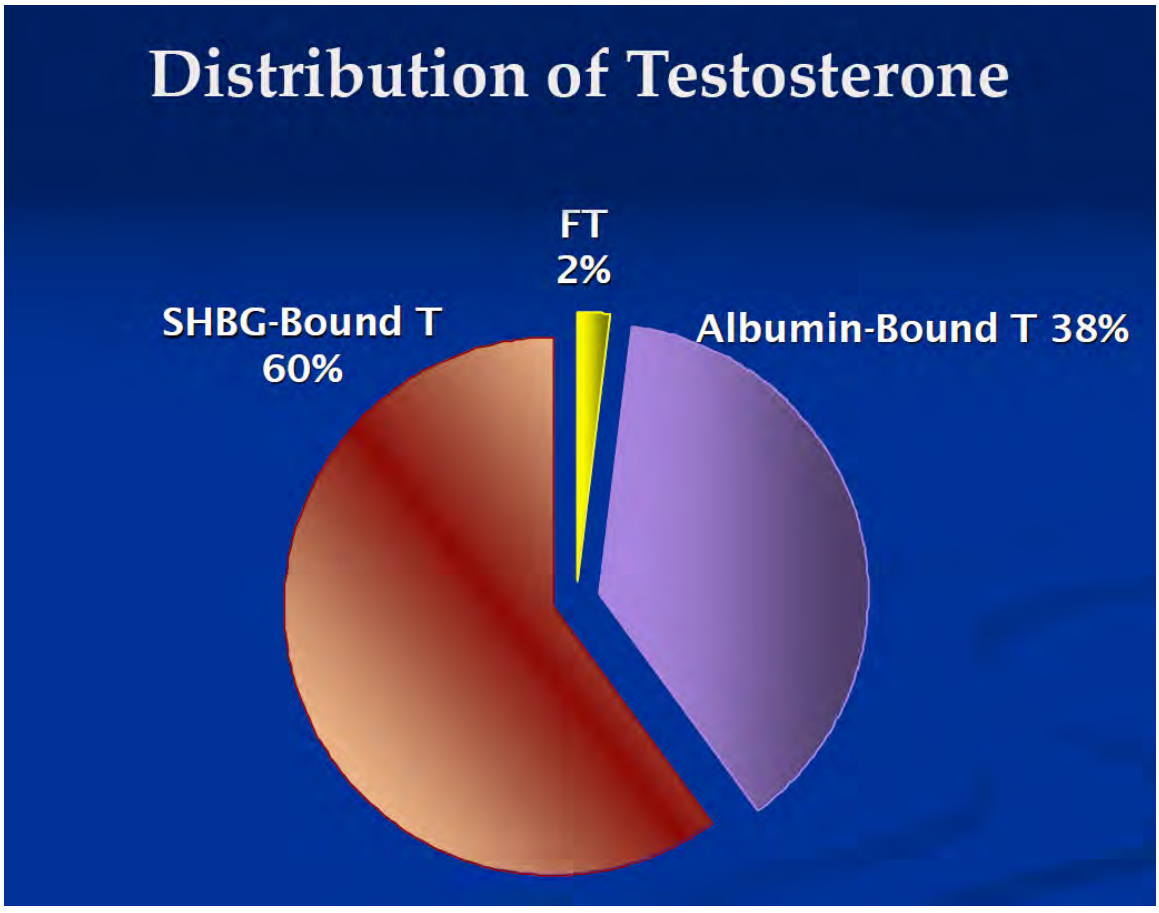
Testosterone, like the gonadotropins is secreted in a pulsatile fashion, which occurs through out the entirety of the day. About 5-7mg/day of testosterone is released. The normal range of total testosterone, depending on the laboratory of course is 348-1197 ng/dL. A total testosterone less than 550 ng/dL is considered low and less than 350 ng/dL is almost always associated with symptoms. More importantly however, is not the number, but how the man is feeling.




Testosterone is converted into two hormones called dihydrotestosterone or DHT and estrogen. The process by which testosterone is converted into estrogen by the aromatase enzyme is known as “aromatization”. Men with high body fat percentages, older men, and men taking certain medications, or males with a genetic predisposition to having higher than normal amounts of aromatase may experience higher conversion rates of testosterone into estrogen.

