

## LOW TESTOSTERONE LEVELS

Over the last 20 years the idea of “Low T” and male hypogonadism has become mainstream public conversation. This is not a surprising development to Endocrinologists. What was heretofore a relatively rare clinical “diagnosis” has EXPLODED coincident with massive publicity campaigns in print, television and on-line costing hundreds of millions of dollars and paid for by the likes of Abbot Labs (Androgel), Abbvie (Androgel), Teva Pharmaceuticals (Androderm), GlaxoSmithKline (Testim) and Eli Lilly (Axiron). How can you afford to spend \$200,000,000 a year on TV ads? Well, when you own a drug like Androderm, and charge each user \$400 to \$650 per month, you can make between \$1 Billion and \$2 Billion every year. And all you need to do is get them started on the drug (it works for precisely the same reason heroin works - read on), and they will continue to buy it for years. With patent protections on these drugs, you’ve got a cash stream of \$15 to \$20 Billion dollars to look forward to before anyone else can start to compete with you. So yes, Big Drug Companies are willing to spend real money to catch the public’s eye and start a “discussion” about off label use of these drugs with anyone willing to listen.

Testosterone replacement therapy has been around for 50+ years. In the past it was given by injection. But newer testosterone formulations that can be delivered transdermally through either patches or gels are more acceptable to “potential clients” than the old standard intramuscular injection every 2 weeks. The new delivery systems (not the drug itself) are **patentable**, and therefore highly profitable. Most importantly, because this “diagnosis” of “Low Testosterone” is so poorly documented and understood (there is no general agreement among experts in this field as to who should be treated and if so for how long) aggressive marketers of these drugs can claim that 10-15% of men age 40 to 60 and 40%+ of men 60 and older should be considered for testosterone replacement! **How crazy is that??** So drug companies are now doing mass advertising to encourage men to get their testosterone levels measured if they have ANY symptom that might be related to a low testosterone level. In addition, great publicity has surrounded many star athletes in the last 20 years about “doping” and the illicit use of performance enhancement drugs such as anabolic steroids and androgenic hormones (including testosterone). Careful studies clearly show that LARGE doses of these drugs (way in excess of what “normal” levels would be) can increase muscle mass, strength, weight and maximum muscle work (Olympic Man Syndrome). Unfortunately, there is also clear knowledge that these high doses of drugs can cause serious harm such as “roid rage”, liver tumors, and quite possibly accelerated atherosclerosis (damage to arteries). Nonetheless, all this publicity surrounding these issues has led many men to question their sexual function, obtain testosterone levels, and then seek referral when one of the numbers appears “out of range.”

To understand the dilemma facing physicians when asked about these “out of range” testosterone levels, you have to first realize that testosterone is a hormone that is secreted from the testes in widely varying levels. That is because the controlling hormone for testosterone production and release, called luteinizing hormone (LH) is secreted from the pituitary in distinct “spikes.” The result is that testosterone levels traverse a very large range of values throughout the day, i.e. LH is secreted in bursts with a rapid blood rise of the target hormone, and then a fairly rapid decline of the level down to the bottom of the range.

**Because of this variation, even in young healthy men 15% of testosterone measurements will fall below the normal range of measurement during the day.** Look at the graphs below of **NORMAL HEALTHY MEN** whose testosterone levels were measured throughout the day (from Heller, JCEM). We also know that as men age there are **FEWER** testosterone spikes during the daytime compared with teenage men. We also know that in general, testosterone levels **DECLINE** in men as they get older, that is, the testosterone spikes are not as high and not as frequent as they were when the individual was younger. It’s no wonder that older men who get their blood testosterone measured will frequently (certainly much more than 15% of the time) get results below the normal range, **EVEN THOUGH** their sexual function compared to their peers is **NORMAL**.

