



## Testosterone Deficiency

*Why should you care and what are the benefits of treatment?*

[A special thanks to Dr. Jeffrey Lije, M.D., of the Cenegenics Institute for providing comprehensive references that you see listed here.]

For all of you men reading this (or the wives/girlfriends of them)...how have you been feeling over the past year? Are you easily tired? Do you find your strength is declining? Is your sex drive, *i.e.*, libido, lower than what you want it to be? Do you feel like you are older than what you actually are? Is your work performance declining? Have you lost height over the past few years? Do you need to take opioids (painkillers/narcotics) for a pain condition on a chronic basis? If so, you may be suffering from a condition known as *male hypogonadism*. Unlike the more severe forms of overall low testosterone production, a more common form is “relative” male hypogonadism or *andropause*. What does this actually mean?

Testosterone is the male sex hormone and it is the hormone that “drives” a man’s body. People tend to think of it only in relation to sexual performance and bodybuilders/athletes who abuse it. **However, what many people do not realize is that testosterone is vital to the overall functioning of a human’s body (male or female).** If a man does not have enough of it in its “free” form, then he begins to suffer from a relative deficiency and he begins to have the above-noted symptoms. In addition, he may have problems controlling his blood glucose values and his cholesterol levels. If he takes narcotics chronically for a chronic pain condition, one side effect of the narcotic is to lower the testosterone production in the body.

What are the effects of low testosterone in a male? Many...and it isn’t just about sex:

- heart disease<sup>1</sup>
- prostate cancer<sup>2,3</sup>
- increase in fat mass<sup>4</sup>
- loss of muscle mass<sup>5</sup>

1 English KM et al. 2000 Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina: a randomized, double-blind, placebo-controlled study. *Circulation* 102:1906-1911.

2 Hoffman MA et al. 1999 Free and total testosterone in the evaluation of prostate cancer: does low free testosterone predispose to more aggressive disease. *J Urol*. 161:321.

3 Massengill JC et al. 2003 Pretreatment total testosterone level predicts pathological stage in patients with localized prostate cancer treated with radical prostatectomy. *J Urol* 169:1670-1675.

4 Rolf, C. et al. Testosterone substitution of hypogonadal men prevents the age-dependent increases in body mass index, body fat and leptin seen in healthy ageing men: results of a cross-sectional study. *Eur J Endocrinol* 146:505-511, 2002.

- senile dementia<sup>6,7</sup>
- osteoporosis and hip fracture<sup>8</sup>
- depression and malaise<sup>9</sup>

### How is it diagnosed?

All it takes is a simple blood test. We look not only at the total testosterone, but we also measure another protein called “sex hormone binding globulin,” (SHBG). SHBG binds to testosterone in the bloodstream to transport it throughout the body. When testosterone is bound to SHBG it cannot enter into cells to work and is therefore inactive. So only the testosterone that is unbound or “free” is active and works the way it should. In many cases, the serum total testosterone is within the normal range but the SHBG is *relatively* too high. If that is the case, then there is a *relative* lack of free testosterone available for the man to use. My Family Nurse Practitioner or I calculate the “Free Androgen Index” using the total testosterone and the SHBG by means of the following formula:

$$\frac{\text{total\_testosterone}}{\text{SHBG}} \times 0.0347$$

This calculates the Free Androgen Index and the normal values range from 0.70 and above. If the resulting number is too low, then testosterone replacement is indicated. We also check the estradiol and estrone levels in the blood. These are estrogens that may be produced in excess at times in a man’s body and need to be monitored. Production of estradiol and estrone in a man comes from an enzyme pathway known as *aromatase*. This enzyme converts testosterone into estradiol and androstenedione into estrone.<sup>10</sup> You must have this pathway activated to a small degree to allow estradiol to stimulate bone production. But you don’t want it “wide open” because an increase in estradiol will cause weight gain that is difficult to lose and it also “bleeds off” the extra testosterone, making what you are taking basically useless. This pathway can

5 Roy, TA et al. Interrelationships of serum testosterone and free testosterone index with FFM [fat free mass] and strength in aging men. *Am J Physiol Endocrinol Metab* 283: E284-E294, 2002.

6 Yaffe, K. et al. Sex Hormones and Cognitive Function in Older Men. *J Am Geriatr Soc* 50:707-712, 2002.

7 Moffat, SD et al. Longitudinal Assessment of Serum Free Testosterone Concentration Predicts Memory Performance and Cognitive Status in Elderly Men. *J Clin Endocrinol Metab* 87:5001-5007, 2002.

8 Zacharin, M.R., (2003) Bone mineral density outcomes following long-term treatment with subcutaneous testosterone pellet implants in male hypogonadism. *Clin Endocrinol*, 58, pp 691-695.

9 Seidman, S.N. Testosterone Deficiency and Depression in Aging Men: Pathogenic and Therapeutic Implications. *J Genet Specif Med* 2001;4[2]: 44-48.

