Review Article

Standard Review Testosterone Replacement Therapy in Orthopaedic Surgery

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ABSTRACT

Testosterone replacement therapy (TRT) is an indicated treatment of several medical conditions including late-onset hypogonadism, congenital syndromes, and gender affirmation hormonal therapy. Increasing population age, medical benefits, and public awareness of TRT have resulted in increased prevalence of its utilization. However, TRT is not without concern for adverse risks including venous thromboembolic complications, cardiovascular events, and prostate issues. In the field of orthopaedic surgery, research is beginning to delineate the complex relationship between TRT and the development of orthopaedic conditions and potential effects on surgical interventions and outcomes. In this review, we discuss current literature surrounding TRT and subsequent development of osteoarthritis, incidence of total joint arthroplasty, musculotendinous pathology, postoperative infection risk, improvements in postoperative rehabilitation metrics, enhancement of osseous healing, and increased bone-implant integration. The authors suggest future areas of investigation that may provide guidance on how surgeons can mitigate adverse risks while optimizing benefits of TRT in the orthopaedic patient.

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Hormone replacement therapy (HRT) is a domain of endocrinology with a goal of hormonal normalization and optimization of the individual's overall health. HRT encompasses numerous organ systems including hypothalamic, pituitary, and thyroid-related dysfunction, but may be most recognized for its role in sex steroid hormone regulation. HRT is commonly used for estrogen replacement therapy in perimenopausal women, and HRT with testosterone is becoming increasingly common for men during age-related androgen decline, as well as individuals undergoing gender-affirming hormone therapy. Utilization of testosterone replacement therapy (TRT) is an accepted treatment of various medical conditions. However, TRT is not without concern for adverse event risk, including cardiovascular events, and development of prostatic pathology.[1] Unlike estrogen replacement therapy, studies have not identified increased risk of venous thromboembolic events (VTEs) in patients undergoing TRT. The

Figure 1

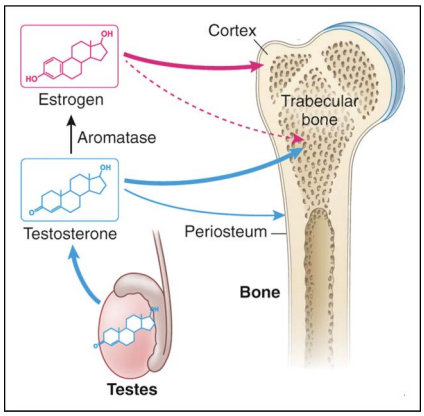

Illustration demonstrating testosterone is produced by the Leydig cells of the testes. It then exerts an anabolic effect on trabecular bone and periosteum. Excess free testosterone is converted to estrogen using aromatase. Estrogen then provides an osteogenic effect on cortical bone. "Adapted with permission from: Radhika R. Narla, Susan M. Ott, Bones and the Sex Hormones, *Kidney International* 2018:94;2:239-242, with permission from Elsevier."

relationship between TRT and the development of orthopaedic conditions and subsequent treatments has become a topic of interest, yet there remains a lack of consensus regarding management of TRT in the orthopaedic patient. The absence of definitive guidance for optimal utilization of TRT in the perioperative period is a gap in understanding that warrants investigation and development of evidence-based recommendations. Investigation of TRT and its effects on the broad scope of orthopaedic conditions and surgical interventions can help inform the surgeon and provide patients with improved clinical outcomes while mitigating adverse effects associated with TRT.

Testosterone Replacement Therapy

As men age, testosterone declines at a rate of approximately 1 to 2% annually after the age of 30 years and free serum testosterone can decrease over 50% by age 75.[2] Hypogonadism in men is clinically demarcated with the development of lethargy, sexual dysfunction, decreased libido, development of depression, and reduction in bone mineral density (BMD) and muscle mass. Diagnosis of male hypogonadism is confirmed with analysis of the serum free testosterone level. Two or more morning samples of serum free testosterone less than 300 ng/dL are considered diagnostic of late-onset hypogonadism. A considerable and growing male population within the United States has been identified as obtaining serum testosterone values consistent with late-onset hypogonadism and subsequently undergoing TRT. Epidemiologic investigations have identified the commonality of low serum testosterone among middle-aged men as high as 12.8% including up to 500,000 men diagnosed annually and initiated on TRT. As of 2011, 3.75% of men in their 60s were prescribed TRT within the past 12 months, which is a threefold increase since 2001.[3] The same investigation depicted prescription sales of TRT increasing from 150 million to 1.8 billion dollars in that same period.

