MY CURRENT BEST THOUGHTS ON HOW TO ADMINISTER TRT FOR MEN

-A RECIPE FOR SUCCESS-

SECOND EDITION

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We have already learned a practical bit about the various hormones composing the metabolic "symphony" which constitutes our hormonal milieu. We know where these hormones are produced, largely what influences modulate their production, as well as the target tissues of their various and varied actions. But we still need to integrate this knowledge into a practical "recipe", if you will, to enable the clinician to return to his/her practice, and immediately begin screening for, and successfully treating, male hypogonadism. In other words, how do we administer Testosterone Replacement Therapy (TRT) for men?

Should EVERY adult male patient who presents at your office be automatically screened for hypogonadism? About half of all men over the age of fifty are in fact hypogonadal (when tested for Bioavailable Testosterone—more on that later). Certainly the responses to Medical History will lead the way toward suspicion of same, yet subjective complaints related to this insidious condition are sensitive without being specific. Clinical suspicion is further clouded because there is no way to correlate either the number of individual complaints, or the relative magnitude of each, to the severity of the hypogonadotropic state upon laboratory assay. Additionally, the foibles of laboratory analysis--either due to variability of hormonal production or inaccuracy unavoidably inherent to testing methodology—renders evaluation of hormonal state, at times, more an art than science.

The number one complaint which should hoist the proverbial red flag is Erectile Dysfunction. Lack of libido is simultaneously superior in sensitivity and specificity. This is also the symptom of hypogonadism which, aside from all the seriously deleterious effects of same (cardiovascular disease, diabetes, osteoporosis, increased risk of cancer, depression, dementia, etc.), is most likely to bring the patient to actively seek TRT—and to remain compliant in your subsequent treatment regimen. As I told writer Pat Jordan, for his article named after me in *Playboy* Magazine, "Dr. T to the Rescue" (April 2007) "As long as you treat his sexual function, a man won't mind you also made him healthier". What Mr. Jordan printed: "You know, it is all about sex".

INITIAL LABWORK

Following a good Medical History, which laboratory assays should be run as part of your initial hypogonadism workup? Following is my list, but certainly other specialists in this area run expanded or attenuated panels, per individual clinical experience and expertise. Of note, additional tests which should be included to complete the true comprehensive Anti-Aging Medicine workup (i.e. inflammatory markers, insulin, good and true comprehensive thyroid study, etc.); this chapter is concerned solely with administering TRT. And as always, the panel is tailored to the individual patient. Here they are:

- Total Testosterone
- Bioavailable Testosterone (AKA "Free and Loosely Bound")
- Free Testosterone (if Bioavailable T is unavailable)
- SHBG
- DHT (perhaps)
- Estradiol (specify "sensitive" assay for males)
- LH
- FSH
- Prolactin
- Cortisol
- Thyroid Panel
- CBC
- Comprehensive Metabolic Panel
- Lipid Profile
- PSA (age dependent)
- IGF-1, IGFBP-3 (if HGH therapy is being considered)

FOLLOW-UP LABS

Four weeks after initiating or changing dose for transdermal, six weeks for IM injection TRT. The time delay provides for stabilization via HPTA suppression and pharmacokinetics of medication:

- Total Testosterone
- Bioavailable Testosterone
- Free Testosterone (if Bioavailable T is still unavailable)
- Estradiol (specify "sensitive" assay for males)
- LH
- FSH
- CBC
- Comprehensive Metabolic Panel
- Lipid Profile
- PSA (for those over 40 with Family Hx of prostate CA, >45 yo. all others)
- IGF-1, IGFBP-3 (if GH Therapy has been initiated already)

INDIVIDUAL ASSAYS EXPLAINED

TOTAL TESTOSTERONE

This is the assay your patients will most focus on, as will clinicians unpracticed in the art. Physicians who do not understand sex hormones will deny patients the testosterone supplementation they want--and need!--when Total T is at low-normal levels. Total T is important for titration of dosing, but its relevance is reduced in older men, by virtue of their increased serum concentrations of SHBG (and therefore lowered Bioavailable Testosterone), in favor of:

BIOAVAILABLE TESTOSTERONE

Where we get the "bang" for the hormonal buck, so to speak. This is the actual amount the body has available for use, as the concentration of hormone available within the capillary beds before the androgen receptor approximates the sum of the Free Testosterone plus that which is loosely bound to other carrier proteins in the blood, primarily albumin. If Bio T is not readily available, Free T may be a second choice substitute, as Bio T and Free T serum concentrations are *usually* well correlated. Bioavailable Testosterone is the gold standard for serum androgen evaluation.

