Testosterone Replacement in Chronic Pain Patients

Adequate testosterone serum levels are required in males and females not just for libido and sexual function but also for cellular growth, healing, maintenance of muscle mass and bone, and central nervous system maintenance of opioid receptors, blood- brain barrier, and dopamine-norepinephrine activity.

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Volume 10, Issue #6

Testosterone deficiency in chronic pain patients has now been recognized by many observers.[1-6] Due to its critical biologic functions in pain control, testosterone testing and replacement (TR) should now become a mandatory component in the treatment of chronic pain. This paper summarizes the physiologic actions of testosterone relative to pain management and lays out practical guidelines for testing and treatment that can easily be adapted to pain practice.

Why the Necessity of Testosterone?

Unfortunately, the mention of the word “testosterone” usually calls to mind a misconception that it is simply the hormone needed for male libido and erectile function. This biologic function is only one of many of testosterone’s critical functions (see Table 1). Furthermore, adequate biologic testosterone levels are as critically equal to the female as male chronic pain patient.[3,7] First, adequate testosterone levels are needed for satisfactory pain control as this hormone is intricately involved in endogenous opioid activity.[8-10] Testosterone is also necessary for opioid receptor binding, maintenance of blood-brain barrier transport, and activation of dopamine and norepinephrine activity.[11,12] Consequently, a lack of testosterone activity in the CNS may result in poor pain control, depression, sleep disturbances, and lack of energy and motivation. In the periphery, testosterone functions as a primary androgenic compound for tissue healing.[7] Adequate testosterone levels have long been known to be necessary for muscle maintenance, exercise tolerance, and prevention of osteoporosis. Compression fractures are known to occur in men and women who have testosterone deficiency.[6] A deficiency of testosterone, therefore, impairs healing and control of inflammation at pain sites.

Table 1. Testosterone Functions in Chronic Pain Patients

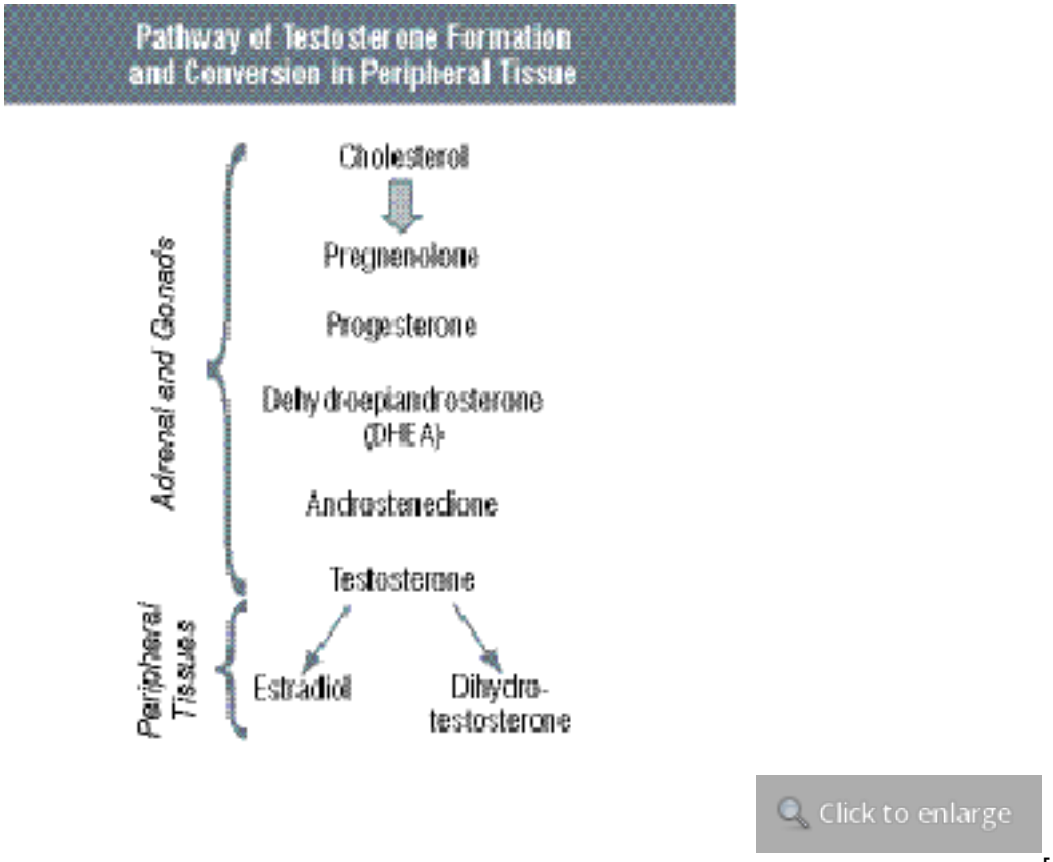
- Opioid receptor binding
- Dopamine-norepinephrine activity
- Maintenance of blood-brain barrier
- Androgenic-healing/tissue growth
- Libido
- Erectile activity (males)
- Maintenance of muscle and bone mass
- Exercise tolerance

