Everything you'd ever want to know about
LOW TESTOSTERONE

(AND PROBABLY A LOT MORE)

THE BASICS

Testosterone in men is produced in the testicles by Leydig cells. These cells are "stimulated" to produce testosterone by luteinizing hormone (LH) release from the pituitary gland. The pituitary itself is stimulated to release LH by gonadotropin releasing hormone (GnRH) which is produced by an area of the brain called the hypothalamus. Both input from neurons in the brain and feedback from testosterone and other pituitary hormones modulate secretion of GnRH. This is a complicated system and is not fully understood even today. The reason I mention this is because problems in any of these areas can cause testosterone deficiency (TD) otherwise known as hypogonadism. When TD is caused by testicular failure it is called primary hypogonadism and when it is dysfunction at the pituitary or hypothalamic level it is called secondary hypogonadism.

WHAT DOES TESTOSTERONE DO?

Testosterone is a type of hormone called an androgen or male sex hormone. Levels are low in men until puberty when an increase causes "male" features to develop: hair growth pattern, muscle development, increased growth, increased bone density, increased sex drive and sexual function, prominent adam's apple, and deeper voice. Levels are high until 20-30 years of age, and then they begin to slowly decline (about 1-2% per year). Even though the term is frequently used, there is no "andropause" or sharp, sudden decline in levels similar to what women experience with estrogen levels during menopause. Normal levels vary widely and levels can fluctuate throughout the day, typically higher in the morning and fall during the day. This daily variation may be more pronounced in younger men before levels begin to decline.

WHY DO TESTOSTERONE LEVELS MATTER?

Recent studies have estimated around 2.4 million men in the US with hypogonadism and there are projections of approximately 480,000 new cases annually. These numbers may even be underestimated because there is still some disagreement on what criteria should be used for the diagnosis. Some feel that lower testosterone levels are normal products of aging. However studies have shown that men with the lowest naturally occurring testosterone levels have statistically significant higher rates of all cause mortality compared to men with the highest naturally occurring levels. Men with low testosterone levels are much more likely to develop T2DM and metabolic syndrome (obesity, high sugar levels, high blood pressure, and lipid abnormalities).

The risk is inversely proportionate; it increases as testosterone levels decrease. In fact, a large study of men with the absolute lowest levels of testosterone, veterans that had received treatment to stop their production of testosterone as treatment for prostate cancer, found significant increases in T2DM, myocardial infarction (MI), stroke, sudden cardiac death, and development of cardiovascular disease. Testosterone levels are also lower in men with several other chronic illnesses such as end stage renal disease, chronic obstructive pulmonary disease (COPD), and HIV. The Endocrine Society recommends screening patients with these chronic illnesses for low testosterone due to these associations. Treating low testosterone in patients with T2DM has been shown to improve sugar levels and increase sensitivity to insulin.

Evidence suggests that men with coronary heart disease (CAD) have lower levels of testosterone. There is also evidence that in men with CAD, lower levels of testosterone are associated with more severe CAD. It is not known if low testosterone is a cause or result of CAD.

The American Heart Association published an article in 2013 reviewing all of the research done on testosterone and its relationship with heart disease. They looked at several meta-analyses of studies that investigated TRT and adverse cardiovascular events (meta-analyses are reviews that pool data from multiple studies together into one). Their conclusion was that existing data from these meta-analyses seem to indicate that TRT does not increase the risk of adverse cardiovascular events.

A new study that was too recent to be included in any of the above meta-analyses showed reduced mortality with TRT. In that study, researchers reviewed the medical charts of 1031 VA patients older than 40 years of age with low testosterone (<250) over 3 years and found that the mortality rate for the men who received treatment with testosterone was 10.3% compared to 20.7% in the untreated group.

So why all the publicity lately about testosterone and heart attack risk? A 2010 study of 209 men was stopped early due to increased events in the treatment group. This group of men was older (average 74 years of age) with limited mobility and a high prevalence of high blood pressure, diabetes, hyperlipidemia, and obesity. The types of events that occurred were mostly mild but there were a handful of more serious events. This was probably not the ideal patient population for testosterone therapy as not only were they older, they were not healthy men and already had advanced disease.

Another VA study published last year was very similar to the previous one in that they looked at charts of men with testosterone deficiency, except these men had also undergone coronary angiography. 3 years of chart data was reviewed. Looking at the actual numbers published, in the treatment group, 10% had died, had MI or stroke compared to 21% in those not receiving testosterone. However, the study authors adjusted their data mathematically to place more importance on the events in the treatment group and concluded that there was more risk with treatment than not. This study has undergone two revisions to correct errors including finding out that chart data of women were included in the study. A large number of scientists and researchers from around the world have written to the journal that published it asking for a retraction but they will not.

Early this year a review of insurance claim data compared heart attack rates in men during the year previous to starting testosterone treatment and the 90 days after starting treatment. In men older than 65 with and without existing heart disease and in men younger than 65 with known heart disease, there was increased risk of heart attack. In men under 65 without known heart disease the risk again was decreased. Men who had a heart attack during the year before starting therapy were excluded.

There are certainly limitations with several of the cited studies, mostly that they were not prospective studies but reviews of charts or insurance data. Also we have no idea what testosterone levels were achieved with therapy or what other lab values were measured, how compliant people were with treatment, among other issues. Better, larger studies are certainly needed.

