

Testosterone Replacement Therapy: A Recipe for Success

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ABSTRACT

Testosterone replacement therapy (TRT) is the restoration of testosterone to healthy physiological levels. This paper will consider how to screen for hypogonadism, the different testosterone delivery systems that are available, medications that can be used in conjunction with TRT, and the contraindications and drug interactions associated with TRT. A protocol for TRT will also be provided.

INTRODUCTION

Testosterone replacement therapy (TRT) is the restoration of testosterone to healthy physiological levels. There are a lot of doctors who take their patients to twice the top of the normal range. I don't believe that it is appropriate, and it certainly is not healthy for the patient. TRT is not about taking total testosterone to above the normal range. It is not about steroids. And it has nothing to do with Viagra. TRT is concerned with the restoration of testosterone to normal physiologic levels.

SCREENING FOR HYPOGONADISM

When thinking about screening for hypogonadism the first thing to consider are the symptoms of low testosterone. What are the symptoms of low testosterone? Two of the most common symptoms are TAT syndrome and USTA syndrome. TAT is an acronym for 'tired all the time' and USTA is an acronym for 'used to be able'. Patients will often complain that they used to be able to hit the golf ball 40 yards further, that they used to be able to enjoy their family in the evenings, that they used to be able to work well into the evening, that they used to be able to enjoy fine relations with their wife, and etcetera. Other symptoms are a loss of muscle mass, fat gain, poor recovery, irritability, depression, decreased memory, loss of libido, and erectile dysfunction. It is actually most useful that erectile dysfunction is a symptom of low testosterone because it will actually bring the patient in and keep him compliant.

The ADAM questionnaire is useful when screening for hypogonadism. It is about 90% sensitive, but only about 50% specific. So, the best thing to do is listen to your patient, get them to fill out an ADAM questionnaire, and then carry out an initial hypogonadism panel. An initial hypogonadism panel should include:

- Total testosterone
- Bioavailable testosterone
- Free testosterone
- SHBG (sex hormone binding globulin)
- DHT (dihydrotestosterone)
- FSH (follicle stimulating hormone)
- LH (luteinizing hormone)
- Estradiol
- Total estrogens
- Prolactin
- Cortisol
- Thyroid panel
- Complete metabolic panel
- Complete blood count (CBC)
- Lipid panel
- PSA (prostate specific antigen) if the patient is aged 40 and above

Total testosterone is notoriously unreliable. A patient will come in with a laboratory printout that says their total testosterone level is 325. The patient has all the symptoms of hypogonadism. But the doctor takes one look at their total testosterone level, says, "You are fine. You are normal. Have some

Viagra. See you next time.” So, that is why I measure total testosterone, free testosterone, bioavailable testosterone, and SHBG.

Free testosterone is a measure of the testosterone that is available and floating loose in the bloodstream. It is useful to measure free testosterone, but I have been told that it is not that stable on its way to lab. When it comes to measuring testosterone levels bioavailable testosterone is the gold standard. The term bioavailable means testosterone that is free and loosely or weakly bound. Bioavailable testosterone is the actual concentration of testosterone that is available at the androgen receptor, and it closely approximates the sum of the free testosterone and that that is loosely bound by carrier proteins in the blood, primarily albumin.

DHT is most responsible for All Things Male. DHT is unfairly deemed as an evil hormone. There are a lot of issues of DHT from hair loss to benign prostatic hyperplasia (BPH). But, we know that is not responsible for prostate morbidity, because if you have BPH and I give DHT, your prostate gets better, not worse. Prostate morbidity is actually caused by estrogen issues. The normal range for DHT is between 30 to 85 ng/dl. I do avoid finasteride. I have never prescribed it. I am currently working with an international group of about 300 men who suffer with permanent serious side effects after using finasteride even for a short period of time. The endocrine disruptors can be a very bad class of drugs. Some of these guys took finasteride for maybe just two weeks. The problem is that their hormone levels may have returned to baseline, but they still find themselves weak, depressed, and impotent. In fact, one of the members of our group recently committed suicide.

