Testosterone

A Review for Orthopaedic Surgeons

Michel A. Arcand, MD

Dominique Poulin, BSN

Edward J. Testa, MD

Nicholas J. Lemme, MD

Investigation performed at Brown University Department of Orthopedics, University Orhtopedics Inc, Providence, Rhode Island

Abstract

» Testosterone replacement treatment (TRT) and anabolic androgenic steroid (AAS) use is common and possibly increasing.

» Diagnosing and treating hypogonadism in men is controversial.

» Hypogonadism and the use of AASs seem to have a detrimental effect on the musculoskeletal system. The current literature on TRT and the musculoskeletal system shows an increased risk of tendon injury.

» There may be a role for testosterone supplementation in the postoperative period.

Testosterone is the male sex hormone responsible for spermatogenesis[1-3]. Leydig cells in the testes produce the hormone under the influence of the hypothalamic-pituitary axis. Its production is regulated by the luteinizing hormone produced by the pituitary gland. Through receptors located throughout the body testosterone influences many organ systems. In men, testosterone plays an essential role in producing secondary sex characteristics, the ability to maintain an erection, sperm production, and libido. It is responsible for increased bone and muscle mass. It increases hemoglobin and red blood cells production. In the cardiovascular system, the heart volume and wall thickness increase under the effect of testosterone. Moreover, hypertension can be seen in patients with elevated testosterone levels. Finally, mood, aggressive behavior, and cognition including concentration are influenced by this hormone.

Low testosterone levels have been associated with androgenic deficiency syndrome. It is thought to influence aging-related prostate gland disease, prostate cancer, benign prostate hyperplasia, and lower urinary tract symptoms. There is now evidence that seems to suggest that low testosterone can cause these disorders by androgen receptor overexpression[4].

Androgenic deficiency syndrome is a syndrome that is characterized by reduced sexual desire and activity, erectile dysfunction, decreased spontaneous erections, incomplete or delayed sexual development, eunuchoidism, small testes, gynecomastia, loss of body hair/reduced shaving, subfertility, reduced bone mass, and hot flushes/sweats. This can also be associated with depressed mood and loss of energy and motivation. Decreased strength, along with increased fat, is seen in this condition. Anemia can present in patients with decreased testosterone levels. Some patients may complain about decreased cognition and possible increase in dementia symptoms. The incidence of this disorder is thought to be increasing worldwide. Treatment of androgenic deficiency syndrome, with testosterone replacement treatment (TRT), especially of late-onset hypogonadism (LOH), may offer a chance to prevent some of the comorbidities associated with this disorder. This preventative measure may, therefore, decrease a large financial burden on society[5].

Orthopaedic patients using testosterone are not easily identified. Indication criteria for prescribing TRT vary widely among

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prescribers. Anabolic androgenic steroid (AAS) use is illicit, which means patients may not want to admit to its use. Consequently, there is a very heterogeneous population of patients taking testosterone. In certain clinical scenarios, which will be discussed in greater detail in this review article, questioning patients regarding TRT or AAS intake may be an important component of eliciting a complete history and physical examination.

Anabolic Androgenic Steroids

Testosterone and its derivatives have long been used as a performance-enhancing drug[6]. AASs have been used successfully to increase strength and muscle mass, especially if combined with strength training[7]. Improved performance has been recognized by athletes for decades[8,9]. These drugs are being taken at supraphysiologic doses; therefore, unsurprisingly, the side effects are more intense and common. Most of the side effects associated with the use of these drugs are similar to those seen with TRT and mentioned in the previous section. Some of the side effects are mild but some can be severe[10]. The true impact of AAS is difficult to study because they are illegal, and they are used in conjunction with other drugs to help prevent or treat associated side effects[6]. This is referred to as "stacking." These drugs are also taken in cycles where athletes take the medication for several days or weeks and then stop them. They may be restarted later to achieve the goals set by the user. This on and off self-medication practice may help with side effect management and avoid detection on drug screens.

There is a high prevalence of anabolic steroid use in the general population[11]. Almost all orthopaedic surgeons encounter patients on AAS in their careers. Being aware of the risks of supraphysiological doses of testosterone and self-medication will help the surgeon counsel patients about potential injuries and complications.