In regards to TRT and prostate cancer, there is currently no evidence that testosterone replacement can initiate or promote prostate cancer in men. In fact, low testosterone levels are associated with increased prostate cancer risk and normal levels may be protective.

CAUSES OF LOW T

Primary hypogonadism can result from infection, injury or other damage of the testicles. Also it is felt that reactive oxygen species (ROS), which are a normal byproduct of testosterone synthesis, can over time cause damage to the Leydig cells. There are some rare genetic abnormalities (Klinefelter syndrome) that can also cause primary testicular failure.

Secondary hypogonadism can result from any disturbance of the hypothalamic pituitary system such as stress, sleep disturbances such as shift worker syndrome, hypothyroidism, and any condition that can elevate prolactin levels such as prolactinomas, etc. Obesity, medications such as narcotic pain medicaions, and conditions that cause chronic inflammation are also known causes. There are also genetic abnormalities that can cause this type of deficiency as well.

Hemochromatosis, an iron storage disease, has the potential to cause either primary or secondary hypogonadism.

SYMPTOMS OF LOW T

The most common symptoms that we see are usually complaints about low energy, motivation, and fatigue. Also sexual issues such as decreased sexual desire and erection quality. Men with low testosterone not only have erectile dysfunction during sex but also have decreased or absent spontaneous erections.

Increased abdominal fat, reduced muscle mass, poor sleep, insomnia, sleep apnea, anemia, and decreased bone density can also be signs of testosterone deficiency.

DIAGNOSIS OF LOW T

Testosterone exists in three phases in the body: free, loosely bound to albumin and tightly bound to sex hormone binding globulin (SHBG). Only 1-2% of your total testosterone is considered unbound and “active”. Controversy exists over what fraction of testosterone is the most important. Total testosterone is more commonly used but bioavailable and free are likely more accurate assessments. This is an area that needs more study. Right now in my clinic I get total testosterone levels and consider less than 350 to be low (LabCorp uses 348-1197 as its normal range). I also get albumin and SHBG levels and calculate free testosterone.

It is usually recommended to draw testosterone in the morning when levels should be at their highest. Some experts however do not feel this is necessary, that the variation is more pronounced in younger men and that older men and those with low levels also do not show significant variation. Also measuring levels on more than one occasion is usually recommended though some experts feel that if symptoms are present along with low testosterone values there is no need.

Pituitary function needs to be evaluated with LH, FSH, prolactin and TSH levels to distinguish between primary and secondary forms. If thyroid or prolactin abnormalities exist, those should be addressed first as testosterone levels can improve with proper treatment of those conditions. Iron levels to rule out hemochromatosis and genetic testing should be considered if these conditions are suspected.

TREATMENT OPTIONS

Testosterone replacement therapy (TRT)

- There are no oral agents to administer TRT that are FDA approved. They caused liver damage and are not recommended.
- Topical treatments including gels or patches. Benefits may be more consistent levels. Cons may be poor absorption or response in general, levels may not get as high as with other treatments, messy, expensive.
- Injections. Typically testosterone cypionate either weekly or every 2 weeks. Has 7-8 day half-life so weekly is the best but every 2 weeks can be done. Benefits include infinite dose adjustment so levels can be tuned to the individual, can improve even the lowest levels. Cons are higher levels right after injection with lower levels as the days go by, having to get frequent injections, discomfort.
- Implanted pellets. Benefits are reduced need for patient to do anything, no gels to put on daily, no frequent shots. Levels are fairly consistent but can fall towards the end of the dose period. Cons are the procedure to implant, pellets can be extruded, no adjustment after pellets are implanted, scarring and discomfort at the site, expensive.
- Troches or buccal forms. Are oral preparations but are not swallowed. Troches are compounded and go between lip and gum where they dissolve. Buccal pellets have adhesive that sticks them to your gums.

Non-testosterone therapy

- HCG-human chorionic gonadotropin mimics LH and stimulates the testicles to increase testosterone production. Obviously should only work in secondary hypogonadism. Is usually only used when fertility is desired. Is also subcutaneous injection like insulin, given 2-3 times a week.
- Clomid. Fertility drug used to stimulate ovulation in females but stimulates increased LH release and increases testosterone production in men. Not FDA approved for men. I usually just use these two drugs when stopping testosterone therapy to help restart the body's own production.

SIDE EFFECTS OF TREATMENT

- Testosterone stimulates red blood cell production. A blood count should be used to monitor therapy. Usually donating blood is enough to control this should it occur.
- Testosterone can cause swelling in the feet and ankles.
- Testosterone can stimulate some prostate enlargement. Caution advised in men with enlarged prostates and LUTS, certainly those undergoing treatment for such.
- May worsen sleep apnea. If sleep apnea is suspected, sleep study should be ordered before starting therapy. If you have known sleep apnea, it should be well controlled.
- Testosterone is converted to estrogen and levels of this can rise with therapy. This is usually a good thing but too high levels can be a problem. Either reducing dose of testosterone or administering a medicine to decrease conversion can treat this easily.
- Decreased fertility is an expected result of TRT. When TRT is administered, LH and FSH will drop resulting in decreased sperm production. If no fertility is desired, this is not as issue. The decreased sperm production can decrease size of testicles which can be concerning to some men.