Chapter 4

Your T is All About Your H (Heart)

It is well known that low testosterone and more specifically low free testosterone is associated with increased mortality from all causes in men. Men with normal levels of endogenous testosterone have significantly lower rates of cardiovascular mortality and from all causes and the survival time of men treated with testosterone versus men left untreated is longer as well.

There are no large prospective trials that have examined the association of cardiovascular disease and testosterone, but there are numerous observational studies that demonstrate the association between low T and cardiovascular disease. It is well known that testosterone therapy in the deficient male improves cardiovascular risk factors and there is no direct randomized controlled trial evidence that testosterone therapy is associated with increased cardiovascular risk.

So what is all the fuss about testosterone and heart attacks? That's because a couple of studies misrepresented their data. In the Finkle study, the pre-treatment rate for the first 90 days was 3.48 events per 1000 people and the post-treatment rate was 4.75 events per 1000 people for a difference of 1.27 events. This is not a significant difference and an absolutely uninformative study. Also, they never address the data set after 90 days wonder why? Possibly because it did not support their hypothesis.

Then there is the Vigen study, which contained major data errors and contamination of the data set that was not identified until after publication rendering the study not credible. This resulted in 29 medical societies and over 220 distinguished researchers and clinicians calling for JAMA to retract the study an issue an apology for printing "false information" that has "harmed public health, distorted medical science, and violated the trust between medical journals and the consumer" and referred to the printing of this article as "medical literature malpractice."

Despite these misguided studies, testosterone replacement therapy's beneficial effects are well documented as to the prevention of cardiovascular disease. The overwhelming majority of medical research does not demonstrate any relationship to increased risk of mortality, myocardial infarction or stroke. There are however numerous studies that do indicate the substantial benefits of TRT.

Testosterone replacement therapy in testosterone deficient, symptomatic patients improves:

- Sexual function and interest
- Bone mineral density
- Muscle Strength
- Increased exercise capacity
- Decreased hip to waist ratio
- Fat free mass
- Lean body mass
- Quality of erections (what we all really want anyways)
- Lipid profiles
- Insulin sensitivity
- Cardiac risk factors
- Mood stability
- Cognitive function
- Quality of Life
- Augments growth hormone secretion
- Increased time to ST segment depression during stress testing

Here are some additional issues with these studies:

- A retrospective cohort study of men with low testosterone levels who underwent coronary angiography and had low serum testosterone, categorized as initiating testosterone therapy if they filled a prescription for testosterone gel, patch, or injections following coronary angiography based on pharmacy-dispensing data. Once initiated, a patient was ASSUMED to have continued treatment until an outcome event occurred or the end of follow-up.

- There is no indication of appropriate follow up, monitoring of testosterone replacement therapy, or continuance of therapy among cohorts of this national retrospective study of men with low testosterone levels.

- Clinical trials have demonstrated that testosterone therapy improves a number of intermediate outcomes and cardiac risk factors. With the exception of the TOM trial (Testosterone in Older Men with Mobility Limitations), a study conducted in older, frail men with a high prevalence of cardiovascular disease, these trials and subsequent meta-analyses did not demonstrate adverse cardiovascular outcomes in men on testosterone replacement therapy.

- A clinical trial evaluating the effect of testosterone therapy on cardiovascular outcomes including mortality, MI, and stroke has not been conducted to my knowledge.

- The association between testosterone therapy use and adverse outcomes observed in this study differs from the association observed in a prior retrospective VA study. In the study by Shores et al, investigators noted a 39% reduction in mortality risk among patients treated with testosterone therapy.

- Elderly men with low serum testosterone levels have an increased risk of mortality and subjects with low values of both testosterone and estradiol levels have the highest risk of mortality (Journal of Clinical Endocrinology and Metabolism 94: 2482-2488, 2009)

So what does this mean exactly? We know definitively that optimized testosterone levels are associated improved health, higher quality of life and with lower rates of death. Additionally, testosterone replacement therapy improves sexual function, cognitive function, lipid profiles, endothelial function, muscle mass, free fat mass, exercise capacity, strength and endurance. Currently, the risk/benefit ratio analysis for the use of Testosterone Replacement Therapy in testosterone deficient men is highly favorable. I would encourage you if you are on testosterone replacement therapy to have a discussion with your physician or a physician knowledgeable in testosterone replacement therapy.