Indications for TRT

Primary hypogonadism refers to an insufficient production of testosterone by the testes. Secondary hypogonadism is present when there is a failure of the hypothalamic-pituitary axis to regulate testosterone production. When the low testosterone is being caused through deficiencies at both the testicular and hypothalamic-pituitary levels, then a mixed hypogonadism is present[3]. Examples of these conditions are listed in Table I. Testosterone usually peaks in men in their thirties. In the following years, there is a loss of testosterone at a rate of 1% to 2% per year until LOH appears[12].

Diagnosing hypogonadism is controversial. The testosterone level that leads to symptoms of low testosterone has not yet been determined. One of the issues is that patients with similar levels of testosterone may or may not experience symptoms. The intensity of symptoms can vary among patients. Some authors have published screening questionnaires to help diagnose hypogonadism. Some have been found to correlate with testosterone levels[13]. The level at which a patient is indicated to start TRT is not well established[12,14]. Recent literature suggests that serum testosterone below 12.1 mmol/L is considered abnormal[15]. A serum testosterone assay should be performed on a fasting patient suffering from no acute or subacute illnesses. Determining which patients require treatment of hypogonadism is controversial[3]. Because testosterone levels can be affected by many chronic diseases, which form of testosterone must be measured can also pose a challenge[16]. Chronic illnesses can affect testosterone-binding proteins and alter the serum levels of afflicted patients, leading to confusion. Young otherwise healthy male patients with symptoms and low serum testosterone levels do not pose controversy for treatment, since clear benefits have been shown in this group. The age at which a patient with LOH should start TRT is more controversial. A risk-benefit discussion should take place between the prescribing physician and patients seeking TRT. The consensus in the literature seems to be that indications for TRT should be tailored to individual patients[17,18]. In summary, TRT can improve the lives of many patients, but determining who is best treated and with which medication is best determined by the patient and his physician.

Testosterone Replacement Treatment

Natural testosterone seems to be the best supplement for patients. Many formulations are available. The risks and benefits of each formulation will not be covered here. Some general principles are known. Historically, oral preparations result in hepatic metabolism of the hormone. After a first pass in the liver, very little testosterone is available in the blood stream. This requires large doses of medication to produce its effect. Newer oral agents have improved blood levels making their use in TRT possible. They have been shown to decrease symptoms as effectively as the more traditional forms of administration[19]. These oral agents have made testosterone use more popular. Most other preparations involve nasal, epidermal, or subdermal delivery methods. They bypass hepatic metabolism and allow testosterone to be available in blood. No matter the delivery method, the goal of the medication is to restore a more normal testosterone level. This will usually lead to symptom resolution, while trying to avoid potential complications.

Patients with primary hypogonadism are expected to obtain significant benefits from the return of normal hormone levels. For example, Klinefelter's syndrome, orchidectomy or radiation treatment may be treated with TRT. Secondary hypogonadism stemming from systemic disorders such as AIDS and diabetes have shown some improvement in symptoms with treatment. Patients suffering from mixed hypogonadism have also been treated successfully with TRT. Patients with LOH can be treated by TRT with improvement of symptoms. The prescribing criteria can vary depending on which guidelines are being used[3].

TABLE I Types of Hypogonadism*

	Primary Hypogonadism	Secondary Hypogonadism	Mixed Hypogonadism
Congenital	Klinefelter's syndrome	Kallmann's syndrome	
Acquired	Orchidectomy	Anabolic androgenic steroid	
	Mumps	Diabetes	
			Testicular torsion/malignant tumor
			AIDS/opioid abuse
			Alcoholism

*Examples of different types of hypogonadism. This is not an inclusive list. The "mixed" category constitutes a testicular disorder and one that involves the hypothalamic-pituitary axis.

Benefits

There appear to be significant benefits to TRT. In the reproductive arena, an increase in sexual desire, decrease in erectile dysfunction, and sexual satisfaction have been seen. Men who are not virilized have noticed improvement in their secondary sexual characteristics such as facial hair, deepened voice, and increase muscle mass. In patients who already have adequate secondary sexual characteristics, TRT allowed them to maintain their virilization[3]. Improvement of sexual function with TRT is still debated. Some studies find improvement in sexual function while others did not[20,21].