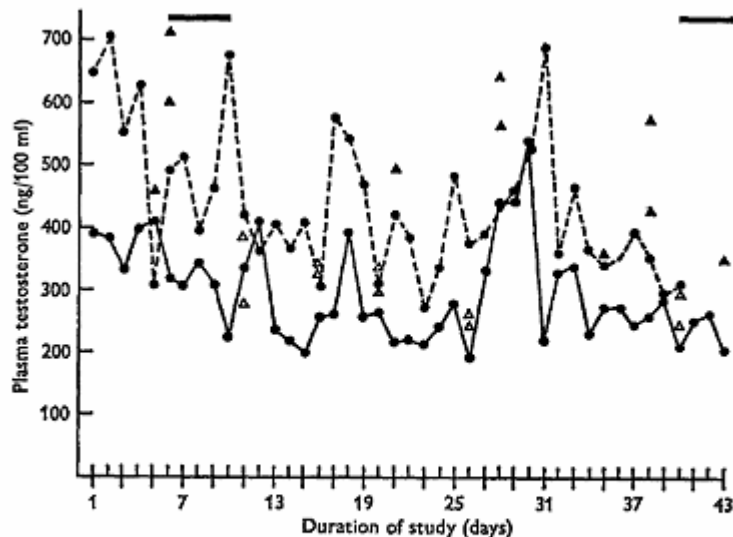


Fig. 2. Plasma testosterone levels in a male subject - second study. Horizontal black bars, menstruation of partner; ● - - ●, control measurements at 08.00 h each day; ●—●, control measurements at 20.00 h each day; ▲, measurements in morning coital blood samples; △, measurements in evening coital blood samples.

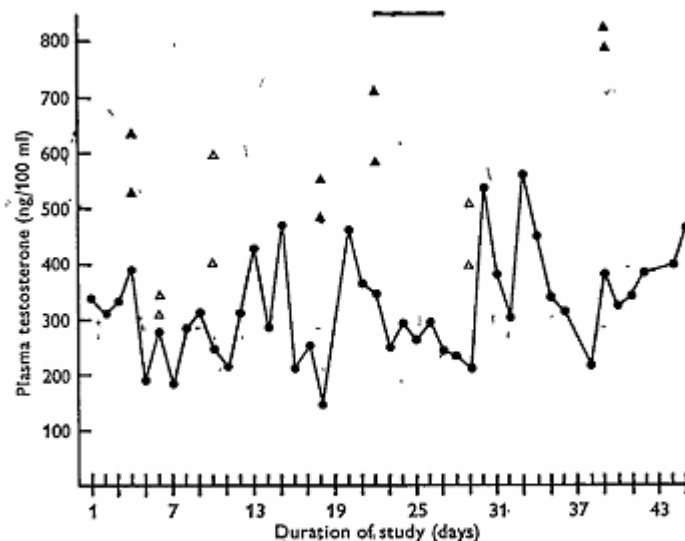


Fig. 1. Plasma testosterone levels in a male subject--first study. Horizontal black bar, menstruation of partner; ●—●, control measurements at 22.00 h each day; ▲, measurements in morning coital blood samples; △, measurements in evening coital blood samples.

The sum total of the above information is that a single random blood testosterone level, **PARTICULARLY in older men**, is NOT a reliable indicator of testicular problems or low testosterone levels. Because there are fewer testosterone spikes in older men, it's more likely that 1 or 2 testosterone blood samples will be drawn at a time that is NOT coincident with a testosterone spike and give a misleadingly low result. Furthermore, we know that testosterone levels are higher at the time of sexual activities such as coitus (see above graphs.) So how sexy do you think it is to come in to the lab and get your blood drawn, particularly if you're not feeling well? To adequately assess testosterone levels in older men, a minimum of 3 determinations need to be drawn to get a better sense of where the typical numbers lie.

Who needs to be treated for a low testosterone level? Men who CLEARLY have hypogonadism, such as from a destructive pituitary tumor, or genetic problem such as damaged testes and obviously low testosterone levels benefit from therapy. When treated they will develop beard growth, increase muscle mass if they have sustained muscle loss, and have improved sexual desire (libido). Their ability to obtain/maintain erections may improve. Pre-pubertal adolescents will go through puberty. In my experience, most of these men present with testosterone levels that are 6, or 10, or 15 ng/dl. They're not in the range of 100, or 150 or 200 ng/dl that most adult otherwise healthy men with concerns about "Low Testosterone" have.

On the other hand, older men who have low normal testosterone levels and NO CLEAR evidence of hypogonadism have **NOT been shown to benefit** from the administration of testosterone. There was a study of 800 patients published in

2017 looking at testosterone supplementation in older men. That study showed some improvement in sexual desire and erections with treatment, but failed to show improvement in exercise tolerance, vitality, fatigue or depression. Furthermore, it is evident that in that study the testosterone replacement was pushed to levels that are HIGHER than normally expected in the average older man, meaning they were recreating the Olympic Man Syndrome. These kinds of studies do NOT show significant increases in muscle mass, exercise endurance, or weight changes. No one has conclusively shown that testosterone supplementation to normal testosterone levels for an age adjusted cohort group will consistently improve energy level, mood or sexual function! Yet added testosterone MAY contribute to prostate enlargement and symptoms, and may exacerbate prostate cancer if that happens to be present. In some men testosterone replacement seems to exacerbate some lipid (cholesterol) problems and may increase the risk of heart disease, blood clots, and strokes. Testosterone replacement is routinely associated with declining sperm counts and testicular atrophy.