DHT

This assay *may* be of value to draw, up-front and at follow-up, if a transdermal testosterone delivery system is preferred by the patient. I'll explain why later. DHT level may also help explain cause for ED symptoms. Experience drawing serum DHT, compared to urinary DHT and intracellular 5-AR metabolites, may show compartmentalization of same in difficult cases.

Instances where patient subjective report is very positive in the face of stable (or even reduced) Total T levels, status post initiation of TRT and compared to baseline, may be explained by increases in DHT; we must keep in mind it is three times more androgenic than testosterone. Of note, I do not believe placebo effect exists for TRT.

I do not consider DHT an "evil" hormone; finasteride and drugs of that class are to be avoided.

ESTRADIOL

There are several reasons why this assay is VERY important, and should not be ignored in ANY hypogonadism work-up (or subsequent regimen). First, you definitely need to draw a baseline. There are cases where T is adequate, yet E elevated or merely disproportionate. Elevated estrogen (in absolute value or proportion) can, in and of itself, explain hypogonadal symptomology. If E is elevated, controlling serum concentrations (usually with an aromatase inhibitor, which prevents conversion of T into E; or withdrawal of estrogen mimics such as soy or flax seed) may, in very rare cases, suffice in clearing the symptoms of hypogonadism. And finally, rechecking estradiol after beginning the initial dose of testosterone will give the astute physician valuable information as to how the patient's individual hormonal system functions, as well as making sure estrogen does not elevate inappropriately secondary to testosterone supplementation. This provides a very rough form of receptor mapping, if you will.

E2 is the major player of interest in foundational TRT. Evaluation of the other members of the hormonal class "estrogen" (E1, E3, as well as other estrogen metabolites), via 24 hour urine panel, may help explain gynocomastia or water retention in the face of acceptable E2, indicate relative cancer risk, etc.

Unless you specify a 'sensitive' assay for your male patients, the lab will default to the standard estradiol designed for females, which is useless for our purposes here. I have run the standard assay and the sensitive assay concurrently on a number of my patients, and the two results may be as night and day. However, patient symptomology is best described by the sensitive assay. The reason is the bell curve from which the test is designed sits well within the "normal" range for females; therefore the hormonal concentration range appropriate to adult males falls on a very flat slope of said bell curve. The same holds for Total Estrogens. Laboratory testing is best when small changes in concentrations result in large changes in subsequent reported result.

Some practitioners believe it is only the T/E ratio which is significant, and therefore, as long as E only "appropriately" rises with elevations in T, all is well. However, the absolute concentration of E is of concern, too, especially in light of new information pointing to elevated estrogen as cause, or adjunctively encouraging, several serious disease processes, including numerous cancers, as well as significant potential for induction of sexual dysfunction (no matter the accompanying androgen load). Therefore T/E ratio is only useful for describing the cause of symptoms, not as a treatment goal.

Estrogen is absolutely necessary for our physical health. Of note, same also provides the emotional component of a mature gentleman's sexual being. This is why estrogens must be evaluated and, when necessary, controlled. The "sweet spot" E concentration depends upon SHBG. Rule of thumb is mid-range for both.

LH

As everyone knows, it is Luteinizing Hormone (LH) which stimulates the Leydig cells of the testes to produce testosterone. A caveat, however: LH has a half-life of only minutes. When you combine this fact with the absolute pulsatile nature of its pituitary release, care must be taken to avoid placing too much weight upon a single draw. A luxury would be to acquire serial draws. However, such would be both inconvenient and probably prohibitively expensive for the patient. Therefore a single LH assay serves only as a proven example of just how much LH the pituitary *can* produce. The most important reason to assay the gonadotrophins is to differentiate between primary and secondary (hypogonadotropic) hypogonadism. This is especially true when a HPTA-recovery protocol, to "restart" LH production, is desired (the details of which remain beyond the scope of this document) secondary to anabolic steroid or prohormones use, as well as other hormone disrupting influences.

Rapidly attenuated LH can serve as proof a transdermal testosterone preparation is indeed penetrating. This can be quite valuable information in confusing cases, especially when the preferred 24 hour urine panels are not available.