Testosterone is a steroid hormone that is produced in the Leydig cells of the testes. It is subsequently secreted and interacts with the androgen receptor. The overall osteogenic effect of testosterone is mainly directed to the expansion of trabecular bone and periosteum. Finally, excess free testosterone is enzymatically transformed through interaction with aromatase to estrogen. In turn, estrogen exerts osteogenic effects primarily on cortical bone (Figure 1).

Aside from late-onset hypogonadism, TRT is used as a treatment of congenital hypogonadism, diabetes mellitus, Turner syndrome, and Kallmann syndrome and in the field of longevity medicine and gender affirmation hormonal therapy. Conservative estimates suggest that there are over 1.5 million transgender patients in the United States, many of who undergo testosterone replacement. As a consequence, there is increased interest in understanding the management of transgender patient in the perioperative period. Particularly, transgender male patients undergoing gender affirmation hormonal therapy with TRT have lower BMD and increased risk of osteoporosis compared with cis men.[4] However, there remains a lack of understanding regarding the role TRT plays in the development of orthopaedic pathology in this patient population.[5]

TRT is prescribed through various preparations including intramuscular injection (IM), oral, gel, patch, and subcutaneous pellet implantation. These variable preparations have individual pharmacokinetic properties that may provide a source of variation in outcomes and adverse events associated with TRT. The various formulations of TRT are summarized in Table 1.

Testosterone supplementation has been shown throughout various studies to increase lean muscular mass, strength, BMD, energy, libido, mood, and cognitive function and improve lipid, cholesterol and triglyceride profile, insulin resistance, glucose metabolism, body composition, depression, and erectile dysfunction.[6] Benefits of TRT have been well documented; however, notable concerns for risks exist associated with TRT.

Table 1. TRT Preparations, Dosages, and Frequency and Application

Testosterone Formulation	Dosage	Frequency and Application
Oral		
Buccal patch—testosterone USP (Striant)	30 mg	Twice daily application to inside of gum
Intramuscular		
Testosterone Cypionate (Depo-testosterone)	50-400 mg	Every one to 4 weeks deep intramuscular gluteal injection
Testosterone enanthate (Delatestryl)	50-400 mg	Every one to 4 weeks deep intramuscular gluteal injection
Testosterone Undecanoate (Aveed)	750 mg	Once every 4 weeks for two doses, then once every 10 weeks
Intranasal		
Gel Pump (Natesto)	11 mg	Three daily intranasal actuations
Pellet		
Crystalline testosterone (Testopel)	150-450 mg	Subcutaneous buttock implantation every 3 months
Transdermal gel		
1% or 1.62% testosterone gel (Androgel)	50 mg	Once daily application to upper arms and shoulders
2% testosterone gel (Fortesta)	40 mg	Once daily application to thighs
1% testosterone gel (Testim)	50 mg	Once daily application to upper arms and shoulders
Transdermal patch		
Testosterone (Androderm)	2-4mg	Daily application to the back, abdomen, upper arms, or thigh
Transdermal Solution		
Testosterone solution (Axiron)	60 mg	Once daily applied to the axilla

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Venous Thromboembolic Event Risk

Given the established VTE risk associated with estrogen replacement therapy in menopausal women, concern has been raised for a similar risk profile with TRT. However, data regarding the risk of VTE men undergoing TRT are lacking. A recent meta-analysis of RCTs found that TRT is not associated with increased risk of VTE.[7] Although data suggest no increased VTE risk in patients undergoing TRT, there have been no investigations of VTE risk for patients undergoing TRT, specifically in relation to the perioperative period after orthopaedic surgery.

Cardiovascular Event Risk in Testosterone Replacement Therapy

Investigations have indicated TRT as a potential cause of increased cardiovascular events. This has resulted in recommendations for limitation of its use. One study garnering concern depicted an increase in nonfatal myocardial infarction within the first 90 days of initiation of TRT, but paradoxically displayed a decrease in event risk after the initial 90-day period.[8] Conversely, multiple more contemporary investigations including meta-analyses of TRT have not depicted any notable increase in cardiovascular events of men undergoing TRT. Furthermore, investigations have depicted that patients with low serum testosterone treated with TRT are at lower risk of all-cause mortality, MI, and stroke compared with men not treated.[9] Current data are mixed, but suggest a mostly favorable cardiovascular safety profile for individuals undergoing TRT. However, no study directly investigates the effect of TRT and cardiovascular events in the orthopaedic surgery perioperative setting.