The widely liberal media has done men in general a disservice with their usual dramatization of the story and often-misguided interpretation, which leads to confusion and misplaced trust. If you are on Testosterone Replacement Therapy, I still strongly recommend the use of Testosterone Replacement Therapy to improve your overall health profile, accompanied by appropriate monitoring laboratory, follow up, therapeutic lifestyle adjustments, exercise, and physician management.

So then why do some men on testosterone have heart attacks or strokes? It's not because they are on testosterone. It's because they have undetected heart disease and heart disease is the number 1 silent killer of both men and women. One out of 3.5 men will die from heart disease. Every decade we age our risk for heart attacks and strokes rise dramatically. If you have preexisting heart disease than your risk for a secondary event is even higher.

In the weeks BEFORE a Heart Attack 95% of people suffer from these symptoms; do you suffer from any of these symptoms?

- Unusual Fatigue
- Unusual Sweating
- Shortness of Breath
- Shoulder Pain
- Neck Pain
- Difficulty Walking Upstairs or to the Mailbox
- Indigestion
- Chest Pain
- Weakness
- Sleep Disturbance
- Feeling Lightheaded or Passing Out
- Feeling like Something Bad is About to Happen

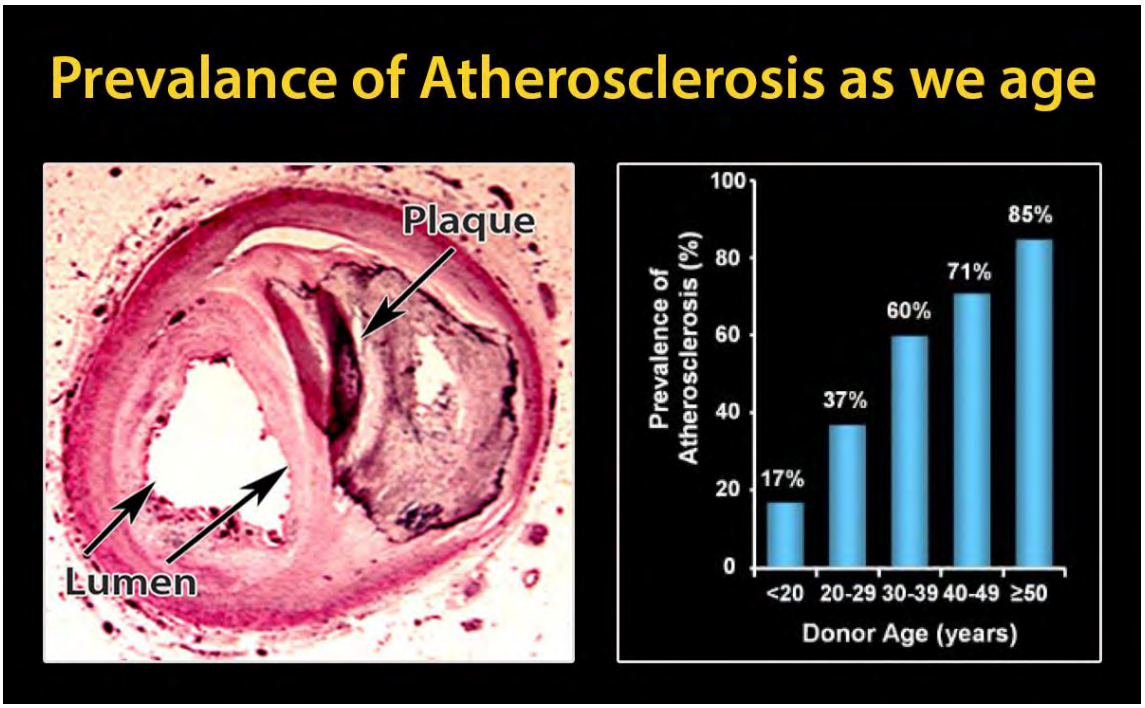
At the time of a Heart Attack people commonly have symptoms of:

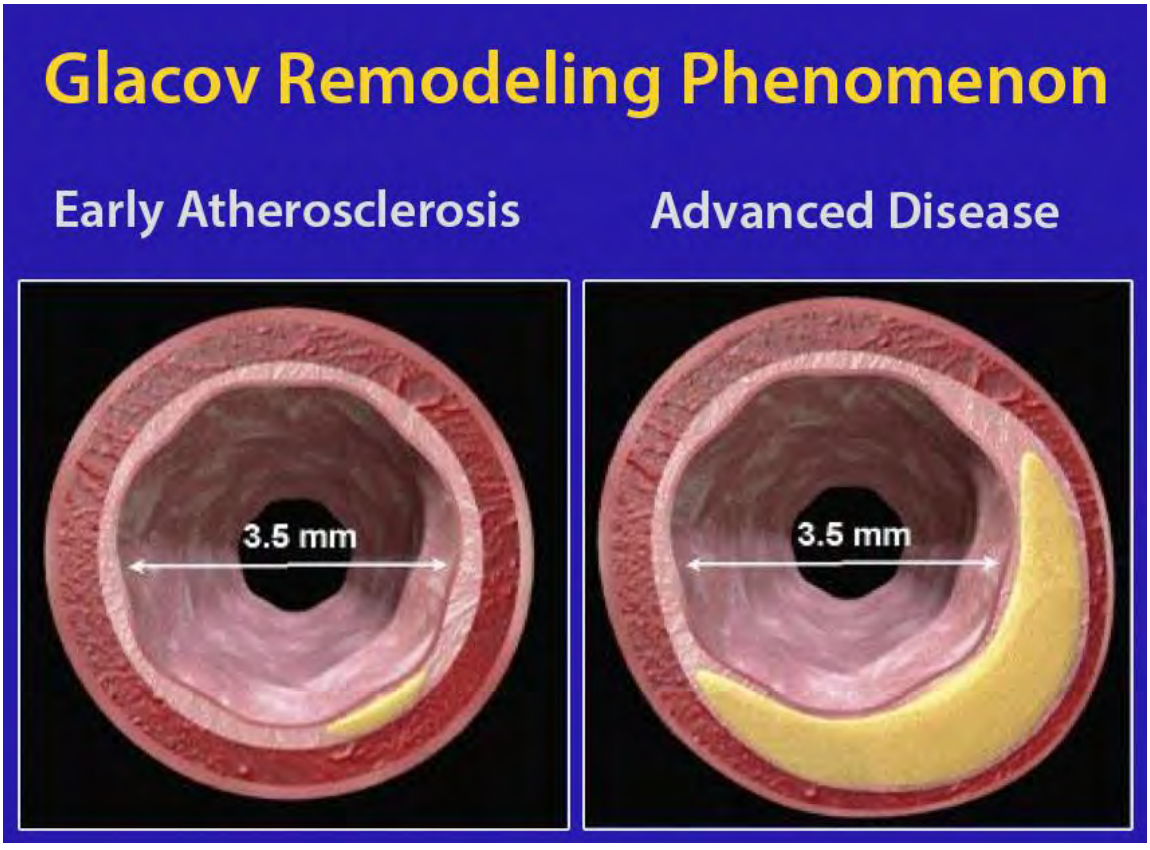
- Shortness of Breath 60%
- Cheat Pain 57%
- Weakness 55%
- Fatigue 43%