FSH

The hours long half-life and less pulsatile production of Follicle Stimulating Hormone (FSH) makes it a better marker for gonadotropin production, at times, when evaluating HPTA activity. It is less an acute phase reactant to varying serum androgen and estrogen levels than LH. Greatly elevated FSH levels could signal a gonadotrophin-secreting pituitary tumor.

FSH also provides valuable information for those patients undergoing TRT who are interested in the state of their fertility. Of note, while there are never guarantees where fertility medicine is concerned, I do not believe appropriate TRT will make a fertile man infertile. Constitutive expression is maintained.

PROLACTIN

A very important hormone, and must not be overlooked on initial work-up. Approaching five percent of hypogonadotrophic hypogonadism is associated with hyperprolactinemia, due to inhibition of hypothalamic release of LHRH. Its serum concentration must be maintained within physiological range (meaning neither too high NOR too low). Greatly elevated hyperprolactinemia, or hyperprolactinemia plus a Total Testosterone less than 150ng/dL, equals a trip to an Endocrinologist for a pituitary MRI.

CORTISOL

True Anti-Aging medicine must be well-familiarized with the ins and outs of this hormone, the only one our bodies cannot live without. Elevated levels can cause secondary (hypogonadotropic) hypogonadism. I try controlling elevated cortisol with Phosphatidylserine, 300mg QD, with good results. It is just as important to watch for depressed or inappropriate cortisol production, AKA Adrenal Fatigue, as well. The assay of choice for that condition is a 24-hour urine, via summation of cortisone and adrenal metabolite production.

THYROID PANEL

I have, for my own convenience, omitted the specifics of the obligatory thyroid function panel you certainly will want to run. Besides the fact thyroid is intimately associated with every function of the body, hormonal and otherwise, (even subclinical) hypothyroidism mimics hypogonadism in several of its effects.

CBC

This is just good medicine. Ruling out anemia is important, of course, as it may be cause for the fatigue which drove the patient into your office. You also want to establish baseline H/H, for the small portion of cases where polycythemia becomes a problem (and we are reminded smokers and sleep apnea sufferers are at increased risk for polycythemia). Above 18.0/55.0 TRT is withheld, and therapeutic phlebotomy recommended.

CMP

Again, just good medicine. Baseline for sodium (which may elevate initially secondary to androgen supplementation) is important. We also want to see LFT's, as elevations in same secondary to androgen supplementation are listed as a possible side effect in the product literature--although I have yet to see this actually happen. I like the BUN/creatinine ratio as marker for hormonal hemo-concentration, and also it gives me a hint of how compliant the patient will be (because I always tell them to make sure to drink their normal "plenty of water" while fasting for the test). Of note, many of my patients consume prodigious amounts of protein each day, due to muscle building interests or specialty dieting, and this is remembered while reading BUN concentration.

Lipid Panel

This is drawn to provide your bragging rights when you drop the CHOL significantly, thanks to your own good administration of TRT. You should expect to see lowered TRIG and LDL's, too. Be advised, this will not happen if you choose to elevate their androgens above the top of "normal" range, i.e. providing what amounts to an anabolic steroid cycle. Of course, this would no longer constitute TRT, as the practitioner is then choosing to damage the health and well-being of the patient.

HDL does frequently drop a bit, is believed due to increased REVERSE cholesterol transport. Androgens also elevate hepatic lipase, and this may have an effect. The important thing to keep in mind is that TRT inhibits foam cell formation. For these reasons I provide my TRT patients a free 10-12 point bump in HDL evaluation.

PSA

For all patients over 45, and over 40 if Family History of prostate cancer. Even though prostate CA is rare in men under the age of fifty, we don't want it happening on our watch. At this time, accelerations in PSA above 0.75 are a contraindication to TRT (until follow-up by an Urologist). You may find, at the initiation of TRT in older men, when serum androgen levels are rapidly rising, PSA may, too. This is especially true when transdermal delivery systems are employed, because they more elevate DHT. Once T levels have stabilized PSA drops back down to roughly baseline. New TRT patients need to be cautioned, and reminded, to abstain from sexual relations prior to the draw, as they may now be enjoying greatly elevated amounts of same.
I get a PSA up front on my over 40 patients, at the one month follow-up in my more senior patients, and every six months after that. DRE (Digital Rectal Exam) is recommended twice per year as well, although the American Academy of Clinical Endocrinologists backs "every six to twelve months" in their 2002 Guidelines for treating hypogonadotrophic patients with TRT.