10 Vermeulen, A et al. Estradiol in elderly men. *The Aging Male* 2002;5:98-102.

be regulated with medication, if necessary, but it must be monitored for that regulation to occur.

So, will you be like the infamous bodybuilders, who abuse steroids, i.e., testosterone? No way! These guys have *normal* levels of free testosterone and are *injecting* relatively large amounts of synthetic, non-bio-identical testosterone to reach *supraphysiologic* levels – which can cause some nasty side effects, e.g., breast development, testicular atrophy, and very low HDL (good cholesterol)<sup>11</sup>. Nevertheless, what will you feel? In approximately one week after starting the therapy, you will find that your feelings of fatigue will begin to fade, your mood will improve, and your quality of sleep will improve. Your libido may take a bit longer to improve depending on the exact reasons why it was low to start.

### **Side Effects of Testosterone – Fact and Fiction**

There are several alleged potential risks to testosterone supplementation including elevation of hemoglobin and hematocrit<sup>12,13</sup>, coronary artery disease, abnormal lipid profiles, increase in severity of sleep apnea, decrease in testicular size or atrophy, decline in sperm count (rare), fluid retention (usually transient), acne (rare), hepatotoxicity (rare except with oral forms), prostatic hypertrophy, and prostate cancer.

The frequency of erythrocytosis (increase in hemoglobin) is most often related to supraphysiologic levels of testosterone<sup>14</sup> but the risk is also greater in patients with emphysema. Injectable testosterone is associated with a greater risk of erythrocytosis than that seen with topical formulations<sup>15</sup>. No testosterone-associated thromboembolic events (formation of blood clots) have been reported to date<sup>16</sup>. Some research indicates that testosterone levels are inversely proportional to the severity of ischemic strokes in men, i.e., the lower the free available testosterone, the

more damage is done with the stroke<sup>17</sup>. Few, if any, data support a relationship between high testosterone levels and heart disease<sup>6</sup>. In fact, several studies suggest that higher testosterone levels may actually have a favorable effect on the risk of cardiovascular disease<sup>18,19,20,21,22,23</sup>. English *et al* found that 22 men with chronic stable angina who were treated with transdermal testosterone had greater angina-free exercise tolerance than 24 placebo-treated controls<sup>18</sup>. In the Rotterdam Study, serum levels of testosterone were evaluated in 504 men and those with the highest levels were at the lowest risks of severe aortic atherosclerosis<sup>21</sup>.

### **How is testosterone replaced?**

So how do you get testosterone replaced? There are five ways for testosterone to be replaced in a man: oral therapy; bi-weekly intramuscular injection therapy; transdermal therapy; sublingual/transbuccal; and pellet implant therapy. Of the five, we recommend and routinely do the last. This is done in our office with a small amount of local anesthetic and it is done in your hip. Two major advantages for this type of therapy: ease of use, i.e., no medications to remember to take; and consistent blood levels of testosterone from the slow dissolving of the subcutaneously implanted pellets. This procedure will need to be repeated between every 2 to 3 months, depending on how your body reacts to the testosterone replacement.

Some have asked why oral therapy is not used in this practice. The major reason is that the use of oral testosterone is linked with liver cancer. In addition, the liver has to metabolize relatively large amounts of it every time you take a dose, i.e., *high first pass*, and this will tax the liver and not help you at all.

The injection therapy is not done routinely here at this office because of the roller coaster effect on your blood levels of testosterone. In addition, it tends to be somewhat painful and you must come into the office every week for your injection or you will “crash”.

Concerning the pellet implant therapy, there have been some problems with reimbursement from the insurance companies concerning the cost of the pel-

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11 Sing AB et al. The effects of varying doses of T on insulin sensitivity, plasma lipids, apolipoproteins, and C-reactive protein in healthy young men. *J Clin Endocrinol Metab* 87:136-143.

12 Sih R, Morley JE, Kaiser FE, Perry III HM, Patrick P, Ross C. 1997 Testosterone replacement in older hypogonadal men: a 12 months randomized controlled study. *J Clin Endocrinol Metab*. 82:1661-1667.

13 Hajjar RR, Kaiser FE, Morley JE. 1997 Outcomes of long-term testosterone replacement therapy in older hypogonadal males: a retrospective study. *J Clin Endocrinol Metab* 82:3793-3796.

14 Dobs AS, Meikle AW, Arver S, Saunders SW, Caramelli KE, Mazer NA. 1999 Pharmacokinetics, efficiency and safety of a permeation enhanced testosterone transdermal system in comparison with bi-weekly injections of testosterone-enanthate for the treatment of hypogonadal men. *J Clin Endocrinol Metab*. 84:3469-3478.

15 Singh et al. 2002 The effects of varying doses of T on insulin sensitivity, plasma lipids, apolipoproteins, and C-reactive protein in healthy young men. *J Clin Endocrinol Metab* 87:136-143.

16 Rhoden EL and Morgentaler A. 2004 Risks of Testosterone-replacement therapy and recommendations for monitoring. *NEJM*. 350:482-492.