Gains in lean muscle mass and a decrease in fat mass are seen in patients undergoing TRT. There also seems to be a strength gain associated with TRT[9]. Patients report increased energy and motivation to exercise[22,23]. This may be beneficial to their overall health and their musculoskeletal system. Increases in bone density of the lumbar spine have been reported, though there is no evidence that there is a corresponding reduction in fractures[24]. In patients with diabetes, there are some studies that seem to demonstrate that better glucose control can be obtained with TRT. Some studies suggest that reduced fat mass may be the reason for these findings[25].

Patients with subclinical depressive states seem to get better improvement of their symptoms after TRT than patients with major depression. Increased activity has also been reported, as well as improved cognition[26]. This effect on mood can make it hard to distinguish metabolic improvement vs. a patient's ability to modify their lifestyle due to TRT increasing their energy and drive. TRT has been shown to improve patients' perception of their quality of life[27].

More recent studies show improved cardiovascular function in patients on TRT compared with men with hypogonadism. This might be attributed to improved lipid profiles. The resulting cardiovascular health has been shown in studies looking at the long-term effects of TRT[28]. Because of these findings, TRT can result in fewer cardiovascular events and possibly decreased costs of medical care in the health system.

Improvement in urological function has been shown in a recent review by Diokno[4]. They found studies that showed low testosterone levels were associated with increased risk of prostate cancer and lymph node involvement[29,30]. Furthermore, there was an increase in aging-related prostate gland disease with declining testosterone levels. They also reported on studies that showed no increased risk of prostate cancer in patients undergoing TRT[31-33].

Most authors also recommend that patients on TRT be monitored for efficacy and complications[3,4]. Hormone levels should also be checked. Counseling patients about the benefits and side effects of TRT is important not only when initiating treatment but also during follow-up visits. TRT has such broad impacts that several specialties may be involved in treating these patients. The potential benefits and possible decrease in side effects of treating patients with hypogonadism may decrease healthcare costs in the future.

Complications of TRT

There are contraindications to TRT. Patients with prostate cancer and/or prostate nodules are not candidates for TRT. Some studies have shown no increase in prostate cancer risk with TRT[31,32]. Lower urinary tract symptoms were not increased, but TRT has been shown to increase prostate size. Intramuscular formulations of administration were found to be associated with an increase in prostate-specific antigen in 1 study[34]. TRT can increase subclinical prostate cancer to clinically detectable prostate cancer[35].

Gynecomastia and breast tenderness can occur with TRT. This is a potential complication that is also seen with AASs. Although there are some isolated case reports that TRT could cause breast cancer in men, there is no strong evidence of this association[36]. Increased male pattern baldness has been reported. It has also been shown to increase oily skin and acne, which may be a concern for orthopaedic surgeons. Upper extremity and spine surgeries that pass through the skin in these areas may be at an increased risk of *Cutibacterium acnes* infections, which can pose diagnostic and therapeutic challenges for the treating surgeon. The use of implants

increases the risk of low-grade infections that can complicate shoulder and spine surgeries.

Other more serious complications include the cardiovascular system. There are studies that suggest an increase in cardiovascular deaths and events with TRT[37]. Some studies on the other hand have not found any difference between patients on TRT and control groups[38].

Among the vascular risks, there is a documented increased incidence of deep venous thrombosis (DVT) with TRT. This complication may be related to erythrocytosis caused by increasing testosterone levels. An increase in red blood cells may increase blood viscosity and lead to clotting in the peripheral venous system. This is especially true for the first 6 months after initiating testosterone replacement. DVT prophylaxis was not recommended for all patients starting on TRT. Screening patients for family history of DVT may be prudent before the start of treatment[37].