IGF-1

For those who are considering the addition of GH to their Anti-Aging regimen. IGF-1 will rise somewhat from testosterone supplementation, and vice versa. Let's grab a baseline now, before that happens. Current thinking is to also assay IGFBP-3.

THINGS TO LOOK OUT FOR

CO-MORBIDITIES. Only breast and active prostate cancer are absolute contraindications for TRT, at this time. Patients with serious cardiac, hepatic or renal disease must be monitored carefully; this is true for any medical therapy, of course. Also, TRT may potentiate sleep apnea in some chronic pulmonary disease patients, although studies have also shown it can actually ameliorate the symptoms of same as well.

DRUG INTERACTIONS. TRT decreases insulin or oral diabetic medication requirements in diabetic patients. Therefore make sure to warn them to closely monitor their sugar. It also increases clearance of propranolol, and decreases clearance of oxyphenbutazone in those receiving such medications.

TRT may increase coagulation times as well. This is minimal, and easily accounted for by proper pre-surgical evaluation. The reverse risk of *increased* coagulation that terrifies surgeons and anesthesiologists results only in cases of severe polycythemia secondary to non-monitored TRT. Again, proper work-up removes risk. On this topic, I am absolutely amazed when surgeons, anesthesiologists, cardiologists, etc. hold TRT prior to their own labors. Let's take inventory of the results of their misguided actions: anabolism turns to catabolism, inflammation runs wild, weakness and fatigue, estrogen goes through the roof, depression, etc. as the body is generally thrown into a state of turmoil. Just what you want while undergoing surgery or an MI! Cases where "specialists" actually consult with the qualified administering physician are rare. Not only is this profoundly detrimental to the patient, same is also a gross violation of medical ethics.

TESTOSTERONE DELIVERY SYSTEMS

Now we have to decide, TOGETHER with our patient, what form of testosterone delivery system we will START with. There are two basic subsets of same—transdermals and injectables. Here are the current options:

TESTOSTERONE GELS AND CREAMS

The only way to go, in my professional opinion, if physician and patient agree on a transdermal (TD) delivery system. Or TRT *at all*. As I have gained knowledge and experience, my position is now that TD's are vastly superior to other modalities in TRT medicine. They are easy to apply, usually well absorbed, and rapidly establish stable serum androgen levels (by the end of the third day). I recommend all practitioners first try a testosterone gel for their TRT patients. Gels are better than creams, as I want the rapid T uptake into the dermal layer, which serves as reservoir for distribution throughout the day. Men do better on lower serum T levels on TD's than IM.

The constant variability of serum androgens provided by T gels mimic the hormones of a young man; the stable daily level provided by T injections mimic the hormones of an old man; those of implantable pellets mimic the hormones of no one. Entropic hormone levels are part and parcel of the process of youth.

Much is made of the risk posed by accidental transferal of testosterone to others, such as children or sexual partners. Simply covering with a T-shirt has been shown to block transfer of the hormone. The testosterone sinks into the skin within an hour. One may shower, or even swim, without worry, usually after four hours. I remind my patients most of us have neither the time, nor the opportunity, for romance until evening (given the usual early morning application), and a quick shower is always nice for a gentleman to "freshen up" prior to same.

Gels and creams, like all transdermal delivery systems, provide a greater boost in DHT levels, compared to injectable testosterone preparations. As DHT is responsible for all the things of manhood--literally, AllThingsMale--the transdermals are better at treating sexual dysfunction than are injectables. However, issues of hair loss (which I treat with a compounded topical DHT blocking mixture) and possible prostate morbidity (a contentiously debatable point, to be sure, but resolved in the negative to my mind) then come into play. This might be a good time to mention I vehemently oppose adding finasteride or similar medication.

To end the debate on this topic, transdermal T gels/creams are more likely to elevate estrogen than injections, as long as the shots are properly administered once per week. That is because aromatase lives in the skin, along with higher concentrations of 5-AR, which converts T to E. Even so, the benefits of TD TRT outweigh the weekly convenience of shots.

Some have reported an increase in hair growth over the application area(s). All physicians who administer TRT must be prepared to disappoint their patients at this time by pointing out, sadly, this same effect cannot be achieved upon the scalp.