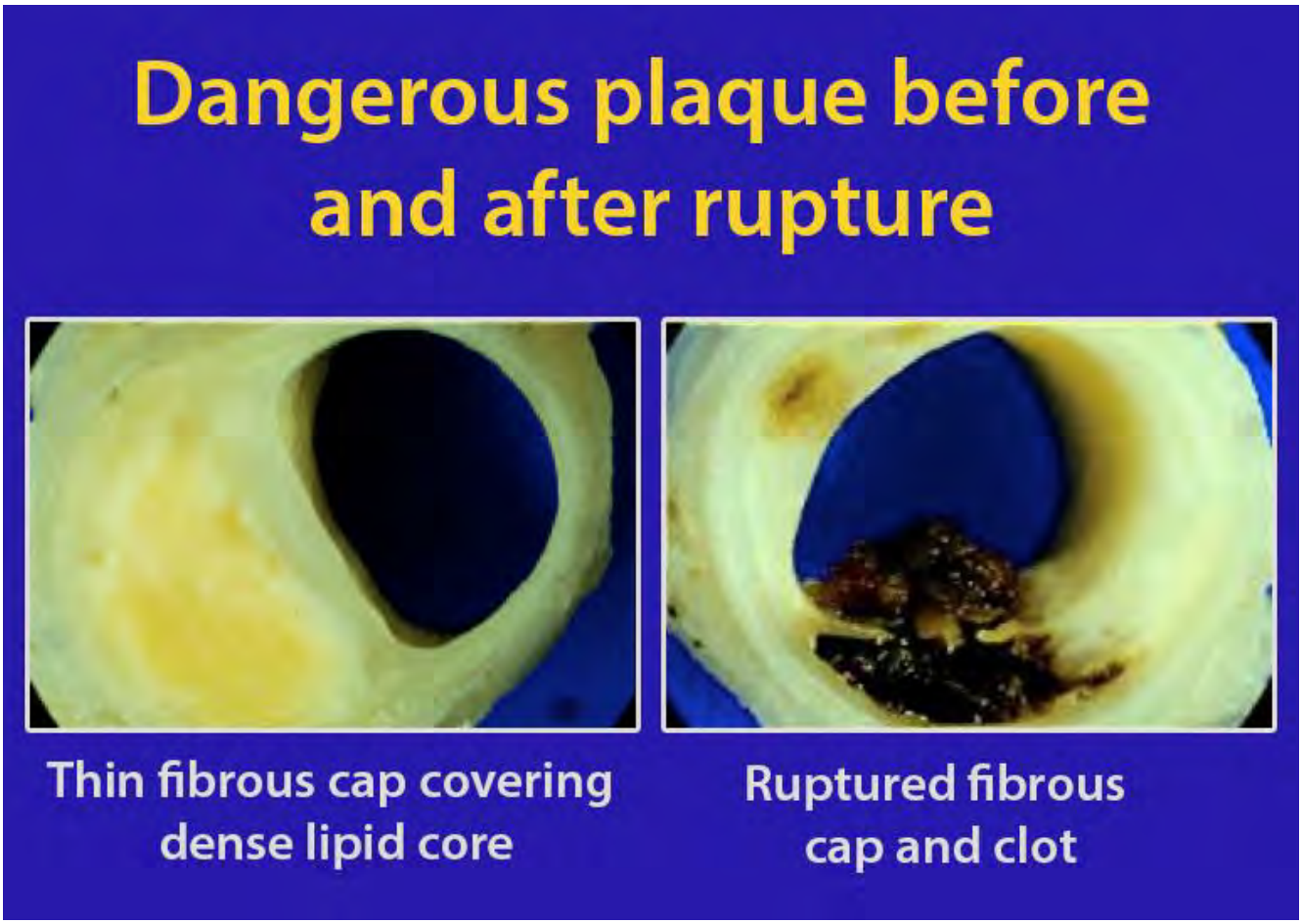
Other Presenting Symptoms at Time of Heart Attack;

- Upper Abdominal Pain
- Abdominal Fullness
- Abdominal Burning Sensation
- Nausea
- Neck, Back, and/or Jaw Pain
- Feeling of Impending Doom

As we age the prevalence of heart disease increases substantially each decade!







Heart disease quietly waiting to strike!

Sudden plaque rupture and heart attack! Over 50% of people having a heart attack have so called "Normal Cholesterol"!

Identifying hidden, active cardiovascular inflammatory disease can make the difference between life and death! Standard cholesterol testing and outdated Risk Assessment Scores will NOT discover your silent heart attack risk. Over 50% of all heart attacks happen in individuals with so-called "normal cholesterol". Before considering testosterone replacement therapy, you must actively seek out hidden cardiovascular disease. What difference will it make if you correct your low testosterone but don't address the possible hidden underlying cardiac threat to your life?

In one particular study researchers discovered that these 3 risk factors; low free testosterone, low high-density lipoprotein (HDL, the good cholesterol), and increasing age where strong predictors of severe coronary artery disease. While not smoking, maintaining normal blood pressures, controlling cholesterol levels, and maintaining a low glycemic state are all positive steps to preventing heart disease there is more that can be done.

In another study published by the American Heart Association, carotid ultrasounds were used to measure the thickness of the carotid arteries located in the neck. What was discovered was that men with low free testosterone levels had a 3.5 times greater progression of the thickening of the carotid artery than men with higher free testosterone levels. What this means to you is a greater chance of having a stroke.

Controlling your blood sugar levels is a step that will not only help raise your free testosterone level but also slow the process of aging and protect the cardiovascular system from disease and dangerous atherosclerosis. One study found that men with elevated hemoglobin A1c also had lower levels of free testosterone, which increased their risk for heart attacks and strokes.

What you need to have done:

1. Specialized Laboratory including:

- NMR Lipoprotein Particles NOT calculated particles!
- Inflammation Oxidation Profile
- Myocardial Stress Profile
- Lipoprotein Genetics
- Coagulation Genetics
- Renal Genetics
- Hs-Omega-3 Index
- Metabolic Profiles

2. Specialized Examinations including:

- VENDYS testing
- Carotid Ultrasound with CIMT
- Ankle-Brachial Index Testing
- VO2 Max Testing
- DEXA Scan
- Cardiac Stress Testing
- CT angiogram
- CT calcium score

Below are the laboratory tests you need to help identify your true cardio-metabolic-stroke risk.