Estrogen is a very important hormone for men at the right concentration and estrogen plays an important role in bone, hair, heart, skin, and brain health as well as other functions in men. About 15%-20% of men will have issues with elevated estrogen levels while on testosterone therapy. Estrogen has some unwanted negative affects in that it down-regulates testosterone receptors and increases sex hormone binding globulin, which decreases the amount of bioavailable testosterone and diminishes the overall response. I will talk more about that later. Large amounts of estrogen can cause mood swings, enlarged breasts or gynecomastia, nipple tenderness, fat gain, water retention and the potential for a strong emotional need to eat chocolates while watch the "Notebook". I wish I could say I was kidding, but I have seen many a man become overly "sensitive" because of high estrogen levels.

The other metabolite of testosterone is dihydrotestosterone. DHT is a very potent androgen and is important for libido. In some men elevated DHT may cause male pattern baldness or benign prostatic hypertrophy. DHT has a positive effect on sexual desire but high levels of 5α-DHT increase the chance of hair loss, acne, oily skin and potential prostate issues.



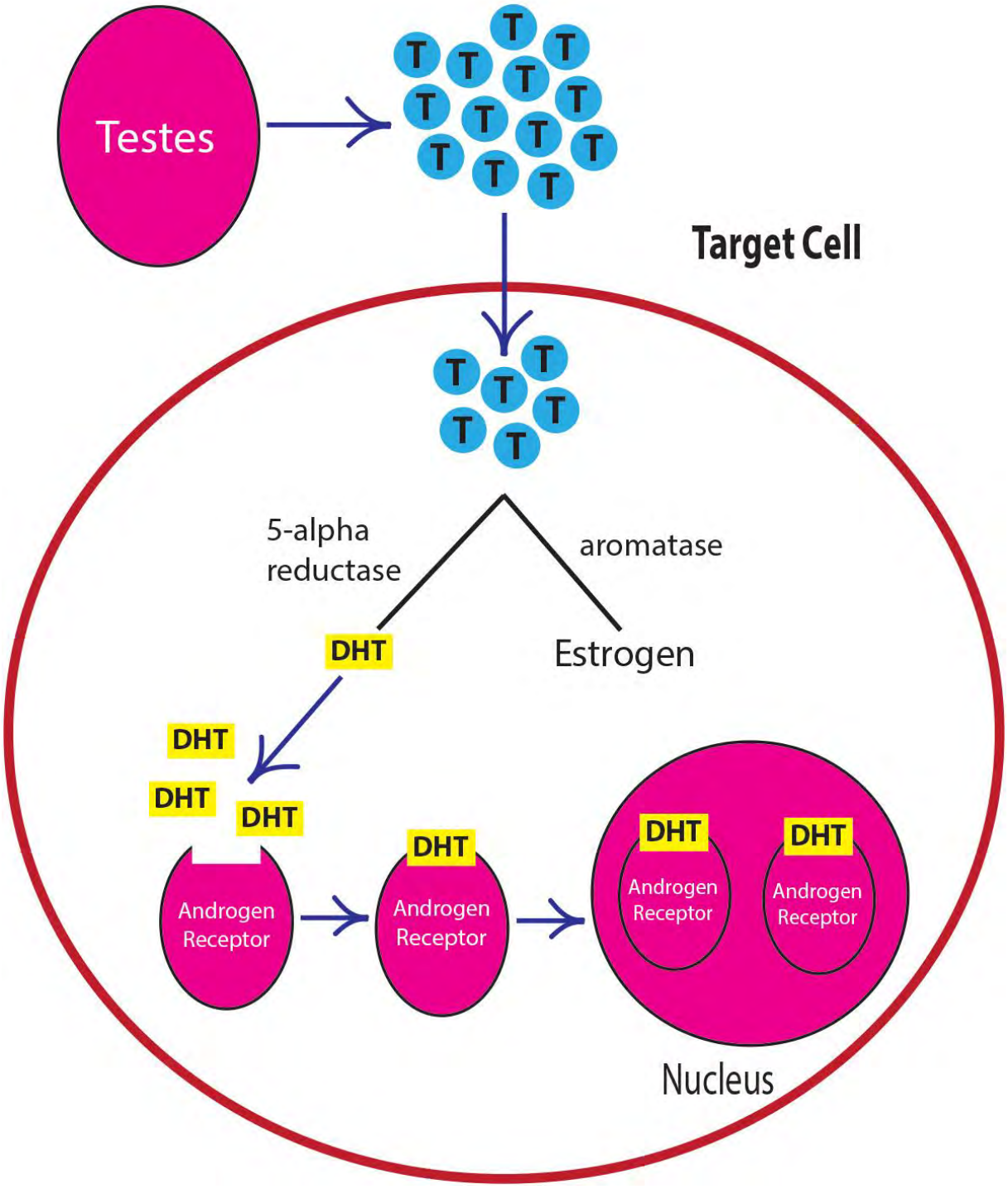
The majority of testosterone circulates in the blood bound to a carrier protein, which is a hormone produced in one area of the body and has its effect on another area it also assists the hormone to travel through the bloodstream. This carrier protein is called "sex hormone binding globulin," or SHBG. SHBG binds approximately 60% of testosterone. When testosterone is being carried by SHBG, it is considered "bound". Bound testosterone does not play an active role in the body; only the unbound or "free" testosterone is able to enter the different cells of the body and exert its androgenic and anabolic effects. Anything that affects the function or the amount of SHBG, like increasing estrogen levels, can also affect the total circulating amount of active testosterone.