TESTOSTERONE PATCHES

These can be effective, however many find inconvenient to use. Approaching 2/3's of your patients will develop a contact dermatitis from them at some point. Another drawback is some patients report they are constantly aware of their placement, and the patches are embarrassingly obvious to other gentlemen in certain public places, such as the locker room.
The scrotal application variety is the most inconvenient. To see what I would be putting my patients through, I tried one. By the middle of the first day, I had more than enough. Most men generally do not enjoy shaving their scrotum. If you go to the gym during the day, they look strange affixed to the genitals, and must be removed, then reapplied, when showering. They do not adhere well in the first place, and even less so once they have been reapplied. Applying a hair dryer to the patch, as they must be warmed first, is also an annoyance, and generally not the type of activity relished in the locker room. Of the two options, I found only the type with the extra adhesive had any chance of remaining in place. The scrotal variety causes the largest increases in DHT—which can be good or bad, as previously explained (this might be a good time to mention I never recommend applying a TD gel to the scrotum).

TESTOSTERONE PELLETS

In my opinion, their use is absolutely Stone Age. Granted, they can provide extra revenue by virtue of a billable office based procedure. However, needlessly exposing patients to the risks ALL surgeries pose—hemorrhage and infection—is unwarranted. Some have issues with pellet

extrusion, but same is highly dependent upon clinician's technique. And the area of insertion will be much tenderer than that following a mere IM injection. But the real issue which selects against pellet implantation is concerned with dosing. Let's say you attempt to establish a "usual" initial dose for the pellets. As will be described in the next section, there is absolutely no way to predict, up front, how a patient will react to a given dose of testosterone, regardless of the delivery system, or patient's body weight, activity level or composition. So you bury these pellets in your patient's backside, and (hopefully) draw follow-up labs in a month or so. What are you to do if the total testosterone ends up greatly exceeding the top of normal range (meaning the patient hyper-responded to the treatment)? And what if the pellets do not elevate T enough? Will you bring them back in to implant more? It may be difficult to sell them on this idea, since they probably are not yet feeling the advantages of TRT enough yet to motivate them into undergoing another surgical procedure. It just doesn't make sense, to my way of thinking. Worse, what if follow-up assay demonstrates markedly elevated DHT? Think about it.

Testosterone pellets do have some benefit in that selected patients may believe it more convenient to come in at longer interval, and then be done with it for a while. If your patient is on his way to conquer Mt. Everest, or extended safari, then TRT via pellet implantation is preferable to abstinence from TRT at physically challenging times.

TESTOSTERONE INJECTION

I'll start out by describing the drawbacks of IM testosterone. They are inconvenient for patients who do not wish to give themselves their own injections, as they must then make weekly trips to your office for same. Why IM test MUST be dosed weekly will be described in detail in another section. And this TRT modality represents hundreds of holes poked in their body over a lifetime. Some patients, as you well know, just hate shots (although I have noticed patients who had initially claimed this, but admitted, once they had come to enjoy the benefits of TRT, came to very much look forward to their shot day). And no doubt an invasive delivery system brings more risk than, for instance, a testosterone gel or cream (the best choice for TRT), although I have yet to hear of a single bad outcome from any of the tens of thousands of IM injections my patients have self-administered.

As a good and proper Osteopathic Physician, I am loath to introduce any substance to the body not absolutely necessary. Therefore the oil and preservative necessary to the injectable preparation are best avoided when possible, in my professional opinion.

When considering dosing of testosterone cypionate, it is important to remember that, due to the weight of the cypionate ester, a 100mg injection delivers, at best, 70mg of testosterone. This is important to keep in mind when comparing the effects of a 100mg weekly injection of test cyp to the 35mg total initial dose provided by Androgel/Testim 5gms QD over the same period.

HCG

Many practitioners consider this incredible hormone treatment of choice for hypogonadotropic (secondary) hypogonadism. Such certainly is intuitive, as supplementing with a LH analog indeed increases testosterone production in patients who do not concurrently suffer primary

hypogonadism. But for some unexplained reason, while serum T levels may be adequately elevated, the patients simply do not report realization of the subjective benefits of TRT, when HCG is administered as sole TRT. You also run the risk of inducing LH insensitivity at higher dosages, and therefore may actually cause primary hypogonadism while attempting to treat secondary hypogonadism. HCG, especially at higher doses (defined as >500IU per shot), also dramatically increases aromatase activity, thus inappropriately elevating estrogens. Progesterone—a feminizing hormone in adult males—also elevates at those dosages. Personally, I recommend giving no more than 100IU of HCG per day, as starting dose. And please give it some time to work.

A real benefit of HCG is that it will prevent testicular atrophy. I do not think we should ignore the aesthetics of that consideration. Your patients will feel the same way. I have provided a paper detailing some of HCG's amazing benefits for TRT medicine at http://www.allthingsmale.com/publications.html.