Another great misconception is that testosterone is purely a male hormone. Even in the female, an adequate testosterone serum level is necessary for libido. Further, all of testosterone’s CNS and androgenic-immunologic functions apply equally to females. The only difference and consideration with TR in females is that females carry a lower serum concentration and a lower dosage is usually required for replacement.

Physiologic Production

The hypothalamus produces gonado-tropin releasing hormone (GnRH) which causes the pituitary to secrete follicle-stimulating hormone (FSH) and luteinizing hormone (LH). FSH and LH assist in testosterone production by the adrenal and gonads. Although testosterone was previously thought to be only produced in the testicles, it is now clear that it can be produced in the adrenal and ovary (see

Figure 1). Of considerable importance is the fact that testosterone converts to estradiol and dihydrotestosterone in peripheral tissue. Estrogens are known to have a potent affect on depression by virtue of activity in the CNS as well as on bone formation. Although our understanding is elementary, it appears certain that severe, uncontrolled pain causes anatomic changes in the CNS by virtue of neuroplasticity. Hormonal therapy is emerging as critical to adequately treat an altered CNS that develops in response to severe chronic pain.



[2]**Figure 1.** *Pathway of Testosterone Formation and Conversion in Peripheral Tissue. (Adapted from Williams Textbook of Endocrinology, 10th edition, Saunders, Philadelphia. 2003. p713.)*

Mechanism of Testosterone Depletion

There may be two reasons for testosterone depletion in a chronic pain patient (see Table 2). One is pituitary insufficiency caused by severe pain, per se. Constant, persistent, uncontrolled pain will, over time, exert enough stress on the hypothalamus and pituitary (GnRH, LH, FSH) to cause the inadequate secretion of testosterone from the adrenal and gonads. When the cause of hypotestosteronemia is hypothalamic-pituitary insufficiency, other hormones such as cortisol, pregnenolone, or thyroid may likely show serum deficiencies. The second and most common cause of testosterone deficiency is opioid administration.[1-2] Low testosterone levels have been observed with essentially all oral and intrathecal opioids.[2,5] Low testosterone serum levels are primarily caused by opioid suppression of GnRH in the hypothalamus. Opioids may also directly impair testosterone production in the adrenal or gonads. Both causes of hypotestosteronemia may simultaneously exist. Also, both cases require testosterone replacement. It is unknown if testosterone suppression by opioids is opioid-specific, dose-related, or related to opioid serum levels.

Table 2. Two Causes of Hypotestosteronemia

1. Pituitary deficiency caused by over- stress of uncontrolled ch
2. Opioid administration

Testing For Testosterone Deficiency

Simply order a morning serum testosterone level. Laboratories now report a patient's serum concentration as well as normal ranges for males and females. Units of measure may vary between laboratories. The total serum testosterone concentration has protein-bound and unbound components.[13-15] The free, bioavailable, or unbound component is generally believed to be the fraction most involved with libido and sexual function. We believe, however, that the total serum testosterone levels may be a more critical evaluation for pain management purposes, since protein-bound testosterone may be necessary to either enter some body compartments such as in the CNS, spinal cord, or pain site to perform its necessary functions. Consequently, pain practitioners should consider low levels of either total serum testosterone or free unbound testosterone to indicate a deficiency that requires replacement.

Who Should Be Tested

If financial resources are available, all chronic pain patients who require opioid administration, including those patients who are currently taking opioids, should be screened. Those patients currently in opioid treatment and who complain of lethargy, inadequate pain control, depression, weakness, and lack of libido, are obvious candidates for serum testing (see Tables 3 and 4).

Table 3. Symptoms of Testosterone Deficiency in Males and Females

1. Lack of energy
2. Loss of libido
3. Depression
4. Poor healing
5. Diminished opioid affects
6. Loss of motivation
7. Apathy
8. Weakness

Table 4. Guideline for Testing and Treatment

1. Single, morning serum test for total and free testosterone.
2. Start patients on a commercial testosterone preparation.
3. Assess treatment response 2 to 4 weeks after starting therap
   libido, motivation, pain relief, and sleep pattern.