INFLAMMATION OXIDATION

- Myeloperoxidase: is an enzyme made by white blood cells. High level is a sign of surface inflammation of the artery wall. Elevated MPO levels are associated with future risk of coronary artery disease, heart failure, heart attack, and stroke in otherwise healthy individuals.
- Lp-PLA2: elevations of this enzyme indicate serious inflammation in artery walls that can be dangerous when blood pressure is also high.
- hs-CRP: identifies inflammation in the body.
- Fibrinogen Activity: high levels of this protein mean you are at risk of developing a blood clot.

LIPOPROTEIN GENETICS

- Apo E Genotype: identifies how people respond to dietary fat and how they carry cholesterol in the blood. Apo E comes in different types, E3 is desirable, E2 is borderline, and E4 is undesirable.

LIPOPROTEIN PARTICLES

- NMR Lipid Profile: clinically reliable test to measure lipoproteins.
- Lipoprotein Insulin Resistance Score: insulin resistance is the precursor to diabetes and manifests its earliest measurable abnormality through changes in lipoproteins.
- LDL-P: the actual number of “bad” cholesterol particles in your blood
- HDL-P: the actual number of “good” cholesterol particles in your blood
- Lp (a): is the worst form of LDL and is an inherited trait that can increase the risk of heart attack and stroke.

MYOCARDIAL STRESS

- Galectin-3: high levels of this carbohydrate binding protein contribute to abnormal thickening and stiffening of the heart muscle and change the heart structure.
- NT-proBNP: stress or strain on your heart can cause levels of this peptide to rise. If your levels are high your heart is being overworked.

COAGULATION GENETICS

- Factor V Leiden Mutation: this factor helps to identify if you are at risk for forming blood clots.
- Prothrombin Mutation: this factor helps to identify if you are at risk for forming blood clots.
- MTHFR: this gene provides your body with instructions to make a protein responsible for folate metabolism. This helps to assess your risk for coronary artery disease and stroke and which medication may be best for you.

RENAL

- Cystatin C: is used as a biomarker of kidney function. High levels indicate a decline in kidney function.

HS-OMEGA-3 INDEX

- RBC EPA+ DHA: these fatty acids are important constituents of cell membranes in our body and are vital to your cardiovascular health.

METABOLIC

- Free Fatty Acid: elevated FFA level can impair your body's response to insulin and cause your blood glucose levels to rise. Higher FFA levels are a precursor to insulin resistance.
- Glucose: excess glucose in the blood can lead to diabetes and may long term complications.
- 25-hydrox-Vitamin D: long-term studies have linked vitamin D deficiency with a twofold-increased risk of heart attack and cardiovascular events.
- Homocysteine: high levels of this amino acid can injure blood vessel walls.
- Vitamin B12 & Folate: your body needs these vitamins to make blood cells and maintain a healthy nervous system.
- HbA1c: levels indicate how well your blood glucose has been controlled over the last 3-4 months. High levels indicate risk for the development of diabetes.
- Adiponectin: is a protein produced by body fat that protects against insulin resistance and inflammation. Adiponectin levels are low in those who are

overweight. If you have low adiponectin levels you are at greater risk for diabetes and heart disease.

- Ferritin: is a protein that binds iron and transports it through the bloodstream. High ferritin levels can indicate problems with your body's ability to store iron. Increased ferritin levels also occur when inflammation or insulin resistance is present in your body indicating an increased risk of diabetes and heart disease.
- Alpha-hydroxybutyrate: is a small molecule produced by the liver during energy production. High levels of alpha-hydroxybutyrate are a early indicator of insulin resistance.
- Linoleoyl-glycerophosphocholine (L-GPC): low levels are an early sign of insulin resistance.
- Insulin: is a hormone responsible for regulating blood glucose levels. High levels of insulin may indicate a problem with your body's ability to control blood sugar.
- C-peptide: is a small protein that is released when insulin is created from proinsulin.
- Proinsulin: insulin is created from a non-active form called proinsulin. High levels of proinsulin may be early signs of damage to your beta cells of the pancreas.
- Anti-GAD: is a type of antibody that is created when your beta cells are being attacked by your immune system.