So in summary the benefits derived from testosterone replacement **ONLY** seem to accrue in men who have clear testosterone deficiency with loss of muscle mass and sexual function. Treating normal men with testosterone has NOT been shown to be helpful in any meaningful way and CAN BE associated with potential harm regarding the prostate, heart and vascular issues.

Currently endocrinologists specializing in the field of male hypogonadism do **NOT** recommend testosterone screening of men with symptoms such as “fatigue” or “low energy” or even decreased frequency of erections. (Why did YOU have a testosterone level drawn?) Screening is **ONLY** recommended for situations where a specific medical condition might cause a low testosterone level. Even in older men with a low testosterone level, the recommendations are **NOT** to routinely treat these people. (Why is that? For all the reasons cited above. You are likely to get a low reading if you check a random testosterone level. It will be meaningless. There is a morass of internet babble, stories, marketing and downright misrepresentations that will lead many people to begin to wonder..... ..maybe this is something I should try. It is a mistake. Read on.)

An extensive review of the literature of testosterone use in men was published by The Endocrine Society in October 2005. There have been no large scale prospective studies done since that time to change any of the conclusions reached in that review. The general conclusions were as follows:

1. Testosterone is the most important sex steroid in the blood in men.
2. There is a wide daily variation in testosterone levels and an age-related decline in testosterone levels.
3. Estrogen levels in men (from the conversion of testosterone to estrogens by fat tissue) are the primary regulator of testosterone production.

4. As men age, effective testosterone levels decline due to diminishing testosterone production from the testes, decreased release of LH from the pituitary, and changes in sex hormone binding globulins (SHBG) in the blood.
5. Abdominal fat and stress are associated with lower testosterone levels (The more overweight you are, the lower your testosterone level.)
6. Acute illnesses and many chronic diseases such as diabetes, chronic lung disease, chronic liver disease, kidney disease and atherosclerosis (hardening of the arteries) are associated with lower testosterone levels.
7. Many drugs, such as blood pressure medications, narcotics, antidepressants, steroids, cannabis, antifungals, diuretics can lower testosterone levels.
8. Declining testosterone levels in aging men is NOT the same as women going through the menopause. There is NO abrupt change in sexual function, mood, potency, or fertility in aging men such as is seen in women. (Read that last sentence AGAIN.)
9. It is unknown if the slow decline in testosterone levels as men get older is part of the normal aging process, or if this is truly an illness per se.
10. It is clear that lower testosterone levels are associated with lower estrogen levels which are associated with lower bone mineral density levels as men age.
11. Declining testosterone levels and declining physical activity in aging men are associated with declining muscle mass and general strength. It is unclear which is due to which.
12. Moderately low testosterone levels in elderly men are associated with an increased frequency of atherosclerosis and coronary artery disease.
13. Declining testosterone levels and decrease in libido and sexual activity are commonly seen in aging men. In androgen dependent men (men who are chronically taking testosterone, for any reason), withdrawal of testosterone leads to decreased spontaneous nocturnal erections within 3-4 weeks.
14. In spite of item 13) above, it is NOT established that the age-associated decline in testosterone actually causes the decreased libido and sexual activity seen in these individuals. Erectile dysfunction has been shown PRIMARILY NOT to be due to testosterone changes. Erectile dysfunction IS, however, commonly related to non-hormonal factors such as many chronic illnesses, alcohol, smoking, stress, infections, blood pressure medications, antidepressants and pain medications.
15. Testosterone levels are inversely related to varying degrees of depression in men. Higher levels of depression are associated with lower testosterone levels and vice versa. Testosterone therapy in such individuals has been shown to frequently help but not to resolve such depressive disorders.

16. Studies have shown that specially designed questionnaires used to screen men for symptoms of testosterone deficiency have only modest sensitivity and low specificity. These questionnaires have been shown to be poor predictors of testosterone levels in aging men.