Treatment Recommendations

There are several commercial testosterone products from which to choose (see Table 5). Each has pros and cons and all are relatively expensive. Third party payment is extremely variable and may dictate your selection. Due to cost considerations, patients without insurance coverage will usually be forced to use injectable testosterone. Some compounding pharmacies will now make a topical testosterone cream or gel for a cost similar to that of injectable testosterone. If you use a compounding pharmacy, we recommend you order a testosterone concentration similar to that found in the commercial gels which is a 1% testosterone concentration. For example, 50mg in 5gms (Testim®, Androgel®).

Table 5. Some Common Commercial Testosterone Preparations

Trade Name	Dosage
Andro-Gel®	
Testim®	
Androderm®	
Generic Injectable	
Note: Starting female dosage is 25% that of male	

All the commercial products are formulated and labeled for male usage. We recommend a starting female dosage that is about 25% that of the male dosage. As of now, testosterone use in females is "off-label" so physicians may wish to utilize an off-label consent form or enter a chart note that documents that the patient is aware of the off-label use.[10] As with all therapeutic classes of drugs, there are nuances between the commercial products that are available. These differences include onset of action, level of serum concentration, length of action, and route of administration. Indeed, patients may request a change in testosterone preparation based on any of the commercial product variations. Consequently, no commercial preference is recommended at this time.

Follow-Up and Monitoring

If the testosterone dosage is adequate, patients routinely report improvement in symptoms such as libido, energy, opioid effectiveness, depression, and weakness. The improvement in symptoms should be recorded in the patient's record to document effectiveness and justify the expense of the treatment.

A follow-up serum concentration is recommended at three to six months and then yearly. Ideally, the testosterone dosage should be high enough to bring the serum concentration into normal range. There is no upper limit on testosterone dosage. The primary goal of treatment is to reduce pain and the symptoms of testosterone deficiency (see Tables 1 and 3).

Side Effects

Unfortunately, the highly-publicized androgenic side-effects of anabolic steroids observed in some athletes have given the erroneous impression that testosterone replacement in males and females is fraught with the same complications. Testosterone is a Schedule III drug under the U.S. Controlled Substance Act and is classified as an "anabolic steroid." Indeed its anabolic (tissue building) affects are desired in pain management. Athletes who use testosterone and synthetic anabolic steroids for competitive advantage use the compounds in dosages that far exceed those used to therapeutically replace testosterone in pain patients. To date, we have not observed any adrogenic side-effects in males or females at the dosages recommended here and by commercial manufacturers. Some of the side-effects reported in athletes who use supraphysiologic dosages include: erectile dysfunction, cancer of the liver or testicule, hypertension, liver degeneration, and cardiomyopathy. Prior to these serious side-effects, testosterone replacement will usually cause acne—or, in females, beard growth—allowing the physician to easily recognize that the dosage is too high before any serious complications can occur. If acne, hair growth, or altered voice are observed, the testosterone dosage would naturally need to be reduced or stopped.

Alternative-Human Chorionic Gonadotropin (HCG)

HCG is marketed as an injectable drug (1,000 units per ml) or it can be compounded to be administered by the nasal route. It raises serum testosterone levels and it can be used singularly or as an adjunct to a commercial testosterone preparation.[17-19] The cost of HCG may be slightly less than some commercial testosterone preparations.

Precursor Therapy

Precursor therapy with testosterone replacement is reported by many pain patients to be a useful adjunct. There are four precursors of testosterone that can be given therapeutic trials: dehydro-epiandrosterone (DHEA), pregnenolone, progesterone, and androstenedione (see Figure 1 and Table 6).

Table 6. Testosterone Precursors

Precursor	Daily Dosage
Dehydroepiandrosterone (DHEA)	50 to 100mg
Pregnenolone	50 to 100mg
Androstenedione	50 to 100mg
Medroxyprogesterone	10 to 20mg

Note: Intermittent, rather than daily, administration is recommended.

The beneficial theory for precursors as adjuncts is twofold:

1. Natural testosterone production is enhanced,
2. Precursors may prevent any negative feedback and suppression of the biologic pathway of testosterone production (see Figure 1).

Although few studies of precursor therapy are available, DHEA and androstenedione have been shown to have a positive effect on corticosteroid or testosterone production.[20-22] Precursors are quite safe and appear quite free of side-effects. To be cautious, we do not recommend they be used on a daily basis but rather on an intermittent basis.