It is not unusual in men over the age of 40 to have a normally functioning Hypothalamic-Pituitary-Testicular Axis producing total testosterone levels above 700 ng/dL with a low free testosterone level of say 24ng/dL., the normal range for Free T is 40-250 ng/dL., and because the liver is producing a large amount of SHBG, they have a high level say at 94 nmol/L, they have very little free testosterone in the bloodstream available for use by the body's tissues and they feel the full effects of having low testosterone.

About 38% percent of the body's testosterone is attached to albumin. Testosterone is not as tightly bound to albumin as SHBG, but it is still bound nonetheless. Like SHBG-bound testosterone, albumin-bound testosterone is biologically inactive. However, unlike testosterone bound to SHBG, the bind between albumin and testosterone is weak and can be easily broken in order to increase free testosterone.

About 2 percent of the testosterone in the body is metabolically available. This "free testosterone" is not attached to either albumin or SHBG that would prevent it from interacting with its receptor.

The normal range for Free T is 40-250 ng/dL. Again what is important is not the exact number but how does the individual feel. It is possible for a man to have a low Free T say of 90 ng/dL and be asymptomatic and another fellow have a high Free T of 220 ng/dL and be miserable with low libido, weak erections, moodiness, and no energy. No two men are alike.



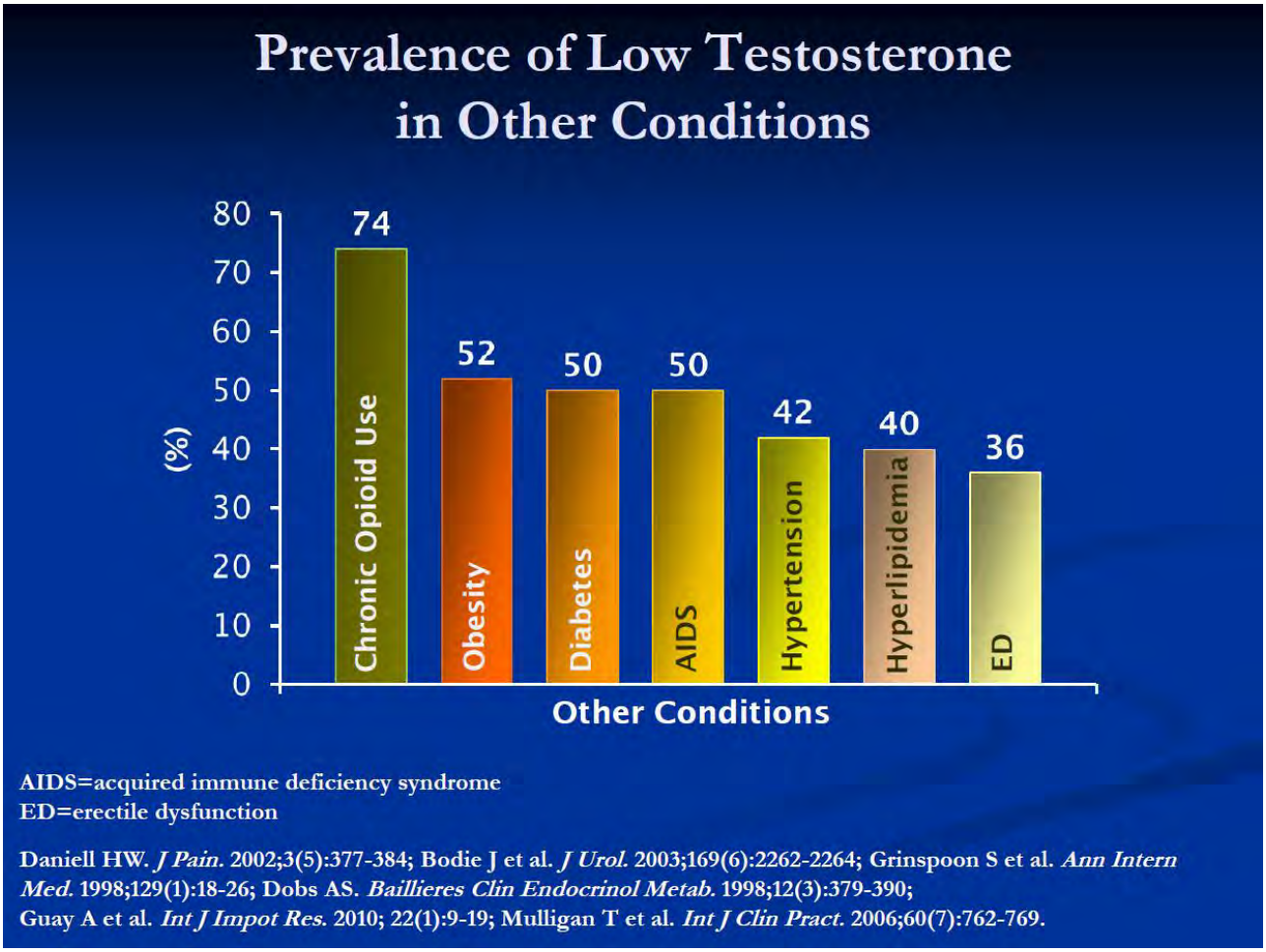

**The diagram above shows the saturation of testosterone into the cell.**

**Symptoms of low testosterone:**

- Can be more subtle than female menopause
- Progresses over 20 year period
- Starts in 30's
- A decline in muscle mass and strength
- Decrease of bone mass
- Increase in body fat, particularly abdominal and chest fat
- Metabolic Syndrome (coronary artery disease and increased cholesterol)
- Decline in cognitive skills, concentration and memory
- Decline in stamina and exertion performance
- Increased frequency of erectile dysfunction
- Decrease in sex drive and frequency of sexual thoughts
- Decreased sense of overall well being, perception of energy level and stamina
- Depression
- Fatigue
- Anxiety