In summary the clinical significance of “partial or mild testosterone deficiency” in aging men is unclear. There is a correlation between **some** aging symptoms in men and lower testosterone levels, but correlation is not causality. The evidence shows that raising testosterone levels does not consistently improve such symptoms.

If you can't rely on symptoms to make a diagnosis of testosterone deficiency in men, then what other evidence is there? First of all, it is UNKNOWN what levels of testosterone are truly NORMAL for aging men. None of the measurements of circulating testosterone reflect the *effective tissue levels* of male hormone, which is where all the actual effects of testosterone are mediated. If we use the normal testosterone levels of young healthy men for ALL men, we would diagnose ~20% of the male population with hypogonadism (testosterone deficiency), which seems ridiculous. Because of this current dilemma, ***at present the diagnosis of testosterone deficiency in its milder forms in men is arbitrary.*** Even if we limit the diagnosis of testosterone deficiency to those men who both have symptoms and have relatively low testosterone levels, ***we still are making arbitrary judgments.*** In the present state of the art, we are unable to make a distinction between “replacement therapy” for low testosterone levels and “pharmacologic therapy” in which we overdose individuals knowing that excess testosterone can have benefits as well as side effects.

As for studies looking at the treatment effects of testosterone “replacement” in men with lower testosterone levels we know:

1. The effects of treatment on reducing bone turnover in men with low bone mass are inconsistent.
2. The effects of treatment on improving bone mineral density in men is indeterminate.
3. There is NO data that indicates that treatment of low testosterone levels in men reduces fracture rates.
4. Most studies demonstrate a modest effect at best of treatment of low testosterone levels in men on improving muscle mass (gain of ~3 pounds) and negligible effect on reducing body fat (0-2 pound fat weight loss). Only when you see much larger doses of testosterone administered do you see bigger changes in muscle gain and fat loss.
5. Most studies demonstrate **NO** effect of treatment of low testosterone levels in men on hand grip, leg strength, other measures of strength, gait, balance or motility.

6. Most studies demonstrate **NO** effect of treatment of low testosterone levels in men on cardiovascular risk, waist or hip circumference (body fat), cholesterol or blood fat levels, diabetes, heart disease or stroke.
7. The balance of blinded studies demonstrate **NO** effect of treatment of low testosterone levels in men on sexual function or perception of sexual function!
8. There are only a few limited studies that suggest a modest positive effect of treatment of low testosterone levels in men on cognitive function.
9. There are only a few limited studies that suggest a modest positive effect of treatment of low testosterone levels in men on depression, but there are other studies that do not show any effect on depression.
10. With regard to safety of taking testosterone, it is recognized that testosterone can accelerate the growth of prostate cancer. Small prostate cancers are present in >50% of men over the age of 60. The widespread use of testosterone in these men could potentially create a significant problem. Older men on testosterone supplements should routinely have a PSA and digital rectal exam.
11. There are anecdotal reports that testosterone supplements may exacerbate sleep apnea. Sleep apnea is a common cause of hypertension in men.
12. Gynecomastia (breast tissue swelling) can occur in some men taking testosterone supplements.

In summary, it appears that age-related changes in testosterone in men may play a contributory role in some of the symptoms accompanying aging, the most convincing of which are changes in muscle mass and bone density. It is also clear that for many of the clinical signs of aging, which might be interpreted as hypogonadism, the data is inconclusive as to whether low testosterone levels are playing ANY role. Furthermore, for the majority of these signs of aging, testosterone replacement has not been shown to be beneficial. The beneficial effects of testosterone supplementation on muscle mass, weight loss and bone mass are modest at best and are not likely to improve any of the symptoms for which testosterone is most commonly prescribed today.

Having said all that, I know from personal experience that a lot of men feel desperate to do ANYTHING they can to improve their sexual function and prowess. Regardless of the lack of data, they want to try testosterone for themselves. They are confident they will be capable of judging themselves whether the testosterone helps them or not. This is called HUBRIS(look it up!). It is well known that there is a strong component of a placebo effect to taking testosterone supplements. In double blind studies the majority of people improve, whether they are taking the real drug or a blank inactive agent. My personal experience with patients using testosterone is as follows: A man thinks he needs testosterone and after evaluation I tell him I see no evidence that it will benefit him. I go through a lengthy explanation, and irregardless, he wants to get