Estradiol (E2) is the major player amongst the estrogens. E2 must be monitored during TRT, because it will mask the benefits of the TRT. You put a guy on TRT and he feels great at first, because his serum enzyme levels are accelerating, however as time goes on, his estrogen levels will rise. Estradiol is an adjunctive cause of serious illness. But it also conveys numerous health benefits with respect to bone deposition and endothelial function. Estradiol must not be driven too low. The normal range is 10 to 50 pg/ml, and I like to see it somewhere in the 20 to 30 range. If you drive it too low it not only leads to some serious deleterious health effects, it also has an emotional impact upon the patient.

LH is produced by the pituitary gland. It has a very pulsatile production and a very short half-life. It is also an acute phase reactant. So, you must be careful in interpretation. One single LH assay really has a very little value. You just have to keep it in mind, if it is high, that is of interest, but if it is low you really do not know if you are looking at secondary hypogonadism or not. To make a determination you need serial LH assays. However, the difference between primary and secondary hypogonadism is really quite trivial because the treatment is the same either way. If LH is very high it is important to think in terms of possibilities such as gonadotrophin-secreting tumors.

FSH is produced by the pituitary gland. It has a half-life of 180 to 240 minutes, and it may actually be a better measure of gonadotrophin output than LH. Again, if you have very high levels of FSH, you will be thinking about an FSH-secreting tumor.

Prolactin is a very significant and common cause of hypogonadism. On autopsy, about 24% of cadavers are found to possess a prolactin-secreting pituitary tumor. However, there are many health benefits of prolactin, therefore you do not want to drive it too low. For instance, you may be compromising immune function. Prolactin is also important for the maintenance of LH receptors. Thus, it is important to maintain it within the normal range. The reference range for prolactin is between 3 and 18. Greater than 300 is a pathologic of a tumor. It is important to remember that eating and sex elevate prolactin levels. I have heard of doctors treating patients for hyperprolactinemia on a single assay of prolactin when they may have eaten or had sex just prior to the draw.

The stress hormone cortisol may be a cause of secondary hypogonadism. Of course, cortisol does have certain benefits and therefore we do not want it too low. We must keep our hormones in the normal range. If cortisol levels are elevated give the patient 300 mg phosphatidylserine (PS) a day, as it has been shown to decrease cortisol levels by 37%. If a patient's cortisol level is too low treat them with very small doses of hydrocortisone.

SHBG really helps me to interpret my hormone assay. What I am looking for when I measure SHBG is to see if it correlates with the testosterone assays that I am running. Total testosterone, free testosterone, and bioavailable testosterone are all related by the amount of testosterone that is tightly bound to SHBG. Generally, high estrogen levels stimulate SHBG production. There is no other reason to keep estrogen controlled.

Some doctors put a lot of weight on the testosterone and estrogen ratio. I don't even give it a thought. I think it is more a measure of how the system is functioning than some kind of a treatment goal.

Certainly, the absolute values of both hormones are more important than the ratio. Of course, I always want to do a thyroid panel because hypothyroidism mimics hypogonadism in many respects. It is important to conduct a CBC on each patient in order to monitor for polycythemia.

Patients on TRT should be monitored every six months. The follow-up laboratory tests that are necessary are:

- Total testosterone
- Bio testosterone
- SHBG
- Estradiol
- Total estrogens
- DHT (especially with transdermal TRT)
- CBC
- Complete metabolic panel
- PSA (if over 40)

TESTOSTERONE DELIVERY SYSTEMS

There are a wide variety of testosterone delivery systems from gels, creams, and patches to implantable pellets, intramuscular (IM) injections, and orals.

Gels and Creams

Gels and creams are easy to apply. Whether they are more convenient depends upon the patient. Gels and creams produce good stable serum androgen levels and they closely mimic the circadian rhythm. In my opinion they are the second best form of delivery for TRT as they give you a stable serum level testosterone level. Furthermore, stable serum levels can be attained quickly – as quick as two or three days. That does not mean you can draw labs then because you still have to deal with the increases of estrogen, which will suppress endogenous production as well as the exogenous testosterone that you are adding to.

One of the problems and benefits of transdermal applications is that 5-alpha reductase is found in the skin and thus when testosterone passes through the skin you do get a DHT boost. I do not consider that to be a bad thing. Aromatase lives in the tissue as well so you are exposing testosterone to that as well. Therefore increased levels of estrogen are more likely than with injectable testosterone. It is important to watch this because estrogen tends to creep up on you. That is why it is important to monitor a patient every 6 months.