- Aches and pains
- Loss of muscle elasticity

Decrease in sex drive, erectile dysfunction, decreasing muscle mass, increasing body fat, less energy, decreased sense of well-being, more fatigue and competition from younger men signals a declining virility. This decline could accompany the aging process, and be reluctantly accepted as fate. But, that does not need to be the case! However, I am also seeing younger and younger men who experience these changes and this is not normal!

What is particularly disturbing is in the last 10 years the number of young men, under the age of 40, and some in their early 30's, that I see with hypogonadism associated with type 2 diabetes (insulin resistant), obesity, high cholesterol, sexual dysfunction, toxin exposure, steroid abuse, and fatigue.




Men with testosterone deficiency are often under-diagnosed and often undertreated. The first signs of decline in testosterone are generally slightly vague: diminished subjective energy levels, increase in irritability, decline in mood, decline in cognitive performance, and loss of early morning erections.

Some men complain of infertility, decrease in beard and body hair, increase in body fat, decrease in muscle mass, gynecomastia (man boobs), increase in belly fat, changes in size or firmness of testicles.

While decreased sex drive and erectile quality are often the most frequent complaints associated with falling testosterone levels, they are actually some of the latest symptoms, with other symptoms present much sooner.

Often, men and their family members attribute these symptoms to psychosocial stressors or "aging" and do not seek medical help from their doctor. As testosterone declines, age-related drops in testosterone levels is associated with identifiable signs or symptoms: a decline in muscle mass and strength, decrease of bone mass, increase

in body fat, particularly abdominal and chest fat, coronary artery disease, increasing cholesterol, decline in cognitive skills or concentration and memory, decline in stamina and exertion performance, increased frequency of erectile dysfunction, decline in sex drive and frequency of sexual thoughts, and decreased sense of overall well-being, decreased energy level and stamina.