OTHER MEDICATIONS

I occasionally hear of physicians trying to use a SERM (Selective Estrogen Receptor Modulator) such as Clomid or Nolvadex, or even an Aromatase Inhibitor (AI), such as Arimidex, as sole "TRT". All have been shown to elevate LH, and therefore Total Testosterone levels. However, patients usually report no long-term subjective benefits from these strategies. An added risk of using an AI is of driving estrogen levels too low, with deleterious consequences for the lipid profile, calcium deposition, endothelial function, libido, etc. The real problem with using these non-testosterone preparations as "TRT" is we do not know what they will do long term.

Finally, Deca-Durabolin (nandrolone), or Winstrol (stanozolol) have no place in TRT medicine. Deca has a nasty side effect profile, including uncontrollable progesterone-like effects (including gynocomastia), profound HPTA suppression, and substantial risk of long-term impotence. And there is no medical indication for the attainment of large amounts of muscle mass, other than in documented cases of wasting disease. Use of the word "steroid" should be avoided in our field.

A FEW WORDS ABOUT LABORATORY ANALYSIS

The best matrix for following transdermal TRT is the 24 hour urine panel. Graphing the serum levels status post application shows why. The best time to draw a serum sample is two hours after application—even that is highly variable. However, a 24 hour urine panel catches all (for practical purposes) the T absorbed, and its metabolites, thus basically providing the area under the curve. Thus we are not merely taking snapshots on a roller coaster of serum T levels.

The astute practitioner must keep in mind proper assay evaluation in TD BID regimen. Serum T levels will appear artificially low with same because only half the daily dose is being measured. Of course, 24 hour urines are free of this, as they catch the area under the curve for the entire day.

I prefer serum testing when following IM TRT. Try to have the patient draw on the same day of the injection week each time. A draw on the second or third day will yield peak values, by the

pharmacokinetics of the cypionate or enanthate ester involved. Patients are more likely, when given the choice, to go in on the last day, because they believe the physician does not understand this is the lowest serum concentration of the week and will therefore increase their dose. Any time the last half of the week is fine with me.

Always test the patient where he lives. That means drawing serum sample within six days of the IM injection, and as close to two hours (to catch the peak). Do not add in HCG to the regimen, or use it the week of the labs during IM TRT, so as to assess testosterone delivery, without clouding the picture.

Once the patient is all set, I like to run follow-up labs every six months. It is important to monitor the general health and well-being of the patient, but also insure compliance with treatment protocols and continued effectiveness of same.

THE MEAT AND POTATOES OF TRT

Now we will delve into the general strategy for administering TRT.

The decision is made, TOGETHER with the patient, as to which of the various testosterone delivery systems is tried first. Be prepared to make adjustments, and try other application methods if necessary. You just don't know which will be best for each particular patient until you try. Besides the simple fact the patient may have a personal preference, or a logistical consideration (i.e. unwillingness to self-inject, or extreme risk of accidental transfer to a female partner who may be/become pregnant) for a given application, every-body reacts differently to hormonal manipulation. Some hyper-respond to a given initial dose, others show hardly any bump in serum T levels on same. Yet when you switch to a different delivery system, on initial dosing, they may convert to supraphysiologic androgen levels. The same is true of the subjective benefits from TRT. I have patients who love testosterone gel because it successfully treated their ED (the expected outcome because of dramatically increased DHT production), others get more from IM testosterone cypionate. My experience thus far has taught me two lessons: (1) You don't know how a patient will react to a given dose/system until you try and (2) NOTHING surprises me anymore.
The question of which testosterone delivery system is to be tried first (IM or transdermal) is one which brings much confusion amongst beginning practitioners of TRT. I would, when possible, always start out a patient on a testosterone gel. Ease of application, avoidance of intrusion by injection, and increased probability of successful ED treatment make this so. Also, stable serum levels are attained quickly, determination of successful treatment is more forthcoming (although the manufacturer of this product recommends at least a couple months as adequate trial of therapy). If the labs AND patient's answers to follow-up subjective report lead to a change to IM testosterone, the conversion is an easy one to make. Simply apply the gel, give the shot, then D/C the gel. However, if a patient is started out on IM test cyp, for instance, yet the patient still does not feel "right", given the pharmacokinetics of the testosterone ester, going to safely and successfully dose the conversion to a transdermal? Care must be taken to not overindulge serum androgen levels. Anabolic steroid-like serum levels may "spoil" the TRT patient, and subsequent subjective expectations needlessly inflated.