Musculoskeletal Risks of TRT

Musculoskeletal risks of TRT are not well known. Recent publications may provide a clue into this issue. These studies are summarized in Table II. A study by Smith et al. showed that a deficiency in testosterone increased the risk of rotator cuff tears by 89%[39]. This significant increased tear rate in men with hypogonadism can probably be explained by the effect of testosterone on tendons. Decreased crosslinking of the collagen fibrils leads to weaker tendons. The lack of testosterone's effect on tendons is probably responsible for this phenomenon. There was a similar increase in tear rate in women with hypogonadism, showing estrogen can also affect tendon strength. This study demonstrates how closely linked the sex hormones are to the musculoskeletal system and its health. Because of this, it is surprising to find a paucity of studies on TRT and the musculoskeletal system.

In a study on TRT and rotator cuff tears, Testa et al. found that TRT increased the risk of rotator cuff tears by an odds ratio of 3.6[40]. This was also associated with an increase in repairs in the testosterone group by 1.6, compared with the control group. Interestingly, the risk of subsequent rotator cuff surgery irrespective of side of the initial surgery, was 26 times higher for patients in the TRT group. Despite controlling for hypogonadism in this study, years of testosterone deficiency before treatment may be an important risk factor of rotator cuff tears in such individuals, providing some potential explanation to this increased risk.

Additionally in similar studies, the same group also showed increases in tendon ruptures and the need for surgical treatment of these injuries in other areas of the body[41-43]. For the quadriceps tendon, the TRT patients had an increased rate of tearing that was 5.8 times higher than the non-TRT control group. There was a 4.7 times higher rate of tears requiring repair[42]. The distal biceps study demonstrated that the TRT patients had a 4.1 times higher tear rate than the matched control group in the first year after starting TRT. This was associated with a 2 times increased risk at all other time points. The risk of requiring surgical treatment was 1.9 times higher in the TRT group[41]. The final study showed a 1.24 times increased risk of having an Achilles tear in the TRT group. A 1.54 times increased risk of undergoing operative repair was noted[42].

Because all the abovementioned studies are database studies, it is difficult to infer the reason these tears are seen. These studies were performed by using patient-matching techniques. Therefore, the groups were similar except for the use of TRT. Theories to explain the differences in rates of tearing include an anabolic effect such as seen in users of anabolic steroids on the muscles and tendons involved. This results in a stiffer tendon that would be more prone to tearing off the bone. There is also decreased remodeling in tendons that are exposed to testosterone. This may cause a relative weakening in the face of an increasingly stronger muscle. As we have seen earlier, testosterone increases lean muscle mass. An imbalance between the force generated by an increased muscle mass and this force on a potentially stiffer or weaker tendon may contribute to the results found in these studies. The mismatch may decrease or increase with time, but this is also unknown. Acquiring more knowledge of testosterone's influence on the tendon and muscles will allow better counseling for patients in the future. The years of testosterone deficiency before tendon tears must also be considered in light of the important role of this hormone on tendon health.

Another potential explanation may have to do with the increased motivation and energy that many users of TRT report. Increased energy levels may lead to more frequent and more intense workouts. This may exacerbate the

TABLE II Summary of Findings of Orthopaedic Complications of Testosterone*

	Testosterone Level	Tears	Surgical Treatment
Smith et al.[39]	Decreased	Increased	N/A
Testa et al.[40]	Physiological	Increased	Increased
Rebello et al.[41]	Physiological	Increased	Increased
Albright et al.[42]	Physiological	Increased	Increased
Meghani et al.[43]	Physiological	Increased	Increased

*This table shows that hypogonadism and testosterone replacement treatment (TRT) both increase the risk of tendon tears. The surgical treatment of these tears is increased in the TRT studies, but this was not evaluated in the hypogonadism study.

imbalance between the tendon and muscle strength leading ultimately to tendon rupture.

What is unclear in these studies is the timing of the tears. The biceps study showed a higher risk in the first year after the initiation of TRT. The risk persisted at a lower level but still at a higher rate compared with the control group. It may be plausible that these tears occur early in the TRT treatment period. Just like in the case of the DVT risk, we do not know if the risk decreases with time to a level similar to the controls'. The distal biceps and quadriceps studies suggest that the tendon is more susceptible to tearing in the first year. The fact that these patients may have suffered from the effects of hypogonadism on their musculoskeletal system before diagnosis is unknown. In this case, the loss of bone, tendon and muscle may have all decreased over years prior to starting TRT. This may not have occurred at a similar rate in all these tissues. The return of a normal testosterone level may have allowed bone, tendon, and muscle mass to also increase at different rates. This discrepancy in the tissues different rate of return to a more normal strength, may result in the weakest link in the chain failing.