**Types of Hypogonadism and Andropause**

**Primary hypogonadism** (hyper meaning high and hypo meaning low) also referred to as hypergonadotropic hypogonadism a condition where high levels levels of GnRH and LH are seen with low levels of testosterone. This occurs when the testicles fail to produce sufficient levels of testosterone for various reasons. This is also known as Andropause. Men in their fifties have usually begun to enter andropause and for some men this can occur even sooner.

**Secondary hypogonadism** results from hypothalamic or pituitary dysfunction resulting in hypogonadotropic hypogonadism and is characterized by disruption of central components of the H-P-T-A resulting in decreased levels of GnRH, LH, and FSH. In this type of hypogonadism, low levels of LH do not allow for the proper stimulation of the production of testosterone by the testes. This combination of low GnRH, low LH and low testosterone can be seen at any age and has multiple causes.

**Primary Causes of Hypogonadism**

- Congenital anorchidism
- Cryptorchidism (undescended testes)
- Mumps orchitis
- Sertoli-cell-only syndrome
- Noonan syndrome: phenotypic and genotypic males with physical signs of classic female Turner syndrome
- Radiation treatment/chemotherapy
- Testicular trauma/surgical procedures
- Autoimmune syndromes (anti-Leydig cell disorders)
- Genetic and developmental conditions: Klinefelter syndrome (1 in 1000 live births; most patients have 47, XXY genotype anomaly; however, mosaicism is also seen); androgen receptor and enzyme defects

**Secondary causes of hypogonadism**

- Pituitary macroadenoma
- Pituitary tumor, granulomas, abscesses
- Cranial trauma
- Radiation treatment
- Various medications
- Concussion
- Genetic conditions: Kallmann syndrome, Prader-Willi syndrome, Hyperprolactinemia

**Mixed causes of hypogonadism**

- Alcoholism
- Toxins
- Aging
- Chronic infections (human immunodeficiency virus)
- Corticosteroid treatment
- Hemochromatosis
- Systemic disease (liver failure, chronic kidney disease, sickle-cell disease)
- Substance Abuse

**Adam Questionnaire**
**Androgen Deficiency in the Aging Male (ADAM) Questionnaire**

1. Do you have a decrease in sex drive?
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 noticed a decreased enjoyment in life?
6. Are you sad and/or grumpy?
7. Are your erections not as strong?
8. Has it been more difficult to maintain your erection throughout sexual intercourse?
9. Are you falling asleep after dinner?
10. Has your work performance deteriorated recently?

If you answered yes to number 1 or 7 or if you answered yes to more than 3 questions, you may have low testosterone.

In order to assess your current health status, you need to gather your biomarkers, and much more must be assessed that just the levels of total and free testosterone. Knowing your current baseline health profile will help to not only guide your therapy but help create an overall health and wellness plan that encompasses lifestyle, nutrition, exercise, and hormone therapy.

Appropriate lab work is crucial in diagnosing the potential different types and causes of hypogonadism and looking for any potential issues that may arise while on therapy. Below is a list of the initial screening labs that should be ordered in a fasting state.

**Initial Screening Labs:**

Total Testosterone
Testosterone Bioavailable or Weekly Bound
Testosterone Free
Cortisol AM
SHBG
HgA1c
Thyroid Panel
(TSH, FT4, FT3, rT3)
LH/FSH
DHT
DHEA-Sulfate
Sensitive Estradiol
Liver panel
Serum Chemistries
CBC
Insulin Immunoassay
Lipid Panel or Lipoprotein panel
Prolactin
Vitamin D
Cardiac CRP
Homocysteine
Iron
TIBC
Ferritin
IGF-1
IGF-BP3
PSA
Lyme titer if relevant by history
Uric Acid
Urinalysis

**Strongly Consider These Labs:**

IgG Food Sensitivity Testing
Micronutrient Testing
Lp-PLA2
MPO
NMR lipid, VAP, Berkley Heart Lab, or Cleveland Heart Lab
MTHFR
APO E

**If you have a family history of an inherited blood clotting disorder or are not sure then you should consider these labs as well.**