Prostatic Hyperplasia and Prostate Cancer Risk

Serum free testosterone converts to dihydrotestosterone (DHT), which is known to increase prostate size and prostate-specific antigen. Questions regarding prostate health and potential for development of prostate cancer in men undergoing TRT have not been seen in the literature. The literature depicts no increased risk of benign prostatic hyperplasia, urinary tract infection, or histological changes in prostate tissue of men undergoing TRT.[10] Furthermore, several studies including meta-analysis of TRT on the development of prostate cancer did not find any notable correlation between prostate cancer development and progression in men undergoing TRT and suggest that it may be safely prescribed without concern for development of prostatic pathology.[11] Additional work is needed to identify any potential relationship between TRT and urologic or prostatic pathology in the perioperative orthopaedic surgery period.

Effect of Testosterone Replacement Therapy on Orthopaedic-Related Conditions and Surgical Interventions

Musculotendinous Pathology

Testosterone may have implications on musculotendinous injuries related to the intricate effect of testosterone on musculotendinous growth, laxity, and healing after repetitive microtrauma of activity.[12] Testa et al[13] (2023) recently investigated the effect of TRT on the development of rotator cuff pathology and surgical outcomes. The study analyzed over 9,000 patients who were prescribed TRT and had a subsequent rotator cuff tear within 90 days. The authors reported that both men and women on TRT have over a threefold greater risk of sustaining a rotator cuff tear compared with matched control subjects. In addition, the TRT cohort of that study was found to have a 1.6-fold greater likelihood for rotator cuff repair compared with non-TRT patients. Furthermore, the patients on TRT undergoing rotator cuff repair were 26.7-fold more likely to require subsequent rotator cuff repair within 1 year regardless of laterality and 1.9-fold more likely to require revision rotator cuff repair. Of note, the study design was retrospective and did not differentiate if TRT was discontinued in the perioperative period. Regardless, this markedly increased rate of rotator cuff injury brings into question the effect of TRT on the soft-tissue injury rate and subsequent healing after surgical intervention. Conversely, Smith et al (2022) analyzed the rate of rotator cuff tear in men with androgen deficiency. The authors of that investigation reported 89% increased odds of sustaining a rotator cuff tear in men with androgen deficiency compared with those with the normal androgen level.[14] Rebello et al (2023) recently investigated distal biceps rupture in patients prescribed TRT and reported that those on TRT were over 2 times more likely to sustain distal biceps tendon rupture compared with age-matched cohorts not on TRT. The authors did not investigate the rate of contralateral distal biceps tear or revision of distal biceps repair rate.[15] These recent retrospective investigations have begun to delineate the role that TRT and endogenous levels of testosterone may have on the development and healing of musculotendinous pathology. Future prospective studies should be developed to investigate the risk of musculotendinous injury and healing in patients on TRT.

Osteoarthritis and Total Joint Arthroplasty

Concomitant with TRT incidence, the demand of arthroplasty is projected to markedly increase in coming years.[16] Given this trend, an understanding of the interplay between TRT, development of osteoarthritis, and rates of total joint arthroplasty among this population is crucial. Investigations of osteoarthritis development in relation to serum testosterone levels have produced mixed results. Prior investigations identified a positive association of serum testosterone and tibial cartilage volume, which the author postulated may indicate a protective effect of testosterone from the development of knee osteoarthritis.[17] Conversely, Hanna et al[18] (2005) reported a notable correlation between increased rate of tibial cartilage loss and higher serum free testosterone levels, suggesting a positive correlation between testosterone and development of osteoarthritis. Investigations of THA and TKA rates related to testosterone levels have also reported mixed findings. One retrospective cohort study measured endogenous male sex hormones including testosterone, dehydroepiandrosterone sulfate, androstenedione, estradiol, and sex hormone binding globulin (SHBG). These patients were followed for two decades and analyzed for incidence of THA or TKA because of osteoarthritis. The study found that only androstenedione was markedly inversely correlated with rates of TKA or THA specifically in overweight or obese men.[19] The authors of that study did not identify any correlation between testosterone and OA risk; however, given the study design, it was limited in its scope and

conclusions that can be drawn. A more recent study has identified a positive relationship between higher levels of serum testosterone and DHT with increased risk of THA, as well as a positive relationship of increased testosterone and risk of hip osteoarthritis.[20] The current available data regarding the effect of endogenous testosterone on the development of osteoarthritis and need for total joint arthroplasty are unclear.

