

TESTOSTERONE REPLACEMENT IN FEMALE CHRONIC PAIN PATIENTS

Since testosterone assists opioids in crossing the blood brain barrier and helps activate a number of central receptors and neurochemicals systems, it is a judicious, ethical, and clinically necessary practice to replace testosterone in female chronic opioid patients—subject to informed consent.

By Forest Tennant, MD, DrPH



Testosterone suppression is well known to occur in chronic pain patients who must regularly take opioids.^{1,2} Replacement of testosterone in male chronic pain patients is now commonplace. To date, however, testosterone replacement in female chronic pain patients is not routine and practitioners are just beginning to recognize the needs and merits of doing so.^{3,4}

Reported here is the female testosterone replacement procedure used by the author. A patient education handout and an off-label consent form is included which practitioners may adopt if desired. Since there is no commercial FDA-approved testosterone product for females, physicians should systematically prescribe testosterone to female patients by diligently providing information about risk-benefit and carefully documenting a need for testosterone replacement.

Symptoms Of Testosterone Deficiency

Pain patients who are being routinely followed may slowly but progressively develop testosterone deficient symptoms (see Table 1). While loss of libido is the

best known of testosterone deficiency symptoms, there are many others.⁵ Testosterone has some critical biologic functions very relevant to pain treatment.^{6,7} Testosterone is a major anabolic compound both in females and males and, therefore, has a major healing and pain reduction function in long-term pain care.⁴ Testosterone levels are apparently necessary for proper transport of opioids across the blood brain barrier and for opioid receptor-site binding.^{6,8} Consequently, adequate levels of serum testosterone are necessary

TABLE 1. Some Symptoms of Testosterone Deficiency

- Lack of energy
- Loss of libido
- Depression
- Poor healing
- Diminished opioid effects
- Loss motivation
- Apathy

for maximal opioid effectiveness. Other central effects are more subjective, but testosterone deficiency is associated with depression, fatigue, apathy, and loss of motivation.

Patient Education

Females, as well as males, need to be educated about the need for adequate serum levels of testosterone. Table 2 presents an educational handout which can be given to all female pain patients. Since testosterone replacement in females is a new procedure and obviously controversial, it is deemed important that practitioners educate all parties on the benefits and necessity of testosterone replacement. Many parties are not even aware that females normally carry a serum concentration of testosterone that is about 15 to 25 % of that in the male. Furthermore, adequate serum testosterone levels in female pain patients is critical for maximal pain control.

Stepwise Guidelines For Replacement

If symptoms of testosterone deficiency are present in a female chronic pain patient,

TABLE 2. Sample Patient Education Handout

TESTOSTERONE INFORMATION FOR FEMALE CHRONIC PAIN PATIENTS

One of the major complications of intractable pain and opioid treatment is a decline in body testosterone levels.

The symptoms of low testosterone, in women and men, are as follows:

1. Fatigue
2. Depression
3. Opioid medication less effective
4. Decrease in libido
5. Loss of motivation and interest in life
6. Poor healing

If you are experiencing the above symptoms, you should have your testosterone blood level checked. This is done by a single blood test taken at anytime of day. The laboratory will determine if you are deficient.

If you are deficient in testosterone, you will be given a low, test dosage of testosterone to determine if your symptoms are caused by testosterone deficiency. If your symptoms improve, you will need a course of testosterone. The dosage you will receive is a fraction of the male testosterone dosage.

After you have taken testosterone for a few weeks, your blood level of testosterone will again be tested to determine if you need to continue it.

At this time, there is no known risk to taking a low dose of testosterone providing your body is deficient. Although, no risk is known to occur in female pain patients who take low dosages of testosterone, it is recommended that you do not take testosterone every day and periodically (e.g., every 3 months) stop taking it for a few days.

obtain a serum testosterone concentration. Laboratories now report normal ranges for serum testosterone in females as well as males. If the female patient demonstrates a low or borderline low level, I give a test dose of intramuscular testosterone ranging from 25 to 50 mg. This test dose is usually therapeutic within 24 hours, as female patients with testosterone deficiency rapidly experience a number of positive benefits as symptoms of testosterone deficiency are ameliorated.

Once testosterone deficiency is documented, the patient is asked to sign an informed consent form for off-label use of testosterone (see Table 3). I use a testosterone gel (Testim® or AndroGel®) at 1/3 to 1/2 the male dosage. Initially, the patient rubs on the gel every other day. This dose can be titrated upward over time. At the end of about 90 days, I repeat the serum testosterone test and require a one week break. If symptoms recur and the serum level is still low, I continue the

testosterone.