Factor V Leiden mutation
Factor VIII
Factor XI
Factor II (Prothrombin Gene)
Anticardiolipin antibody IgG/IgM
Lupus Anticoagulant

**What labs to consider after the initiation of testosterone replacement therapy?**

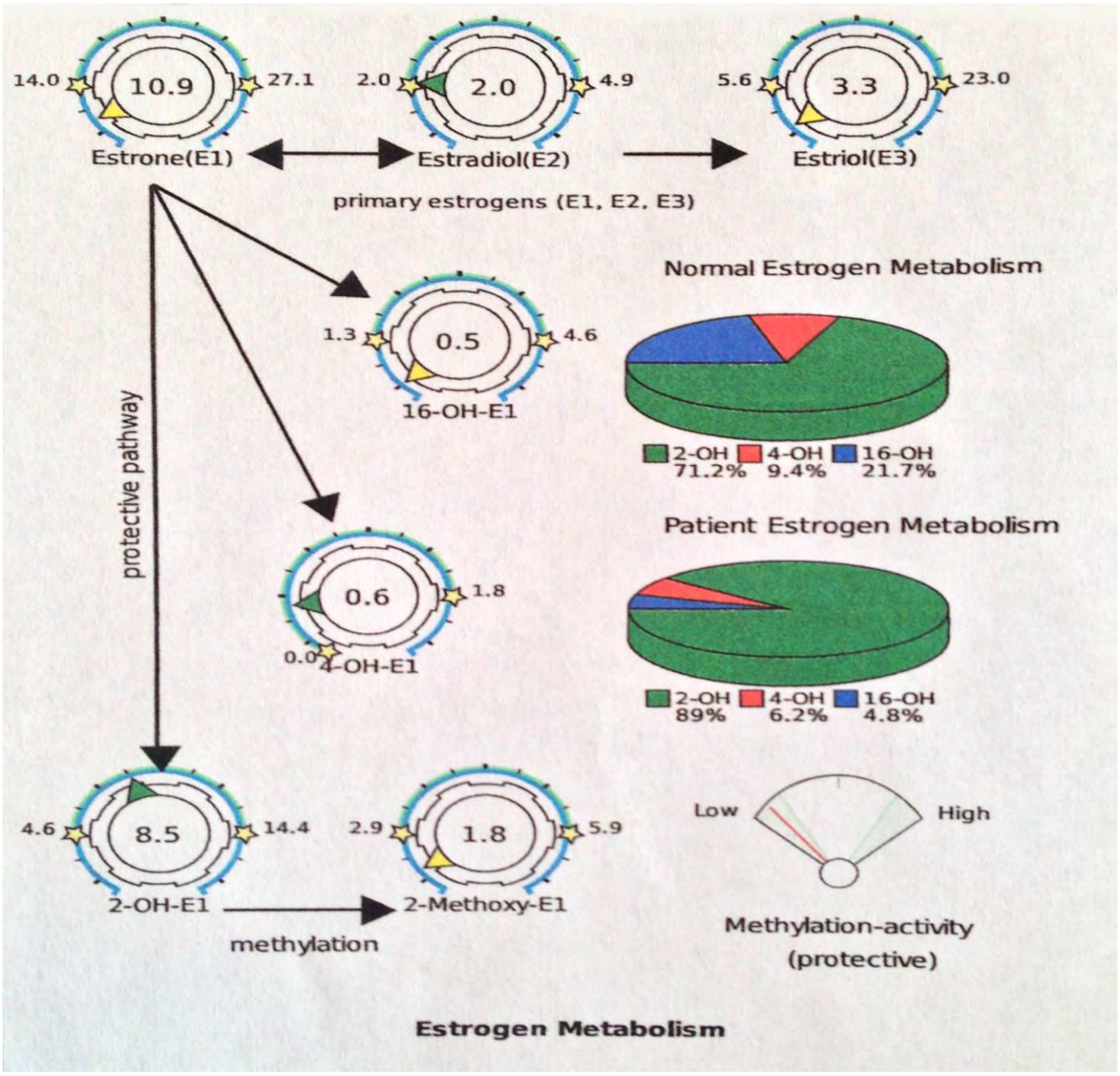
Follow up labs can be run at three to four weeks after starting therapy or changing the therapy dose or delivery method. This short amount of time provides for stabilization of the H-P-T-Axis, Sex Hormone Binding Globulin adjustment, and the pharmacodynamics of the testosterone delivery system. It takes time for the body to adjust to your chosen therapy delivery system.