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17 Jeppesen, LL et al. Decreased Serum Testosterone in Men With Acute Ischemic Stroke. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 1996;16:749-754.

18 English KM et al. 2000 Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina: a randomized, double-blind, placebo-controlled study. *Circulation* 102:1906-1911.

19 Webb CM et al. 1999 Effects of testosterone on coronary vasomotor regulation in men with coronary artery disease. *Circulation* 100:1690-1696.

20 English KM et al. 2000 Men with coronary artery disease have lower levels of androgens than men with normal coronary angiograms. *Eur Heart J*. 21:890-894.

21 Hak AE et al. 2002 Low levels of endogenous androgens increase the risk of atherosclerosis in elderly men: the Rotterdam Study. *J Clin Endocrinol Metab* 87:3632-3639.

22 Sieminska L et al. 2003 *Med Sci Monit* 5:162-166.

23 Muller, M et al. Endogenous Sex Hormones and Cardiovascular Disease in Men. *J Clin Endocrinol Metab* 88:5076-5086.

lets themselves. We have found a solution for some of you who have a mail-in pharmacy with your insurance. We will write you a prescription for the pellets with a year refill. Once you have received your pellets in the mail, you call us for an appointment to have them implanted and you bring them with you to get them implanted. Order a refill for the next three months and come in at that time for the next series of pellets. Another option is for you to pay for the *cost* of the pellets. The cost is \$15/pellet and we normally start you with eight to ten 75 mg pellets (\$120 - \$150). We ask that you pay at the front desk the day of the procedure after it has been done.

Another possibility is the use of bio-identical transdermal testosterone therapy. This would be compounded at a special pharmacy and the strength of the dose would be adjusted according to your response. The cream or percutaneous gel is applied every morning to your inner forearms.

A similar option is to use the standard transdermal testosterone available in local pharmacies. The two available forms are AndroGel® and Androderm®. AndroGel® is a goopy liquid gel that must be rubbed onto the body every morning. Androderm® does not involve rubbing gels into the skin but does involve the use of a patch you place on your skin at night and replace the following night. You need to rotate sites of application. Skin irritation with the patch is unfortunately a common complaint and a steroid cream is needed frequently. These two are not as good as the compounded prescriptions but are available locally.

A final possibility is a compounded, bio-identical sublingual testosterone. This would be a pill that is placed under your tongue every morning (or sometimes twice a day). The dose would be adjusted according to how you respond. Again, this is not available at general pharmacies but is made in a compounding pharmacy. There is a transbuccal form of testosterone on the market now known as Striant® and is placed on your gum twice a day. It is an adhesive disc that will dissolve completely in your mouth and the testosterone would be absorbed through your gum. I don't like to prescribe it due to the adhesive to your gum can be so strong that bleeding results when the remnant is removed for the next dose.

You will need to have a blood test one month after starting replacement therapy to note the response and rise in your Free Androgen Index. We will also again check the estrogens in your blood to ensure that your body is not misdirecting the supplemental testosterone to the wrong pathway. After that, you will get your

testosterone checked periodically and your PSA checked every six months. The testosterone will be checked especially if you feel as though it is not working. If you are using the pellets, *you* will know when your testosterone is low because your serum levels will begin to drop and you will have the symptoms of fatigue, *et.al.* return. When that occurs, you will call and make an appointment to get the next set of pellets implanted. We will draw your blood at that time for our records. Because of the increase in testosterone, this will sometimes cause an enlargement in your prostate. This is not the same as cancer, only that the prostate becomes enlarged and you may have a difficult time urinating. Taking Saw Palmetto 160 mg twice a day along with Stinging Nettle Root extract and Pumpkin Seed Oil easily solves this problem. You can buy that combination at *The Vitamin Shoppe*.

#### ***Why must I have a PSA done?***

***Testosterone replacement therapy has not been linked to prostate cancer,*** but prostate cancer does “feed” on testosterone<sup>24</sup>. Therefore, if you had a few cells of prostate cancer inside you, the testosterone can cause it to grow. Interestingly, there is some research to show that a chronic, low testosterone *increases* the incidence rate of prostate cancer<sup>25</sup>. Either way, with testosterone replacement therapy in any form, you must have your PSA checked every 6 months. If it rises above 4.0, then you will have another blood test done (Free PSA) to ascertain if this is an enlarged prostate or cancer. If it appears to be cancer-like, then we will refer you to an urologist. The likelihood of cancer that will shorten your life span is slim, *but always present*.

If you are interested in finding out if you need replacement therapy, please call and make an appointment to see either the nurse practitioner or myself. Both of us are able to diagnose the condition, counsel you, and either prescribe the appropriate medication or do the implant procedure.

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24 Vermeulen A 2001. Androgen replacement therapy in the aging male—a critical evaluation. *J Clin Endocrinol Metab* 86:No. 6 2380-2390.

25 Massengill JC et al. 2003 Pretreatment total testosterone level predicts pathological stage in patients with localized prostate cancer treated with radical prostatectomy. *J Urol* 169:1670-1675.