Therapeutic Trial Without a Blood Test

Many pain patients lack the financial ability to obtain a serum testosterone level. In these cases, take a history of testosterone deficiency symptoms (see Tables 1 and 3). If the patient is taking opioids and relates an abundance of these symptoms, a therapeutic trial without a blood test is warranted. Simply give 1.0ml (200mg) of injectable testosterone or a one-week supply of a commercial testosterone product. If their underlying cause of symptoms is testosterone deficiency, within one week the patient will report significant improvement in symptoms. Once a relationship between low testosterone and symptoms is established, an on-going treatment plan for testing, treatment, and evaluation based on financial resources can be developed.

Concomitant Use of Erectile Dysfunction Drugs

Although testosterone is critical for erectile function, neurologic and vascular mechanisms may also cause erectile dysfunction. Neuropathic injury to abdominal, pelvic, or spinal nerves are particularly common in pain patients. Pain patients also have a high prevalence of vascular disease due to relative inactivity, hypercholesterolemia, and corticoid disturbance. If testosterone replacement does not resolve erectile dysfunction, the use of sildenafil (Viagra®), tadafil (Cialis®) or vardenafil (Levitra®) can be concomitantly used with testosterone replacement.

Consultation With Other Physicians

Testosterone testing and treatment is easily accomplished. If patients require multiple hormone replacement that is seen in hypothalamic-pituitary suppression, consultation with an endocrinologist and co-management is an option that should be considered.

Case Reports

Case 1: Simple Testosterone Replacement—Male. A 54-year-old male has intractable pain due to a cervical neck/ shoulder injury with subsequent right neck, shoulder, and arm neuropathies. His pain is severe, constant and requires multiple long and short-acting opioids and a bed-time sedative for control. His serum testosterone level was 204ng/dl (normal range 241-227). He maintains on depotestosterone, 200mg every two weeks. If he misses an injection he suffers lethargy, pain flares, insomnia, depression, and loss of libido.

Case 2: Testosterone Replacement With Adjunct Therapy—Male. A 44-year-old male suffered three lumbar herniated discs which required fusion and placement of metal rods. He was started on multiple opioids but did poorly and was referred for medical evaluation and management. His serum testosterone was 154ng/dl (Normal 241-827ng/dl). Within days of starting a testosterone gel of 50mg a day, his pain dramatically decreased and his energy, motivation, and libido increased. An addition of oral medroxyprogesterone 10mg, twice a day, considerably improved his libido and physical abilities. With testosterone and the precursor, progesterone, he has gone from a bed/house-bound state to one in which he is active each day and can work part-time.

Case 3: Simple Testosterone Replacement—Female. A 48-year-old female was in a car accident at age 31. She suffered facial and dental fractures which resulted in constant intractable pain of the face and neck. Fibromyalgia symptoms followed. She has now been on opioid therapy for about 17 years.

Serum testosterone con-centration was 6ng/dl (normal rage is 12-90ng/dl) after which time she was started on topical 1% testosterone gel, 25mg every other day. Within two weeks she observed an increase in libido, pain control, endurance, and energy.

Case 4: Testosterone Replacement With Adjunct Therapy—Female. A 53-year-old female had a traumatic Cesarean section with the birth of her fourth child. Internal bleeding required post-operative surgery. She has experienced six prior pelvic surgeries and one for breast cancer. Subsequently, she developed constant, severe intractable pain which required multiple, high dose opioids for pain control. After about 10 years following onset of her pain she developed severe lumbar spine degeneration which prompted hormone testing. Her serum testosterone concentration was .16ng/ml (normal range is 1.75-7.81ng/ml) indicating severe deficiency. She now maintains on testosterone topical gel, 25mg every other day and she uses human chorionic gonadotropin, 1,000 units, every other day. This regimen allows her to have good pain control, libido, endurance, and energy. She is a health professional and with her regimen of opioids and hor-mones she is able to work about half-time. Her spine degeneration appears to have ceased.

Summary

Testosterone deficiency may occur in a severe, chronic pain patient due to over-stimulation and hypofunction of the hypothalamic-pituitary-adrenal-gonadal axis or by chronic administration of opioids which may suppress the hypothalamus and pituitary. Adequate testosterone serum levels are required in males and females not just for libido and sexual function but also for cellular growth, healing, maintenance of muscle mass and bone, and central nervous system maintenance of opioid receptors, blood brain barrier, and dopamine-norepinephrine activity. Testosterone deficiency produces a syndrome of poor pain control, weak-ness, lethargy, depression, sleep disturbance, and loss of libido. Due to the critical functions of testosterone in pain patients, pain practitioners should incorporate testosterone testing and replacement into their pain practice. Although somewhat uncertain, testosterone re-placement may prevent some of the neurologic and bone-related degeneration that is common in pain patients.

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First published on: July 1, 2010

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