There simply is no way to predict how a particular patient will respond—not Medical History (i.e. number or severity of symptoms), body weight, baseline hormone levels, even anabolic steroid history. I have had very slight gentlemen barely elevate on 100mg of test cyp per week, and massively muscled former steroid athletes who went to nearly two times the top of "normal" range on the same dosage (they had similar baselines). Likewise, one man may see only a modest increase in DHT on 5gms of Testim/Androgel, another may become quite supraphysiologic on same.

In most cases, I start my guys out on either testosterone cream/gel 5mgs QD or testosterone cypionate 100mg per week. The IM test cyp must be administered in weekly injections, as opposed to taking twice the dosage every other week. Some physicians even dose every third or fourth week, producing wide swings in serum androgen levels. Where else in medicine do physicians dose medications completely void of consideration for the pharmacokinetics of same? This puts the patient on an emotional roller coaster, increases the risk of developing polycythemia, greatly accentuates aromatase activity (and therefore unnecessarily elevated E production requiring expensive aromatase inhibition), and actually leaves them lower than they were when they started for the last half of the injection "cycle".

In order to get the serum androgen concentration to a stable level more quickly, I usually "frontload" 200mg the first injection (unless converting over from a gel/cream, then sequential taper of both preps is affected).

No other medications which manipulate hormone levels are provided until follow-up labs are returned (i.e. aromatase inhibition). For IM test cyp patients, the second panel is run following the sixth injection. I also keep in mind the coordination of the injection with the lab draw, as peak serum levels are attained at about the 48 hour point, then fall as the week goes on.

Transdermals can be rechecked in as early as two weeks, but a full month provides complete stabilization. TD's produce stable serum levels, as previously mentioned, for most by the end of the second or third day. Logistically, it makes sense to send the patient for follow-up labs after a fortnight, as there is then time to get the labs back, and bring the patient in, before the initial 30-day supply of the medication runs out. This is better if an adjustment in dosage is mandated by the follow-up labs. When TD's fail to produce appropriate rises in serum androgen, especially when verified by 24 hour urine testing, look to thyroid function, particularly low/low-normal Free T3.

Dosing changes are made, TOGETHER with the patient, once follow-up labwork is back AND the patient is interviewed regarding their subjective reports of changes in libido, sexual performance, fatigue, strength, mental outlook, etc. Do not allow them to see their labwork prior to your interview, as doing so may artificially influence subjective report. Besides, lay persons are not qualified to interpret laboratory results—no matter what they think.

Often they will tell you they felt "incredible" the first couple of weeks (and bursting with libido), but they don't feel quite as good now, but still much better than before they started the TRT. This is because subjective findings are the best while serum androgen levels are accelerating. Adjunctive to this phenomenon is the fact their HPTA was not yet suppressed, so their endogenous production was higher then than it would be by the end of the month, and there is a burst of dopamine playing

to upregulated dopamine receptors in the first days as well. TRT patients are always HPTA suppressed to greater or lesser degree. And estrogen may not have risen yet, so same is not masking the benefits of the testosterone supplementation.

Much weight is placed upon the patient's subjective findings, as they are not likely to remain compliant in the TRT program unless they feel noticeably better, irrespective of the much less obvious long term improvements in health. Certainly, if the patient reports they are quite happy at a Total Testosterone level of 600ng/dL, I feel there is little reason to increase their dosage. As a practical limit, the top of "normal" range for Total Testosterone provides a ceiling, more or less, above which we can expect to find the benefits of TRT beginning to reverse them. Actions following androgen receptor binding dramatically improve health and happiness as we go from the hypogonadal state to the top of "normal" range, but beyond that the Lipid Profile and level of insulin sensitivity, for instance, are damaged.

Changes in IM dosing are made in small increments, as response to same is not linear. It is convenient and practical to increase, or decrease IM dosing by 20mg at a time, as this is one "tick mark" on the side of the syringe (for the 200mg/mL concentration) for the patient. For Androgel/Testim patients, we are more limited by their provided dosing, whereas more flexibility is provided through compounded products for those committed to employment of transdermal testosterone delivery systems.