Osteoporosis

Serum testosterone and its metabolite DHT directly influence osteoblast differentiation and proliferation resulting in an anabolic environment for bone production and subsequent bone density. Male hypogonadism is associated with the development of osteoporosis and subsequent increased fracture risk.[21] Although osteoporosis and fracture are less common in men than women, it is associated with increased mortality risk when fracture occurs.[22] Studies have investigated the effect of TRT on BMD and have depicted notable increases in BMD for osteoporotic hypogonadal men treated with TRT.[23] A double-blind placebo-controlled study of men with low testosterone identified a notable positive relationship of increased volumetric BMD and increased estimated strength of the osseous elements of the spine and hip in men who received TRT.[24] Current research suggests that exogenous TRT increases BMD, but no direct investigation of the relationship between TRT and potential risk reduction of osteoporosis or subsequent fracture exists.

Bone-Implant Integration

Successful surgical outcomes are often dependent on bone-implant integration success. Failure of orthopaedic implant integration with osseous elements can lead to malunion and nonunion after fracture surgery as well as implant loosening after arthroplasty surgery. Lack of implant-bone integration can result in additional revision surgery that carries increased risk of infection, morbidity, and cost and the overall decreased rate of successful outcomes because of lack of bone stock from prior surgery.[25] The growing commonality of press-fit implantation, especially in the TKA literature, provides an added focus of attention regarding optimization of bone-implant integration.[26] There have been various applications of testosterone investigated for improvement of implant integration. A recent in vivo animal study provided evidence that testosterone incorporated into a bioceramic and polymer composite may improve osseous integration at the cellular level. That study found that the addition of testosterone to the bioceramic composite increased osteoblastic activity and enhanced extracellular matrix production and mineralization compared with the control bioceramic composite without testosterone.[27] Another study applied testosterone coating to titanium screws and implanted them in an in vivo femoral condyle defect rabbit model to analyze the effect on bone-implant integration and healing. The study reported that implanted screws coated with testosterone resulted in a markedly increased bone-implant contact surface area and BMD and produced greater bone volume compared with screws not coated with testosterone.[28] These current studies suggest that testosterone incorporation into implant surfaces may encourage increased osteogenesis; however, they do not attempt to assess the relationship of endogenous testosterone level and bone-implant integration. Future investigations may examine the influence of direct testosterone implant integration and systemic TRT on bone-implant integration and healing.

Recovery and Rehabilitation

TRT has been linked to increased lean body mass, strength, and decreased rate of sarcopenia.[23] Theoretically, TRT may, therefore, assist individuals in the postoperative recovery and rehabilitation period. Randomized controlled trials of geriatric men in rehabilitation programs have identified notable improvement in functional independence, physical performance, grip strength, and lean body mass of geriatric men treated with TRT versus those given placebo.[29] Regarding the use of TRT during postoperative rehabilitation from orthopaedic surgery, Amory et al (2002) investigated the utilization of testosterone supplementation for TKA rehabilitation. This study provided preoperative supraphysiologic levels of testosterone by injection of 600 mg testosterone enanthate intramuscularly weekly for 4 weeks preoperatively and measured rehabilitation outcomes after TKA. The authors found notable improvement in functional independence and trends toward improvement in ambulation and stair navigation for patients obtaining supraphysiologic serum testosterone concentrations before surgery.[30] Notably, this study provided supraphysiologic levels of testosterone, which is above the recommended dosing for TRT, and may be associated with additional adverse events. Freystaetter et al[31] (2020) measured serum testosterone levels in men and women at 6 to 8 weeks postoperatively after TKA and reported higher levels of testosterone in both men and women to correlate with improved Western Ontario and McMaster Universities Osteoarthritis Index pain scores in the operated knee as well as

lower disability scores of both women and obese men. Expedited rehabilitation after elective orthopaedic surgery has recently become increasingly important. Future investigations may analyze the effect of TRT protocols on expedited rehabilitation to facilitate ambulatory surgical procedures.