The reduction and amelioration of testosterone deficiency symptoms is often remarkable. At this early phase of female testosterone treatment, I have not witnessed complications or long-term side-effects.

Laboratory Testing and Interpretation

All major clinical laboratories now test for total and free serum testosterone. They will report their normal values for sex and age which makes it easy to diagnose hypotestosteronemia.

At this time there is a raging debate among some endocrinologists and urologists as to the meaning of serum free and total testosterone and sex hormone binding globulin. The issue stems from the fact that most (over 80%) of serum testosterone, is bound to serum proteins including sex hormone binding globulin. Some experts believe that only about 1% of serum testosterone is "active," due to the protein/globulin binding nature of

testosterone. They even argue that the remaining protein-bound testosterone is irrelevant and apparently some sort of biologic waste product. At this time, it is recommended that pain practitioners let the testosterone debates rage on and simply use laboratory-reported serum levels of free or total testosterone in combination with clinical symptoms as the reason to initiate a low dose clinical trial.

The author does not believe that serum testosterone, which is protein bound, is simply biologic waste and irrelevant to pain treatment. Endocrinologists and urologists are primarily interested in the sexual effects of testosterone and, indeed, the small serum fraction of testosterone that is unbound may be the essential, active component that raises libido. Pain practitioners, however, must know that we need testosterone to assist opioids cross the blood brain barrier and help activate a number of central receptors and neurochemicals systems.^{6,7} Also, testosterone may enter pain sites and other tissue compartments in the periphery to help healing. Rather than biologic waste, the serum proteins that bind to testosterone may be required to transport or store testosterone in select anatomic sites and even release testosterone in these sites. The academic question of the eventual fate of protein-bound testosterone is intriguing and may have great relevance to the anabolic, immunologic, and neurochemical properties of testosterone in pain treatment.

Off-Label Use

At this time, there is no commercial, female testosterone product that has United States Food and Drug Administration approval. Consequently, testosterone replacement in females is an off-label use. A great deal of lay and professional publicity has been recently published on off-label use of drugs by physicians. It is not only legal but ethically desirable that physicians judiciously utilize select drugs off-label.⁸ Testosterone replacement in female chronic pain patients who require opioids is a judicious, ethical, and clinically necessary practice as long as the patient is clearly educated on the risks and benefits and gives informed consent.

Summary

While testosterone replacement has emerged as a rather standard practice for male chronic pain patients who require long-term opioid therapy, it is now clear

TABLE 3. Sample Consent for Testosterone Replacement (Females)

1. I, the undersigned, have read the information about testosterone's functions in females.
2. I understand that my blood test for testosterone is below normal, and I have symptoms that are likely the result of low testosterone levels.
3. I am aware that excess testosterone intake over a considerable time period may cause complications including, but not limited to, facial hair growth, clitoral enlargement, acne, muscular development, and hypertension.
4. To avoid any complications, I understand that my testosterone dosage will be a fraction of that given to males. Also, I will take testosterone only as prescribed and such regimen requires me to skip some days without taking testosterone ("drug holidays").
5. I am aware that testosterone replacement may have many benefits for me including, but not limited to, more energy, mental concentration, pain relief, and libido.
6. I believe the potential benefits of low dose testosterone replacement outweighs potential risks, and I consent to a 90-day trial.

Signed _____

Today's Date

TABLE 4. Some Cautionary Recommendations for Female Testosterone Replacement

1. Educate patients about the complications of hypotestosteronemia and potential benefits of testosterone replacement.
2. Document low serum testosterone.
3. Record in patient's record that she has symptoms of testosterone deficiency.
4. Use a testosterone replacement consent form.
5. Use a testosterone dosage about 20-25% of the usual male dosage.
6. Consider a short-term, test trial (e.g., one week) before embarking on a longer trial.
7. Skip some days of administration such as every other day dosing.
8. Stop therapy after 90 days and resume if serum testosterone is still low and/or symptoms return.

that many females with chronic pain who require opioid therapy also need testosterone replacement. Although it is universally known that testosterone enhances libido, it is less well appreciated that testosterone is required for energy, mental concentration, mood, anabolic healing, and even proper opioid pain relief. These necessities for pain treatment are forcing pain practitioners to embark upon female testosterone replacement before other medical fields have begun this practice in earnest. Although clinical trials for female testosterone commercial products are in the pipeline for future FDA approval, females who now need treatment can be effectively and safely given testosterone by following the cautionary guidelines presented in Table 4. ■

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