The Relationship Between Exogenous Testosterone Use and Risk for Primary Anterior Cruciate Ligament Rupture

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Background: In the United States, testosterone therapy has markedly increased in recent years. Currently, there is a paucity of evidence evaluating the risk of ligamentous injuries in patients taking testosterone replacement therapy (TRT).

Purpose/Hypothesis: The purpose of this study was to quantify the association between TRT and the incidence of anterior cruciate ligament (ACL) injuries and the subsequent risk of ACL reconstruction (ACLR) failure. It was hypothesized that individuals receiving TRT would demonstrate an increased risk for index ACL injury and ACL rerupture.

Study Design: Cohort study; Level of evidence, 3.

Methods: This is a retrospective cohort study utilizing the PearlDiver database. Records were queried between 2011 and 2020 for patients aged 18 to 59 years who filled a testosterone prescription. A matched control group based on age, sex, Charlson Comorbidity Index, tobacco use, diabetes, and hypothyroidism consisted of patients aged 18 to 59 years who had never filled a prescription for exogenous testosterone. International Classification of Diseases, 9th and 10th Revisions and Current Procedural Terminology (CPT) codes were utilized to identify patients with ACL injuries and those undergoing reconstruction. Multivariable logistic regression was used to compare rates of ACL injury at 6 months, 1 year, and 2 years after initiating TRT. ACLR failure was also examined at 1-year intervals for 5 years for individuals filling a TRT prescription.

Results: A total of 851,816 patients were enrolled, with 425,908 patients in the TRT and control groups, respectively. The TRT cohort was significantly more likely to experience an ACL tear during 6-month (OR, 2.66; 95% CI, 2.17-3.26), 1-year (OR, 2.46; 95% CI, 2.11-2.86), and 2-year (OR, 2.22; 95% CI, 1.98-2.48) periods. The rate of reconstruction failure did not differ between the 2 cohorts at up to 5 years of follow-up ($P > .05$).

Conclusion: Patients receiving TRT were significantly more likely to sustain a primary ACL rupture but were not at a statistically significant increased risk of reconstruction failure.

Keywords: anterior cruciate ligament; reconstruction; testosterone; hormone replacement therapy

Testosterone is an androgen, or male sex hormone, that plays an integral role in an array of orthopaedics-related physiological processes, including muscle growth, bone metabolism, and fat distribution.[9,10,38] While exogenous testosterone use is typically associated with anabolic steroids aimed at improving athletic performance, there has been an increasing trend in prescribed testosterone replacement therapy (TRT) for men between the ages of 18 and 45 years.[12,17,25,38] The most common indication for initiation of TRT is hypogonadism in men, but there has been growing evidence suggesting that TRT may be efficacious in improving libido, bone density, body composition, lean muscle mass, depression, and cognition.[5,13,19,32] The deleterious effects of anabolic steroids on tendinous health have been well documented and are attributed to the alteration of matrix metalloproteinase concentrations in addition to imbalances between muscle and tendon strength.[2,9,14,16,26,36] The effect of testosterone on ligament health, however, has not been well characterized.

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Anterior cruciate ligament (ACL) ruptures represent a substantial physical, psychological, and economic burden to patients with an increasing incidence approaching 250,000 per year.[7,15] While this increase has been seen in all age groups, there has been a dramatic rise in the number of patients ≥40 years of age undergoing ACL reconstruction (ACLR) as surgical techniques and rehabilitation protocols have improved. Interestingly, while ACLR using autograft has shown superior results to ACLR using allograft in younger athletes, there is evidence to suggest no difference in outcomes in patients ≥40 years of age.[6,27] Historically, these injuries have demonstrated greater frequency in women and have led to investigations exploring the influence of sex hormones on the ACL. Although most studies have focused on the role of the female sex hormones estrogen and progesterone, the presence of testosterone receptors on the ACL has been established.[1,11,21,24,30] To date, studies examining the effect of testosterone on the risk of ACL injury have been limited to observational and animal studies. While animal models have demonstrated increased ACL strength with testosterone supplementation, human studies have produced mixed results, with evidence supporting both deleterious and protective effects.[28,29,34] In addition to its potential influence on ACL injury, postoperative testosterone supplementation has been a topic of interest as testosterone levels have been shown to decrease postoperatively.[37] One prior investigation on the effect of testosterone supplementation after ACLR demonstrated significant differences in lean mass, suggesting that exogenous testosterone may help to mitigate the effects of postoperative muscle atrophy and enhance recovery.[40] Given the paucity of studies, there are substantial limitations in our current understanding of the effect of TRT on one's risk for initial ACL injury as well as reinjury after ACLR.