a prescription for it. I give him a prescription and he starts taking the medicine. Miraculously in 1-2 weeks he is doing MUCH better. His symptoms are all gone, he has more energy, is going to the gym 3 times a week and feeling "like his old self". But then 3 months goes by, he comes back in to the office. His testosterone levels on the supplements are now all in the mid-normal range. Yet he tells me, "Doc, the medication is no longer working. I quit going to the gym. My energy level is down again, my sex drive is gone, and I'm back to where I was in the beginning. The pharmacy must be giving me a generic, or the dose must be inadequate." I tell him that no, the dose is O.K. because the testosterone level is in the mid-normal range. He says, "No, it can't be. It must be wrong. You need to increase the dose of testosterone. I know that's what I need.(it's called HUBRIS)" So finally under pressure I relent and let him increase the dose. Again, after a week, this seems to work and he says he is doing better. Three more months go by and he comes back in. Again, he is feeling tired with a low sexual drive. Now his testosterone level is ABOVE the normal range. I then tell him, "Look, the medicine is just not working. The testosterone level is ABOVE normal. You can't increase the dose any more. Let's try stopping it for a couple of months and see if it makes any difference." Eventually, after a few more months, he agrees to go off the testosterone and get re-tested. He comes back next visit and says, "Ya know, Doc, I'm not sure I felt ANY better on the testosterone. I feel the same now as I did when I was taking the drug." THAT, I tell him, is the PLACEBO effect. I'm sorry you had spend so much money on the drug, get all the labs done and spent the time for follow up visits to discover that you really didn't need it (benefit from it) in the first place. You'd have been better off just going to the gym 3 days a week and exercising regularly instead of wasting all the time and energy on "trying a magical potent "to help you feel better.

There is another reason why I really don't like to prescribe testosterone to men who I really don't think will benefit from it. THIS IS A CONCEPT YOU REALLY NEED TO UNDERSTAND. Testosterone is produced in the testes. The testes are driven to produce testosterone by the pituitary gland at the base of the brain in the head. It does that by secreting the hormone luteinizing hormone (LH). And the pituitary's production of LH is controlled by the hypothalamus (part of the brain posterior to the pituitary) by another hormone known as gonadotropin releasing hormone (GnRH). But how does the hypothalamus know when to make GnRH? Well, in both men and women the body produces both testosterone and estrogen. In men the testosterone from the testes can be converted by fat tissue into estrogen compounds. It is these estrogen compounds that circulate in the blood and feed back to the hypothalamus to signal that yes, there is adequate testosterone around. If these estrogen levels drop, the hypothalamus makes more GnRH, that stimulates the pituitary to make and release more LH, which act on the testes, and therefore more testosterone is produced. This is called the hypothalamic-pituitary-testicular (HPT) axis.



Now, in a normal male who starts taking testosterone supplements, this feedback pathway is interrupted and suppressed. Testosterone levels are relatively high, estrogen levels rise too high, and suppress GnRH production from the hypothalamus. The pituitary stops making LH and the testes are no longer stimulated. The hypothalamus GnRH producing cells and testes after several months will start to shrink (atrophy) in size and sperm production declines significantly. The longer the testosterone supplementation continues, the stronger the suppression of the hypothalamus. So, when the testosterone supplementation is stopped, the hypothalamus takes time to recover. In fact, depending on the duration of the testosterone supplementation, the hypothalamic suppression may persist for months to a year or more (typically not much beyond a year, except perhaps in older individuals). So now, when the individual stops the testosterone supplements, the testosterone level REALLY does fall significantly, and the individual REALLY does feel worse going off the supplements and effectively goes through a physiological withdrawal process (It is the same process a drug addict has to go through to quit. This is also what happens to women who were put on estrogens for post-menopausal symptoms. They effectively experience withdrawal symptoms. The symptoms are TRUE LACK OF ESTROGEN and are MUCH WORSE than the general symptoms of low energy or sexual disinterest that brought the individual to the doctor in the first place. It can be VERY difficult to get them to stay off the estrogens because of the rush of symptoms following the abrupt cessation of estrogen. It is why drug companies such as Wyeth Pharmaceuticals, who made Premarin, spent so much money convincing Obstetrician-Gynecologists that they should put every menopausal woman on estrogens to “help” their menopausal symptoms. This was a tremendously lucrative drug for 30 years and made Wyeth billions of dollars! This continued until the Woman’s Health Initiative, a very large prospective study, conclusively showed that estrogen “replacement” carried more risks than benefits when used in this fashion. Then the FDA dropped most of the post-menopausal indications for prescribing estrogens. It was a tremendous financial loss for Wyeth, and the company was eventually so weakened that it was purchased by competitors. Now we have a group of drug companies doing the same thing with testosterone for men. People who do not learn their history are doomed to repeat it. Now do you understand some of my cynicism?) Eventually, if the individual stays off the testosterone, the HPT axis will typically go back to normal function. But, there is no guarantee.