Improved early recovery may also be beneficial in the setting of hip fracture and other urgent orthopaedic surgery. One ongoing multicenter trial is enrolling women with recent hip fracture and applying topical testosterone gel versus placebo to investigate the effect of testosterone on post-hip fracture surgery rehabilitation.[32] There are currently no data on the role TRT may play on early recovery in these settings. Evidence suggests higher endogenous levels of testosterone and exogenous supraphysiologic TRT can improve recovery rates after TKA. However, no study draws direct assessment of physiologic TRT on postoperative orthopaedic surgery rehabilitation outcomes.

Infection Risk

Surgical site infection, deep implant infection, and periprosthetic joint infection (PJI) are of notable concern after orthopaedic surgery. Given the morbidity and costly consequences of such infections, there is a large effort to minimize infection risk within the field of orthopaedic surgery. One recent meta-analysis investigated sex-related differences in the treatment of PJI with débridement, antibiotics, and implant retention. The meta-analysis found a higher rate of successful infection eradication in women and suggested that testosterone may play a role in immune system suppression.[33]

A correlation between serum testosterone level and infection risk after total shoulder arthroplasty (TSA) has been reported. Within the shoulder arthroplasty prosthetic joint infection literature, there is a reported PJI incidence of 0.4 to 2.9% after TSA. Of those infections, the most common organism identified is Staphylococcus Aureus at 31%. However, the second most common organism causing approximately 19% of these infections is *Cutibacterium acnes*.[34] There also exists a known correlation between serum testosterone level and skin burden of *C. acnes*. In a recent investigation of 51 TSAs, Schiffman et al (2021) collected the preoperative levels of free serum testosterone, total serum testosterone, and SHBG as well as cultures of the patient's skin for *C. acnes* in the clinic preoperatively, the operating room just before antiseptic preparation, and on the dermal wound edge of the incised skin. Schiffman et al[35] reported that serum testosterone is an independent predictor for high skin *C. acnes* load. The authors also identified an increased level of testosterone and increased load of *C. acnes* in patients on TRT, which accounted for five of the 51 patients in the study. However, the study did not define TRT preparation, dose, serum concentration, length of treatment, or whether the TRT was prescribed by a physician. The authors reported that the mean skin burden of *C. acnes* was 50% greater in the five patients taking TRT compared with those who were not. Although this increase in *C. acnes* load appears high, because of the small sample size of patients on TRT, this did not reach statistical significance. The authors, therefore, concluded that although there may be an increased risk of *C. acnes* skin colonization with TRT, there are not enough data to recommend the cessation of testosterone supplementation in the perioperative period. In another relevant study, Matsen et al (2020) investigated revision TSA for PJI by preoperatively culturing patients' skin and reported that the presence of *C. acnes* is a reliable predictor for deep *C. acnes* infection.[36] Although current reports are limited, the literature supports an increased risk of *C. acnes* PJI in TSA for individuals with higher serum testosterone and that this risk may be exacerbated by TRT use. Outside of studies on TSA, there is minimal literature regarding TRT and infection risk in all other orthopaedic subspecialties and associated procedures. This paucity of data is concerning because infection with *C. acnes* have also been reported after THA, TKA, and arthroscopic procedures.[37] At this time, appropriate assessment of the relationship between testosterone and perioperative infection risk cannot be made. Furthermore, *C. acnes* has also been reported as the offending pathogen in native joint septic arthritis.[38-40] The relationship of serum testosterone and skin burden of *C. acnes* at anatomical locations other than the shoulder has not been investigated. Given the mortality rate and poor outcomes related to PJI and deep implant infection, future investigation of the effect that endogenous testosterone and TRT have on postoperative infection risk is warranted.

Conclusion

In this review, we summarize the current literature surrounding risks and potential clinical benefits of TRT in the orthopaedic patient. The current data on TRT and risk of VTE, cardiac events, prostatic pathology suggest minimal risk, yet to date few studies assess these events in relation to orthopaedic surgery. There are presently data suggesting TRT may be correlated with

increased risk of musculotendinous injury and subsequent repair failure. Moreover, there is a potential correlation of TRT and *C. acnes* PJI. There is also a potential benefit of TRT in improved rehabilitation, recovery, and bone-implant integration. TRT in the field of orthopaedics requires additional investigation to outline its safety, efficacy, and potential for an effect on clinical outcomes.

SMARTQC

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