Further explanations include patients requesting TRT may be more health conscious and may complain more about joint and muscle pain leading to an increased diagnosis of tears. Activity levels may also make asymptomatic tears symptomatic. These data cannot be mined in the used database. A more controlled longitudinal study is required to detect these effects.

Although the strength of database studies is the number of available participants that can be studied, they rely on proper coding of patients by busy clinicians. Errors and improper coding might explain the contradiction between a study that shows an increase in tearing both within groups of patients with hypogonadism and those on testosterone supplementation. There may be patients on TRT because they want to use them as AASs, not to treat low testosterone symptoms. This could explain why there is an increased tear rate in patients on TRT. As we have seen earlier, there is a lot of controversy in the diagnosis of LOH and hypogonadism in general.

There is also controversy in when to prescribe TRT and at which level the testosterone should be maintained. Most men have never had their testosterone levels checked in their thirties. We, therefore, do not know what a patient's peak level was. Some patients do not get testosterone levels checked once started on treatment. The databases used do not provide the testosterone levels that patients started with or maintain. A patient on TRT could have supraphysiologic or potentially hypophysiologic levels of testosterone in the same study. Therefore, the TRT groups in these studies may not be uniform. Some patients might also have higher than normal and/or lower than normal testosterone levels because of noncompliance to their drug regimens. The patients who started TRT after several years of hypogonadism may not be the same as patients as one who never really enter the low testosterone state. This may make the TRT groups more susceptible to the effect of anabolic doses of testosterone or both hypogonadism and resulting tendon weakness. Either way, this gives the impression that TRT can increase rupture rates.

Future

Obviously, more studies are required to elucidate the mechanism causing testosterone supplementation to increase the rate of tears. Finding the reason that TRT and hypogonadism are both causing an increase in rupture rates is important and would allow the patients' healthcare team devise strategies to mitigate this risk.

In a recent article, Thomson et al.[44] reported on testosterone levels before and after anterior cruciate ligament reconstruction. This study reports that in the postoperative period, male patients had lower testosterone levels. These levels correlated with the patient's Patient-Reported Outcome Scores. They suggest that testosterone supplementation may help return the patient to preoperative activity levels quicker than waiting for the hormone to return to baseline. A more normal testosterone level would help improve the rate of return to function during the rehabilitation period. A similar study performed on rats by Tashjian et al.[45] demonstrated that supplementation of sex hormones after rotator cuff repair may allow a faster return to preoperative activity and histologically superior tendon healing. These studies suggest that patient outcomes, activity levels, and tendon healing may be improved by supplying missing testosterone in the postoperative period. This may have implications in a lot of other surgical fields. These studies may also change the pharmacology used as postoperative regimens after major and minor orthopaedic surgeries.

A lot of work remains to be done in this domain. It is important to recognize that most surgeons will encounter patients taking these medications, as TRT or AAS, throughout their careers. Given the attention that testosterone is receiving in the lay press, it is important that we, orthopaedic surgeons, have at least basic knowledge of TRT.

Although the role of the orthopaedic surgeon is not to initiate TRT or AAS, being aware of the complications these treatments can cause is important. Patients taking hormones seem to be at a higher risk of tendon injury. When treating these patients, having a high index of suspicion for tendon injuries is important. Counseling patients who are contemplating or using these hormonal treatments is an important part of the surgeon's responsibilities. Raising awareness of these complications among our colleagues helps everyone's patients.

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Michel A. Arcand, MD[1],
Dominique Poulin, BSN[1],
Edward J. Testa, MD[1],
Nicholas J. Lemme, MD[1]

[1]Department of Orthopedic Surgery, Brown University, Providence, Rhode Island

Email address for corresponding author: marcand@universityorthopedics.com

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