If you are convinced you need testosterone and truly decide that you want to be one of those people to try testosterone for yourself, I will prescribe it for you. If you have not convinced me after 6 months that you are doing better, I will try to convince you to stop it. I would rather you be treated by a skeptic willing and able to help you withdraw from and recover off of testosterone than a physician who simply prescribes it to you for the next 25 years regardless of necessity.

There is one other option we could pursue prior to a “testosterone trial.” That would be using a fertility drug that is approved for use in women to help induce

ovulation, called clomiphene. It is a drug that blocks estrogen from stimulating estrogen receptors in the hypothalamus. In men this fools the hypothalamus into sensing that there is NO effective testosterone around. GnRH levels rise, LH levels rise, and stimulate the testes to produce more testosterone as a result. So if a man is given Clomid and after several weeks or months the testosterone level rises into the normal range, it is a good demonstration that the hypothalamic sensing function, the hypothalamus function, the pituitary function, and the testicular function are all intact and working properly. The end result is the SAME as taking supplemental testosterone, but in this case it is your own body that is making the testosterone, in the natural way. And men do not go through withdrawal symptoms going off clomiphene. Everything about their HPT axis remains normal. The drug is substantially cheaper than supplemental testosterone. It is available as a generic. Some of the articles about the use of clomiphene to treat men with low testosterone levels are listed below. Like all medications, clomiphene can have side effects. The most serious one relates to a slight tendency, like estrogens, to increase the likelihood of blood to clot. So one rather uncommon (probably 1 in several hundred men who take the drug) side effect is blood clot (thrombosis) in the retinal vein of the eye, which can cause visual shimmering or changes. Were that to happen, you need to stop the drug, immediately take an aspirin, and call me to discuss what is going on and possible treatment. Clomiphene is typically dosed in men as 25-50 mg every other day.

Outcomes of Clomiphine Citrate Treatment in Young Hypogonadal Men, Katz, DJ, et. al. [BJU Int.](#) 2012 Aug;110(4):573-8. doi: 10.1111/j.1464-410X.2011.10702.x. Epub 2011 Nov 1.

Clomiphene Increases Free Testosterone Levels in Men with Both Secondary Hypogonadism and Erectile Dysfunction: Who Does and Does Not Benefit? , Guay, AT, et. al. [Int J Impot Res.](#) 2003 Jun;15(3):156-65.

Twenty-five Milligrams of Clomiphene Citrate Presents Positive Effect on Treatment of Male Testosterone Deficiency. DaRos, CT. et. al. [Int Braz J Urol.](#) 2012 Jul-Aug;38(4):512-8.

Clomiphene Citrate Effects on Testosterone/estrogen Ratio in Male Hypogonadism. Shabsigh, A. et. al. [J Sex Med.](#) 2005 Sep;2(5):716-21.

Testosterone Supplementation Versus Clomiphene Citrate for Hypogonadism: An Age Matched Comparison of Satisfaction and Efficacy. Ramasamy, R. et. al. [The Journal of Urology, Volume 192, Issue 3](#), September 2014, Pages 875–879

P.S.

If you're still not convinced that testosterone is a bad idea for most middle-aged men with lowish normal testosterone levels, think about this:

Doctors are paid by the amount of work they do, the number of patients they see, and the number of prescriptions they write. I'm paid by that method as well. What is the incentive for me to tell you NOT to use a prescription medicine like testosterone? What is the incentive for me to tell you that you are healthy and don't need to take an expensive supplement, and you can go back and be followed up by your PCP? I don't get paid to tell people they don't need my services. The answer, of course, is that all the above information in this long handout is working AGAINST my financial interest. Fortunately for you, I'm in a position where I can afford to tell you the truth and let the chips and the financial fall-out fall where they may. I went into medicine as part of a life-long dream. I'll be retiring from medicine knowing that I have helped many, many people and ALWAYS supported their health and well-being. Think about this, long and hard. Your doctor.

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