The biggest problem with the gels and creams is the risk of accidental transfer. Although, it has been shown by numerous studies that simply covering up with a T-shirt completely eliminates that risk. Most men apply their testosterone in the morning after the shower before they go to work.

Testosterone Patches

Testosterone patches are convenient because you just pull the back off and stick them on. They may be more convenient. They may not be. There is no risk of accidental transfer. They do produce stable serum androgen levels and like all the transdermals they give you a DHT boost and a potential estrogen boost. Two thirds of men who use testosterone patches will develop contact dermatitis at some point or another. I am not in favor of them for that reason.

Testosterone Injections

Testosterone injection produces less stable serum levels. Testosterone has to be injected weekly. There are still a lot of doctors out there who give injections once a fortnight, once every three weeks, or even monthly. That is not correct. Giving 400 mg testosterone all at once is a steroid dose. Serum androgen levels accelerate rapidly, and the men love it for the first four, five, or six days. The problem is that when the serum androgen level is rapidly accelerating, aromatase seems to want get more active, so you end up with a huge boost in estrogen. Estrogen is more persistent than testosterone, so on day six or day seven, testosterone levels are already starting to come down and men notice that. They notice the direction that their testosterone levels are going in as much as what the actual level is. If you give monthly injections the patient will end up spending three of those four weeks bottoming out, and about

half the time with a testosterone level lower than their baseline level. Therefore, it is very important that testosterone is injected on a weekly basis.

Another bonus of testosterone injection is ease of dose titration. We can tweak it exactly as we want to, which makes it very convenient. Of course, it does expose the patient to the risks of everything that is invasive, namely infection and hemorrhage. Even so, I consider testosterone injection to be the gold standard because it gives me so much control over the patient. However, I am not totally comfortable injecting cottonseed oil in the patients, and I do not like the idea of the benzyl alcohol either. Therefore as time goes on, I am getting more and more interested in the transdermals.

Implantable Pellets

Implantable pellets produce stable serum androgens levels, and the rise in estrogen is less because they are so stable, but there is a more serious risk of surgical procedure, and we have had to extrude them from some patients. There is also the added cost of the surgical procedure. I think we should be trained to keep the cost of TRT down. We should be working to bring it to the masses.

The real issue with implantable pellets is the titration difficulties. There is no upfront way to predict what the final dose of testosterone is going to be for any patient at any given time. I have had 150-pound patients take twice the dose that a 300-pound patient did. Even when both of them started out the same baseline and both ended up at the same goal. You have just got to give them some, let it stabilize, draw some follow-up labs, and then titrate and repeat until you get it perfect. If you do put enough in the pellets and your labs come back and testosterone levels are not high enough, what you are going to do? Stick in some more? Then you have got some serious problems. You will have different pellets dissolving at different rates, and different times. What happens if a patient's testosterone level goes too high? And that is going to frequently happen. This is not good for his health. What happens if you put him on testosterone pellets and you see an increase in his PSA? Well, then you have got to dig them back out again. Currently, an increase in acceleration in PSA of about 0.75 is an indication for withholding TRT.

OTHER MEDICATIONS

Human Chorionic Gonadotrophin

Human chorionic gonadotrophin (HCG) is traditionally the treatment of choice for secondary hypogonadism. That makes sense because it has a beta-subunit that closely resembles that of LH. Thus, it directly stimulates the leydig cells that produce testosterone. That makes a lot of sense. The problem in my experience is that patients who are on HCG simply do not derive the same subjective benefits from HCG as they would from TRT. I also feel the same way about selective estrogen receptor modulators (SERMs). For me, the best way to use HCG is to add it to whatever other form of actual testosterone that you are using.

Selective Estrogen Receptor Modulators

A lot of endocrinologists are currently using SERMs for testing the intactness of the hypothalamic-pituitary-adrenal (HPA) axis. But, what does it matter if the treatment is going to be the same anyway? Inhibiting or antagonizing estrogen at the hypothalamus and pituitary does indeed increase testosterone levels as long as there is a coincidental primary hypogonadism. So, the SERMs like Clomid, Nolvadex, and Evista really are for testing purposes only, or for rescue treatment when your patient has what I would like to call nipple issues.