The current study aimed to quantify the association between TRT and the incidence of ACL injuries as well as the subsequent risk of ACLR failure. We hypothesized that individuals receiving TRT would demonstrate an increased risk for both index ACL injury and ACL rerupture. To our knowledge, this represents the largest epidemiological investigation into the relationship between TRT and ACL injuries.

METHODS

Data Source

This retrospective comparative analysis was performed using deidentified data from the M161Ortho data set within the PearlDiver Mariner database (PearlDiver Technologies). This insurance claims database is generated and updated using all Humana Incorporated insurance claims from their >161 million insured patients between January 2010 and April 2022. These data provide researchers the ability to longitudinally characterize and analyze short-, medium-, and long-term rates of various conditions and complications using International Classification of Diseases, 9th (ICD-9) and 10th (ICD-10) Revisions and Current Procedural Terminology (CPT) codes. For the current study, these data were used to calculate rates of index ACL tears and revision operation in those who underwent surgery among patients who filled prescriptions for TRT and to compare them with rates of a matched control population.

Generating the Cohorts

The MOrtho161 data set within the larger Mariner database was queried for all patients who filled a prescription for TRT, which returned 2,191,194 patients. This cohort was subsequently filtered to include patients only between the ages of 18 and 59 years to capture the population primarily affected by ACL injuries. Patients were excluded if they were not active within the database for at least 2 years (ie, changed providers, lost insurance, or died) to minimize the amount of patient drop-off during the study period. Similarly, only patients who filled their prescriptions before April 30, 2020, were included. Lastly, patients with a previous diagnosis of connective tissue or rheumatological disease, metastatic cancer, Paget disease of the bone, hyperparathyroidism, or multiple myeloma were excluded from the study. This query returned 1,073,383 patients in each cohort and was then limited to a randomized sample of 500,000 to facilitate data handling for the matching process. This cohort was subsequently matched based on age, sex, Charlson Comorbidity Index, tobacco use, diabetes, and hypothyroidism to a randomly generated control cohort that met the inclusion criteria. This created 2 overall cohorts of 425,908 patients.

Calculating the Rate of ACL Tears and Primary Reconstruction

The rate of ACL tears was calculated over 6-month, 1-year, and 2-year periods after the initial filled TRT prescription and compared with the same time periods within the control group. These injuries were identified using ICD-9 and ICD-10 codes. Only index ACL tears were included in the rate analysis.

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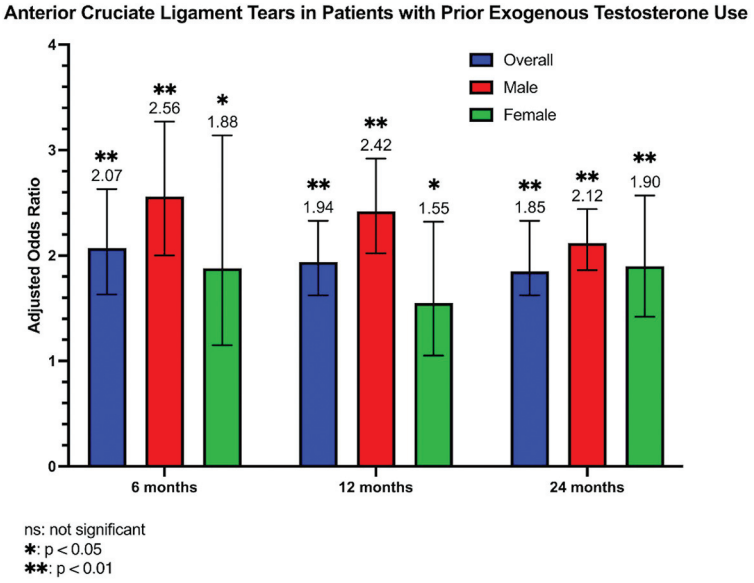

Figure 1. Rate of anterior cruciate ligament reconstruction in patient cohorts receiving testosterone replacement therapy. Control adjusted odds ratio = 1.