As previously mentioned, another risk of jumping the dosage too much is that, should serum androgen levels greatly exceed the top of "normal" range, the patient risks becoming "spoiled" at that level. They would then feel the subjective benefits steroid athletes report, and it would be difficult to get the patient then to be happy at a more moderate—and proper—dose. It is likely you would also therefore produce elevated estrogen activity as well, and further muddy the waters with respect to how the patient feels—and looks (due to emotional changes and even water retention issues from the elevated estrogen). It is far better to make changes in dosing conservatively.

If by laboratory assay AND subjective report from the patient, you may need to address any side effects due to elevated estrogen levels which have occurred. I do not use an AI initially, even when E2 is elevated, because some patients will actually see a drop in estrogen over baseline on follow-up. We would have otherwise added an unnecessary (and relatively expensive) medication. Should the patient develop any "nipple issues" secondary to accelerating serum androgen levels and/or elevated estrogen, you cannot start them on a SERM right away because doing so will invalidate your estradiol assay at follow-up. Of note, males can experience said "nipple issues" even while estrogen levels are within physiological range, due to mere changes in hormone levels. A drug of the class SERM is treatment of choice in this case, until symptoms subside. I do not favor SERM's long term, even though they have been shown to elevate T levels, because we simply do not know what they do long term. Reassure your patient he will not grow breasts in one month.

If a patient has "nipple issues", even while estrogen is within normal range, I add a SERM, emergently. I prefer Nolvadex over Clomid. Clomid often induces untoward visual effects (i.e. "tracers"), and can cause emotional lability by virtue of its estrogen agonistic effects at the more peripheral (emotion) brain sites. Nolvadex is then initiated, should they experience nipple swelling

or sensitivity, at 40mg per day until the symptoms abate, and then taper down 10mg every 10 days to discontinue.

My TRT male patients who suffer E2 elevations above the top of normal range are placed on between 0.25 and 0.5mg Arimidex every one to third day, depending upon the specific situation. It is possible to cut the tiny 1mg tabs into quarters, but here a compounded prep, to convenient dosing, makes a lot of sense. A month later I recheck E2, (as subsequently lowered SHBG will affect subjective response as well) and make further adjustment if necessary. Always remember it is important to not lower estrogen too far.

So now let's say we have the patient in a state where Total Testosterone is in the upper quartile of "normal" range, Bioavailable Testosterone is nicely elevated, with E2 safely in check. At this point I offer the patient my HCG protocol. I add in 250-500IU of HCG, on day five, and day six, of the injection week, for those who use the IM injection. In other words, the two days prior to their test cyp shot. For those using a transdermal delivery system, 100-250IU SC (HCG is best administered subcutaneously) every one to third day. For the IM patients, this compensates for the drop off in serum androgen levels by the half-life of the test cyp.

Patients nearly always report they feel dramatically better once the HCG regimen is initiated (and they were properly tuned up on testosterone before they started it). HCG, as a LH analog, increases the activity of the P450 SCC enzyme, which converts CHOL to pregnenolone. Thus all three hormonal pathways are stimulated in patients who may be either entirely, or very nearly, HPTA suppressed. It is my belief this may be a factor in the heightened sense of well-being my patients report throughout the week—far in excess of what a nominal dose of HCG would produce by virtue of induced testosterone production.

Many TRT practitioners add in HCG for a short course every few months, to re-stimulate the testes. My opinion is that it is far better to keep them up to form and function all along the way. The physicians who intermittently use HCG also use it as a "break" in TRT, much the same way hormonally-supplemented athletes manage the typical anabolic steroid cycle. TRT should not be "cycled". Once I get my patients properly tuned up, I want them to stay that way. They also erroneously believe this allows the HPTA to recover, when it clearly does not. The HCG-induced testosterone production is every bit as suppressive of the HPTA as the TRT, and the supplemented testosterone is still at suppressive serum levels during that time, anyway.

I nearly always add HCG, DHEA and pregnenolone to the TRT regimen. Inserting these hormones helps restore natural hormonal pathways, "backfilling" them, if you will, once we have suppressed the HPTA with TRT. We will probably never know all the intermediary steps in these pathways, much less all the actions of each substance upon the body. In my professional opinion, this is the current state-of-the-art in TRT medicine.

My hope is the preceding diatribe will gainfully assist the practitioner in implementing Testosterone Replacement Therapy regimens for their qualifying patients. Be prepared, however, to blush as they shower you with accolades following their vast improvements in health and happiness. You may even receive thank you notes from their wives!

Please watch for coming articles and books by John Crisler, DO on this, and other, continuing subjects related to Anti-Aging Medicine.

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