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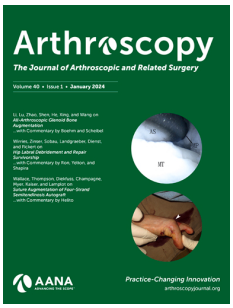

Editorial Commentary-Testosterone Replacement Therapy and ACL Injury Risk: Insights and Cautions for Clinical Application

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Abstract
The relationship between testosterone replacement therapy (TRT) and anterior cruciate ligament (ACL) injury risk has garnered attention in recent orthopaedic research. With TRT's popularity on the rise, understanding its potential musculoskeletal risks is important for orthopaedic and sports medicine providers. While some studies suggest an association, confounding variables such as activity level, number of hours of sport participation, dosing variations, physiological versus supraphysiological levels of testosterone, and individual patient characteristics may influence outcomes. In addition, the etiology may not be biologic, as patients undergoing TRT may experience increased motivation and energy levels, leading them to engage in higher risk activities. Our research shows supraphysiologic testosterone supplementation (for short periods of time) increases lean body mass postoperatively, suggesting a potential benefit in recovery following ACL surgery. Clinicians should remain vigilant, ensuring that TRT is prescribed judiciously, with a thorough assessment of each patient's unique risk profile.

Perspective/Commentary

The recent study by Brinkman et al., titled "Prescription Testosterone is Associated with an Increased Risk of Anterior Cruciate Ligament Injury," explores an understudied area within sports medicine and identifies a correlation between TRT use and ACL injury.[1] With TRT's popularity on the rise, understanding its potential musculoskeletal risks is important for orthopaedic and sports medicine providers. The authors' use of a large, retrospective cohort with over 160,000 patients in each group is impressive and enables a powerful statistical analysis that shows an increased ACL injury risk among TRT users. This level of analysis provides clinicians with helpful preliminary data on an emerging area of interest.

However, while the study's findings are intriguing, we believe it is premature to imply causation between TRT and ACL injuries based solely on these results. One primary concern is the number of confounding variables that may have influenced the association observed. The study lacks detailed data on key factors such as activity levels, specifically the number of hours spent in sports and recreational activities.[2-4] These factors are crucial and well-documented risk factors for ACL injury. Multiple studies,[2-4] as well as anecdotal experiences from sports medicine specialists, attest that increased exposure time raises the likelihood of ACL injury. Patients undergoing TRT may experience increased motivation and energy levels, leading them to engage in more high-impact physical activities than non-TRT patients in the same age group, potentially predisposing them to ACL injuries independent of TRT's effects. Young age (less than 25 years) is also a well-documented risk factor for ACL injury. Activity level in the young population is considered to play a major role in the risk of ACL injury. In the current study, the average age was 50 years old, and the group with the strongest association for ACL tear and TRT use was between 55 and 65 years of age. Interestingly, in the study, there was no statistically significant correlation between TRT use and ACL injury in the patients under 25 years of age. We interpret this finding as supporting our hypothesis that activity level is playing a bigger role than TRT use alone. As a result, TRT use may have increased the older cohort's exposure hours to sports and recreational activities and therefore their risk of ACL injury. As there is no way to examine this variable in this database study, we therefore can neither prove nor disprove our hypothesis.

The study's authors note limitations associated with the CPT code 29888, which may encompass both primary and revision ACL reconstructions. The study also does not control exercise intensity, body composition, or concurrent medications, which significantly complicates causal inference. While the authors cite studies noting an association between TRT use and

tendinous injury, suggesting that TRT directly increases ligamentous injury risk may be overstated without further control over these influential variables. Including a wider range of patient-specific data would strengthen the argument and offer a clearer picture of TRT's role in ligament health. Furthermore, if elevated testosterone levels were a significant risk factor for ACL tears, one might expect men to experience ACL ruptures at a higher rate than their female counterparts.

Another limitation of the study is the lack of differentiation between physiological and supraphysiological levels of testosterone. This leaves room for speculation about the precise impact TRT might have on ligamentous structures. In patients diagnosed with hypogonadism, the goal of TRT should be to reach physiological testosterone levels and not supraphysiological levels. While there is evidence that supraphysiologic levels of testosterone can increase the risk of tendon rupture,[5] this risk has not been as clearly demonstrated for ligamentous injury. In the present study, we do not know the actual drug dosages or the testosterone levels that were obtained following TRT administration.

It is also essential to consider findings from other studies, such as one published in the New England Journal of Medicine in January 2024, titled "Testosterone Treatment and Fractures in Men with Hypogonadism." This study demonstrated TRT was associated with a higher fracture risk in men with hypogonadism vs placebo despite TRT radiographically improving bone mineral density and bony microarchitecture.[6] As with the TRT and ACL rupture risk study, the investigators did not include physical activity which again could potentially be a confounding variable for fracture risk. Over the past 15 years, multiple studies[7-9] have helped elucidate testosterone's role in modulating motivation, reward and effort-related behaviors through multiple different neurological and biochemical mechanisms in the brain. It is now well documented that testosterone affects the brain's perception of effort and rewards effortful activities.[10-13] Testosterone therefore directly influences dopamine regulation, neuroplasticity, and reward circuitry centers in the brain. The relationship between TRT, activity level, and injury risk is a critical area of research that warrants further exploration before discounting TRT's potential musculoskeletal benefits.

In 2017, we published our results from a randomized controlled trial, "Perioperative Testosterone Supplementation Increases Lean Mass in Healthy Men Undergoing Anterior Cruciate Ligament Reconstruction," where we found that supraphysiologic testosterone supplementation increased lean body mass postoperatively, suggesting a potential benefit in recovery following ACL surgery.[14] Currently, we are now involved in two separate randomized controlled trials attempting to optimize the post-operative period with a short course of supraphysiologic doses of synthetic derivatives of testosterone; the purpose of which is to decrease the effects of catabolism from the initial trauma and subsequent surgery in patients who have suffered knee dislocations and are undergoing multiple ligament knee reconstructions. My co-authors and I are dedicated to investigating the potential role of testosterone in muscle mass preservation and improved functional recovery after orthopaedic surgery. While TRT aims to normalize levels in patients with hypogonadism or conditions resulting in testosterone deficiency, our research studies involve the administration of supraphysiologic levels of testosterone to healthy patients (for short periods of time) for the purpose of optimizing surgical recovery. Therefore, the research being conducted by our group is not accurately classified as a TRT related study and direct comparisons are difficult.

In our clinical experience, while TRT can offer symptomatic relief for hypogonadism, it is crucial to approach its prescription with a comprehensive understanding of potential risks. This includes a thorough evaluation of patient activity levels, musculoskeletal health, and individual risk

factors for injury. We advocate for a personalized approach, where the decision to initiate TRT is made collaboratively with the patient, considering both the potential benefits and risks. Additionally, we emphasize the importance of patient education, ensuring individuals are aware of the possible implications of TRT on their musculoskeletal system and encouraging them to engage in preventive measures, such as strength training and flexibility exercises, to mitigate injury risk.

In conclusion, while the study by Brinkman et al. contributes valuable data to the ongoing discussion regarding the role of testosterone treatment and musculoskeletal health, it is imperative to interpret the findings with caution. The potential for confounding variables necessitates a careful and individualized approach to TRT prescription. Further prospective studies, with rigorous control of confounding factors, are essential to elucidate the true relationship between TRT and ACL injury risk. Until then, clinicians should remain vigilant, ensuring that TRT is prescribed judiciously, with a thorough assessment of each patient's unique risk profile.

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