Calculating the Rate of Revision ACLR

In this second analysis of revision ACLR, the M161Ortho data set was queried for all patients who underwent arthroscopic ACLR (CPT-29888), and the previously utilized exclusion and inclusion criteria were applied, creating a new sample population. Only index ACLRs were included in the analysis. Only patients who underwent ACLR and had an associated ICD-10 code that specified laterality (ICD-10-D-M23611, ICD-10-D-S83511A, ICD-10-D-S83511D, ICD-10-D-S83511S, ICD-10-D-M23612, ICD-10-D-S83512A, ICD-10-D-S83512D, ICD-10-D-S83512S) were included in the study. This allowed for the identification of which knee was operated on and limited the analysis to only those patients who underwent a revision ACLR on the same knee previously operated on, excluding those patients who subsequently underwent ACLR on the opposite knee. Patients who elected to not undergo revision ACLR were excluded from the cohort. This cohort was divided based on whether the patient filled a prescription for TRT within the year after their ACLR. Rates of revision ACLR within 2, 3, 4, and 5 years of the initial surgery were calculated and compared.

Statistical Analysis

A sample-size calculation was performed for each time interval based on the observed proportions to minimize the risk of type 2 error. A significance level of .05 and power of 0.8 were used for these calculations. Multivariable logistic regression controlling for age, sex, Charlson Comorbidity Index, diabetes, tobacco use, hypothyroidism, chronic kidney disease, obesity (BMI $>$ 30 kg/m^2), morbid obesity (BMI $>$ 40 kg/m^2), osteoporosis, alcohol use, osteoarthritis, lung disease, congestive heart failure, and hypogonadism was used to compare rates of ACL tears and revision reconstructions. Adjusted odds ratios and 95% CIs were generated and reported for each comparison. To protect patient identity, cohorts consisting of $<$11 patients are reported as "–1" by PearlDiver and thus are reported as "$<$11" throughout this paper. Statistical analyses are still able to be performed on these smaller cohorts, but the specific value is simply not reported. A P value $<$.05 was determined to represent statistical significance a priori. Post hoc power analysis was performed to confirm the validity of study findings using a significance level of .05 and power set to 0.8. All statistical analyses were performed using the R Statistical Package (Version 4.2.1; R Core Team 2022) embedded within PearlDiver.

RESULTS

The median age of both the TRT and control cohorts was 48 years (range, 18-59 years), and 75.4% were of male sex. The percentages of patients who use tobacco or have diabetes were 27.5% and 28.7% from the TRT and control groups, respectively. The calculated sample sizes were 34,515 participants per group for the 6-month interval, 22,054 per group for the 12-month interval, and 15,300 per group for the 24-month interval. Within 6 months after filling a prescription for TRT, 343 patients experienced an ACL tear, compared with just 129 patients in the control cohort (adjusted OR, 2.07; 95% CI, 1.63-2.63). Within the male-specific groups, the patients using TRT were 2.56 times more likely to experience an ACL tear. Similarly, the TRT patients in the female-specific cohorts were 1.88 times more likely to experience an ACL tear (Figure 1).

TABLE 1
Rates of Primary Anterior Cruciate Ligament Tears in Patients With and Without a History of Testosterone Replacement Therapy Use[a]