Nandrolone Decanoate

I feel that nandrolone decanoate, or Deca, has no place in TRT medicine. I have yet to look at laboratory printout and proclaim that this patient is Deca deficient. I have had patients who have become impotent for 18 month after one single injection of Deca. I do not think it is funny. Most of the doctors using Deca in TRT these days are basically Internet or steroid-dealing charlatans who are wanting to hook their patients on steroids in order to make money.

CONTRAINDICATIONS AND DRUG INTERACTIONS

The contraindications of TRT are prostate cancer and breast cancer. Relative contraindications are:

- If PSA goes above 4 – and now we are learning to look at rises above 2 or 2½ ; or of course, an acceleration greater than 0.75.
- Polycythemia over 18 or 55.
- Sleep apnea
- Cardiac, hepatic or renal disease.

TRT interacts with several types of drugs. You have to be careful with people taking medication for diabetes. Testosterone is the most profoundly effective drug ever developed for type II diabetes. So, before starting a diabetic patient on TRT you need to remember to reduce their diabetic medications and monitor them much more closely. TRT also increases the clearance of beta-blockers, such as propranolol, and interacts with oxyphenbutazone and anticoagulant drugs.

BASICS OF TRT

Initial Dosage

I like to start my guys out on 5 grams of transdermal testosterone. I have my patients squeeze the gel out into their palm, cuff it in their palm, and then touch their palms together. This way, when you separate your hands, you will have roughly half on each side. I then have them rub it across the shoulder and off and then finish by wiping down the flanks. It is important not to get any in the antecubital fossa.

If they are not comfortable with the transdermals I move them on to an injectable course of TRT. I give my patients 100 mg of IM testosterone cypionate each week. I give them a double dose the first time, and that is known as a front load. This helps the patient to establish a stable serum level a little more quickly. Front loading does not boost estrogen unnecessarily.

Follow-Up Labs

With patients who are using testosterone cypionate, I wait for five or six weeks before I carry out follow-up labs. I am actively engaged in TRT. This is my thing. This is what I do. It is my favorite subject. A non-endocrinologist might prescribe TRT and tell the patient to come back in three months for follow-up testing. My guys want to get tuned up. They wanted to get tuned up yesterday. So, I do my follow-up labs for testosterone cypionate after five or six weeks because that is how long it takes to stabilize serum testosterone levels, and also allow for any HPA-axis suppression to do its dirty work.

With patients that use transdermals I carry out follow-up labs after two weeks. Theoretically, you could run the transdermals follow-up labs after about four days, but it is more important to let the body re-equilibrate itself.

Estrogen Issues

Estrogen management, in my professional opinion, is the new frontier of TRT medicine. I usually do not do anything to treat estrogen until I get to the follow-up labs. I might see a guy come in with his estrogen way at the top of the normal range and you could predict that TRT will boost it higher so that it becomes a little bit over the top of normal range. However, I wait for things re-stabilize before I treat it, because I have seen cases of estrogen actually dropping with TRT. I like to maintain estradiol at mid-range, and if necessary I use anastrozole. I typically start with 0.25 mg every other day and titrate from there.

DHT Issues

DHT is not the evil hormone it is portrayed to be. It may rise with androgen acceleration, but then it drops back down again, and this is especially true in your more senior patients. For some reason, the older guys tend to get bigger spikes of DHT following initiation of the TRT than younger guys do. But, the important thing is that it does drop back down to baseline levels. If DHT levels rise to high, stop giving the patient transdermals and prescribe IM testosterone cypionate instead. I am not in favor of finasteride. There is a growing body of men who are now suffering permanent hypogonadism and/or erectile dysfunction because of finasteride.

THE CRISLER HCG PROTOCOL

The legitimate problem with the injectables is the short half-life of the cypionate ester, which is variable from individual to individual. Thus, we have to inject it every week. We also have the issue of HPA-axis suppression and testicular atrophy – and I do not think that we should ignore that it is an important anesthetic consideration; you are never going to hear a patient tell you that he is glad his testicles are smaller.