Total Testosterone
Bioavailable Testosterone or "Free and Loosely Bound"
Free Testosterone if Bioavailable T is unavailable
Sensitive Estradiol
DHEA-S
FSH/LH
Hemoglobin and Hematocrit
Comprehensive Metabolic Panel

I would also recommend within the first 3 months of therapy to also test for the downstream metabolites of estrogen: 4-hydroxyestrone, 2-hydroxyestrone, 16-hydroxestrone, and the metabolites of testosterone, alpha DHT and beta DHT.

The hydroxylation of 2-hydroxyestrone (2-OH) and subsequent methylation to 2-methoxyestrone (2-MeO) produces the ”beneficial” and balancing estrogens that every man needs for overall health especially for the positive cardiovascular, brain, and mood effects. These estrogens are eventually harmlessly excreted from the body. However, the hydroxylation of estrogens into 16 alpha hydroxyestrone (16α-OH) and its further reduction and binding to alpha and beta estrogen receptors can trigger the expression of target genes within the cell which may affect the health, function, and growth of estrogen responsive tissues in the uterus, breast, ovaries, cervix, bones, testicles, and prostate. This is where xenoestrogens like plasticizers, chemicals, drugs, and pesticides exert their harmful effects.

Even nastier is the hydroxylation of estrogen into 4-hydroxyestrone (4-OH) that is oxidized and is genotoxic and able to exert its potential carcinogenic effects upon the body’s DNA. Desirable is the methylation of 4-hydroxyestrone (4-OH) into 4-methoxyestrone (4-MeO) with its eventual excretion from the body. The consumption of foods that contain and supplementation of vitamins A, C, E, α lipoic acid, lycopene, green tea, N-acetylcysteine for glutathione production, curcumin, selenium, carotenoids, and flavonoids help to reduce the potential oxidation of 4-hydroxyestrone into the unhealthy 3,4 Quinones.




When it comes to estrogen metabolism, Estradiol (E2) is the more potent estrogen and along with Estrone (E1) and Estriol (E3) should be evaluated. Looking at the pathways from estrogen you can see that the desirable, protective pathway is to 2-OH-E1, the "good" estrogen. The pathways to 16-OH-E1, the "bad" estrogen, and 4-OH-E1, the "genotoxic", "carcinogenic" estrogen are not desirable. This is where healthful nutrition definitely comes into play in aiding the clearance of these harmful estrogens. There are also supplements that can assist here as well. The final step of estrogen metabolism is its methylation, which helps to protect the body against any potential harmful effects.

The above "hormone metabolite assessment" on this particular patient discloses that his hydroxylation of estrogen is in a healthful range, however phase 2 methylation activity is low and requires support and may be potentially linked to a genetic mutation. This particular patient was homozygous for the MTHFR A1298C variant 2 SNPs (single nucleotide polymorphism) affecting his ability for appropriate phase 2 methylation of estrogens. Supporting his body's methylation ability would be advisable.

MTHFR is extremely important in controlling the metabolism of the B vitamin known as folic acid. Folic acid is crucial to numerous functions of the brain, heart, blood, and immune system. The simple supplementation of 5-methyltetrahydrofolate from a nutritional supplement will decrease his risk for heart disease, dementia, depression, and improve his methylation. As it turned out this man had high levels of homocysteine as well, in which 5-methyltetrahydrofolate supplementation would assist in lowering. Numerous studies have demonstrated the deleterious effects of high homocysteine levels. Epidemiologic studies have shown that *higher levels* are associated with *substantially higher risks* for:

- Congestive Heart Failure
- Heart Disease
- Heart Attacks
- Strokes
- Vascular Endothelial Dysfunction
- Increased Blood Clotting
- High Blood Pressure
- Diabetes
- Thyroid disorder

On my first rotation as a third year medical student many years ago a very wise internist said to me, *"The eye only sees what the mind knows."* I have never forgotten these powerful words and nothing could be truer when it comes to testosterone replacement therapy. We are only beginning to scratch the surface of this powerful therapy and we do not know what we don't know yet, which is why testosterone replacement therapy is not to be taken lightly.