In a study conducted by Dr. Charles Glueck of the Jewish Hospital Cholesterol and Metabolism Center, his research found that men who developed blood clots after starting testosterone therapy, not one of the men knew previously that they had an inherited clotting disorder that put them at greater risk of developing a blood clot.

Dr Glueck stated in an interview; "The incidence of DVT-PE or other clots in men on testosterone therapy is not known, but our best estimates are that about 1-2% of men taking testosterone will develop blood clots related to underlying inherited clotting abnormalities or to acquired thrombophilia, the antiphospholipid antibody syndrome."

"These men who landed in the hospital with dangerous and potentially lethal blood clots in the deep veins of the legs or in the lungs developed these clots within three months of starting testosterone therapy. None of them knew previously that they had an inherited clotting disorder that put them at greater risk for developing clots, nor did their providers test them before putting them on testosterone therapy."

Dr. Glueck suggests all men should have a simple blood test to determine whether they are at high risk for blood clots before starting testosterone replacement therapy.

If you have a history of a previous thromboembolism (blood clots), 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)

Before you start testosterone replacement therapy insist on a complete cardio-metabolic workup that includes laboratory as well as screening of the cardiovascular system. Then ensure you get appropriate monitoring laboratory, make therapeutic lifestyle adjustments, get regular exercise, stop smoking, stop eating excessive sugar, and maintain follow up and physician management. Remember, you are the commander of your own health.

Low T Patient Profile: **What's Binding You Up?**

Rob - Age 48: Dentist

48 year old, professional male with a 3-year history of growing persistent fatigue, lethargy, altered sleep, losing muscle, decreased libido, and erectile quality. Also senses a decreased enjoyment in life and inability to make it through the day without the need for constant caffeine.

DXA: Excellent bone mineralization, body composition 16% free fat mass
VO2: Excellent results
Neurocognitive evaluation: Decreased executive function and verbal memory
Carotid Ultrasound with CIMT: No signs of plaque or thickening
VENDYS Testing: Good to excellent

Labs:

Glucose: 89mg/dL
HgA1c: 5.1
Liver panel: normal
CBC: normal
PSA: 0.9
Insulin: 8.0uIU/mL
Lipid Panel: normal
Prolactin: 6.0
Cortisol AM: 16
LH: 5.0 mIU/mL
Total Testosterone: 533ng/dL
Free Testosterone: 5.9pg/mL
Sensitive Estradiol: 9.0pg/mL
DHT: 48ng/dL
SHBG: 74.0nmol/L!
DHEA Sulfate: 230/dL
Vitamin D: 40.2ng/mL
Serum Iron: 123ug/dL
Serum Ferritin: 195ng/mL
TSH: 1.0 uIU/mL
fT3: 3.8 pg/mL
fT4: 1.09 ng/dL

Physical Examination revealed:

Obviously fatigued appearance, but well-nourished with poor muscle structure
Normal blood pressure 118/74
Average testicles
DRE: unremarkable

Considerations for Differential Diagnosis:

Androgen Deficiency secondary to Excessive SHBG
DHEA Deficiency
Vitamin D deficiency
Zinc deficient by Zinc Tally Test
Excessive Caffeine Intake

Therapy and Recommendations:

10 Day Liver Detoxification along with a Mediterranean diet
Nettle Root 300mg three times daily
Testralin two daily
Zinc 75 mg two daily
Omega 10 one daily
Vitamin D 5000IU Sublingual QD

DHEA 25mg twice daily
8 oz. warm water with Sea Salt QAM
No Alcohol
No caffeine
Restorative Sleep in bed by 10PM

Subjective Patient Report

Feels drastic improvement inside 10-day period
No longer feels the need to have coffee

Follow Up Lab at 90 days:

Liver panel: normal
CBC: normal
Lipid Panel: normal
Prolactin: 6.0
Cortisol AM: 17.0
LH: 4.0 mIU/mL
Total Testosterone: 782ng/dL
Free Testosterone: 17.0pg/mL
Sensitive Estradiol: 14.6pg/mL

DHT: 68ng/dL
SHBG: 32.0nmol/L
DHEA Sulfate: 379.0ug/dL
Vitamin D: 60.2ng/mL
Serum Iron: 145ug/dL
Serum Ferritin: 195ng/mL
TSH: 1.0 uIU/mL
fT3: 3.7 pg/mL
fT4: 1.09 ng/dL

Take Home Point

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