To overcome these problems, I have started adding small doses of HCG. A couple of years ago, my thoughts were that HCG was a much more powerful hormone than it was given credit for. A recent study showed that 125 units a day of HCG in completely HPA-axis suppressed patients, brings them almost to baseline. So, in another words, a very small dose of HCG is extremely effective at increasing intratesticular testosterone levels.

I never give more than 500 units of HCG at a time, and I usually give 250 mg of HCG subcutaneously twice a week. There are only so many leydig cells, and therefore you can only stimulate so much testosterone production. And when you go above 500 units of HCG, you do not produce more testosterone, what you actually do is produce a lot more estrogen. You also produce a lot more progesterone. I have seen a study that suggested that HCG may be directly responsible for gynecomastia, and that is another reason why we use very low levels of HCG.

For transdermal patients we add 250 units HCG every third day. Patients who receive IM injections of testosterone cypionate, take a little bit of HCG on day five and on day six, and then on day seven, they are given their testosterone injection. This produces a very stable serum androgen level, which is certainly a goal of treatment. It also prevents testicular atrophy, and it stimulates all three hormonal metabolic pathways. The wonderful thing about HCG is, for some reason, it produces a phenomenal increase in libido in many of your patients and also a sense of wellbeing. I have no proof of it. I suspect, as time goes on, we will find that there are LH receptors in many other tissues in the body. Some LH is actually produced in the brain, and I have read that there may be LH receptors in the periphery of the emotional areas of the brain. HCG is a wonderful drug. But its best use, in my professional opinion, is adjunctively to a testosterone product as well.

Nipple Issues

Sometimes when you put men on TRT they will call you up and they will say their nipples are itching, burning, and/or swelling. Men do not like it when their nipples start itching, and they will complain to you about it. This is not gynecomastia. They are not developing gynecomastia in their first month of TRT. That is not happening. Nipple itching can be caused by very minor changes in hormone levels – even when you are within physiological ranges.

To combat these 'nipple issues' I start my patients on 40 mg of tamoxifen until the issue subsides and then I taper. It is very important to taper. What I do is cut the dose in half every five days, until they are just taking 2.5 mg. I prefer tamoxifen to clomiphene because clomiphene has untoward emotional side effects. Clomiphene makes some men really emotional. For some men this will actually improve their relationship because they become more attentive to their partners. I think that raloxifene (Evista) is probably the best androgen antagonist of the breast, but it is very expensive.

TRT CYCLING

A lot of doctors are cycling TRT. This concept is historically borrowed from steroid use, however there is no benefit, whatsoever, to be gained from cycling TRT. I heard of one clinic that was cycling TRT because they were afraid of causing pituitary calcification. There is one single case study out there documenting pituitary calcification and that was in a steroid user. I am not going to base a whole treatment protocol on that. There is actually no evidence of any benefits whatsoever to having your patients on TRT for three months and then taking them off it and so on. The body thrives on regularity. Cycling is a dirty trick to play on the body. When you change your hormone levels, it is like dropping a pebble in the pond. The ripples extend out to the entire matrix of the endocrine system. There is also no evidence that TRT cycling allows the HPA-axis to recover. There is no evidence of that. All that will happen if you stop TRT is that testosterone levels will return to baseline. All cycling does is provide your patient with substantial periods of let down, and that does not make any sense. Humans thrive on regularity, the best thing you can do is get them tuned up and keep them that way.

CONCLUDING REMARKS

TRT is concerned with the restoration of testosterone to normal physiologic levels. Of the various methods of testosterone delivery available, weekly IM injections of testosterone cypionate is the preferable method because it gives the physician the greatest amount of control over the patient. There is no benefit to be gained from cycling TRT. The body thrives on regularity. All TRT patients need to be monitored regularly, and follow-up laboratory tests need to be conducted every six months.

ABOUT THE AUTHOR

Dr. John Crisler is an Osteopathic Physician located in Lansing, Michigan. He has distinguished himself in the field of Anti-Aging Medicine by developing two new treatment protocols for Testosterone Replacement Therapy. Commanding a substantial Internet following, Dr. Crisler founded the first Internet Forum on HRT for men in the world moderated by a physician. He now enjoys training fellow physicians in this area of medicine, and is known as a dynamic and informative speaker. Dr. Crisler recently delivered the very first lecture ever on male hormone replacement therapy before the Michigan Osteopathic Association at their 2004 Annual Convention.