Taking control of your man health is ultimately your responsibility. You are the Commander of your own health, it is up to you to work with your physician to understand and develop your personalized "plan of attack" to conquer and mitigate potential disease risk before it strikes. Gathering your personal biomarkers (labs and tests) for your physician is just like a commander in the military supplying his warriors with the necessary weapons and tools to get the job done in battle. The more ammunition and weapons you help your physician collect the more personalized your health care will become. Health care for men has taken a substantial move forward over the last decade thanks to the tireless work of numerous researchers and physicians we may never have the privilege of knowing, but to whom we certainly owe a debt of gratitude. Taking control of your man health and living a life full of vitality and free of disease honors their tireless efforts to improve our lives.

Low T Patient Profile: **Iron is for Lifting not Drinking!**

Doug - Age 38: Real Estate Developer

38 year old, athletic male with a 2-year history of declining endurance and athletic performance complaining of growing persistent fatigue, lethargy, altered sleep, decreased libido, and erectile quality. Also senses a decreased enjoyment in life and inability to make it through the day without feeling like he has to lie down. "I feel like someone turned off my internal battery!"

DXA: Excellent bone mineralization, body composition 9.8% free fat mass
VO2: Fair results but feels "wiped out" after test, experienced palpitations at 158bpm
Neurocognitive evaluation: Decreased verbal memory and speed
Carotid Ultrasound with CIMT: No signs of plaque or thickening
VENDYS Testing: Excellent

**Labs:**

Liver panel: normal
CBC: normal
PSA: 0.7
Insulin: 9.0uIU/mL
Lipid Panel: normal
Prolactin:
Cortisol AM: 2.3!
LH: 7.0 mIU/mL!
Total Testosterone: 237ng/dL!
Free Testosterone: 6.2pg/mL!
Sensitive Estradiol: 12.6pg/mL

DHT: 56 ng/dL
SHBG: 26.8nmol/L
DHEA Sulfate: 168.9ug/dL !
Vitamin D: 24.2ng/mL!
Serum Iron: 300ug/dL!
Serum Ferritin: 195ng/mL
TSH: 4.0 uIU/mL!
fT3: 3.1 pg/mL
fT4: 1.09 ng/dL
Glucose: 79mg/dL
HgA1c: 5.0

**Physical Examination revealed:**

Obviously fatigued appearance, but well-nourished with excellent muscle structure
Low normal blood pressure 112/64, 110/62, 108/60
Mild thyroid swelling
Small testicles
DRE: unremarkable

**Considerations for Differential Diagnosis:**

Mixed Hypogonadism
Excessive Iron Intake vs. Hemochromatosis (an iron storage disease)
Subclinical Hypothyroidism
DHEA Deficiency
Vitamin D deficiency
Adrenal Fatigue
Parasympathetic Overtraining Syndrome (addisonoid)

**Further investigation Reveals**:

Drinks water exclusively from home well
Tests on well water reveal high iron level!

**Therapy and Recommendations**:

Don't drink your well water!
Heavy Metal Detoxification Program
Ergocalciferol 50,000 IU weekly x 4 then, Vitamin D 5000IU Sublingual QD
DHEA 25mg BID
Armour Thyroid 30mg Q AM
8 oz. warm water with Sea Salt upon rising in the AM
No Alcohol
No caffeine
Restorative Sleep in bed by 10PM
No training x 4 weeks, then return to training at 60% effort 3 days per week not to exceed a heart rate of 120bpm.

**Subjective Patient Report**

Feels drastic improvement inside 14-day period
No longer feels the need to lie down in afternoon
Anxious to workout

**Follow Up Lab at 90 days:**

Liver panel: normal
CBC: normal
Lipid Panel: normal
Prolactin:
Cortisol AM: 17.0
LH: 4.0 mIU/mL
Total Testosterone: 702ng/dL
Free Testosterone: 18.0pg/mL
Sensitive Estradiol: 16.6pg/mL

DHT: 58ng/dL
SHBG: 26.0nmol/L
DHEA Sulfate: 399.0ug/dL
Vitamin D: 60.2ng/mL
Serum Iron: 145ug/dL
Serum Ferritin: 195ng/mL
TSH: 1.0 uIU/mL
fT3: 2.1 pg/mL
fT4: 1.09 ng/dL

**Take Home Point:**

**Investigate the cause of the hypogonadism and correct underlying deficiencies before committing yourself to a therapy that is not clinically needed… Just yet!**