	No. of Tears		Unadjusted Analysis		Adjusted Analysis	
Population and Timeline	Prior Testosterone Use	Control	OR (95% CI)	*P*	OR (95% CI)	*P*
Total	425,908	425,908				
6 mo	343 (0.08)	129 (0.03)	2.66 (2.17-3.26)	<.001	2.07 (1.63-2.63)	<.001
12 mo	572 (0.13)	233 (0.05)	2.46 (2.11-2.86)	<.001	1.94 (1.62-2.33)	<.001
24 mo	982 (0.23)	443 (0.10)	2.22 (1.98-2.48)	<.001	1.85 (1.62-2.11)	<.001
Male sex	321,188	321,188				
6 mo	292 (0.09)	104 (0.03)	2.81 (2.25-3.51)	<.001	2.56 (2.00-3.27)	<.001
12 mo	494 (0.15)	190 (0.06)	2.60 (2.20-3.08)	<.001	2.42 (2.02-2.92)	<.001
24 mo	830 (0.26)	370 (0.12)	2.25 (1.99-2.54)	<.001	2.12 (1.86-2.44)	<.001
Female sex	104,720	104,720				
6 mo	51 (0.05)	25 (0.02)	2.04 (1.26-3.29)	.004	1.88 (1.15-3.14)	.014
12 mo	78 (0.07)	43 (0.04)	1.81 (1.25-2.63)	.002	1.55 (1.05-2.32)	.030
24 mo	152 (0.15)	73 (0.07)	2.08 (1.58-2.75)	<.001	1.90 (1.42-2.57)	<.001

[a]Data are given as n (%) unless otherwise indicated.

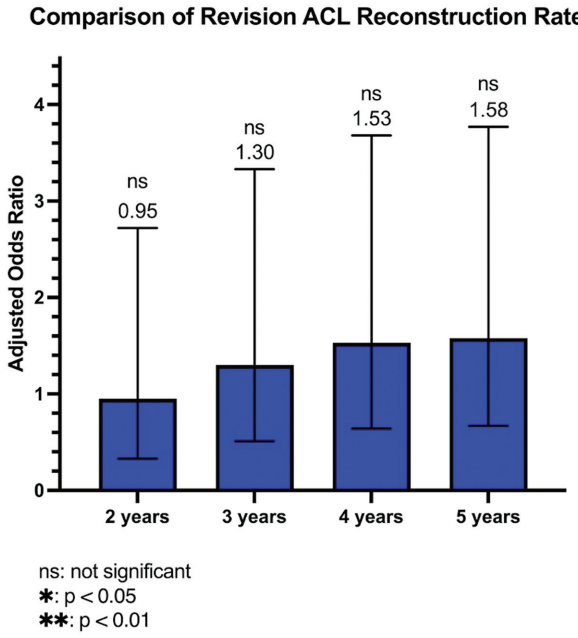

Figure 2. Rate of revision anterior cruciate ligament (ACL) reconstruction in patient cohorts receiving testosterone replacement therapy. Control adjusted odds ratio = 1.

Table 1 demonstrates the unadjusted and adjusted analyses for the 6-month, 12-month, and 24-month time points. The analysis of primary ACLR that subsequently required revision demonstrates no statistically significant difference between the TRT cohort and the control cohort at 1-year intervals for 5 years (Figure 2, Table 2). Post hoc power analysis demonstrated a power of >0.8 at all time intervals for the primary ACLR group. The revision cohort did not reach the threshold of $\beta \geq 0.8$ and achieved a maximum power of 0.47 at the 5-year interval.

DISCUSSION

While the number of individuals receiving TRT has continued to climb over the past several years, little is known about the potential effects of exogenous testosterone on ACL injury.[38] The results of the current study suggest that patients filling TRT prescriptions demonstrate an increased risk of ACL rupture at 6, 12, and 24 months after initiating therapy. This increased risk was maintained in both male and female cohorts, with the highest risk at 6 and 24 months, respectively. This association was not maintained in the revision setting. Although no statistically significant difference was observed in the revision cohort, the increasing trend was statistically underpowered. To our knowledge, this is the first study to demonstrate an association between exogenous testosterone use and an increased risk for ACL rupture.

Epidemiological studies on ACL injuries have revealed notable disparities in injury prevalence between men and women, prompting heightened interest in elucidating the role of sex hormones in explaining the increased risk of ACL injuries observed in women.[33] Historically, substantial attention has been given to sex hormones such as estrogen, progesterone, and relaxin, and their relationship with ACL injuries in female patients.[1,24,33,34,39] For example, there is research describing a higher rate of ACL injuries during certain phases of the menstrual cycle.[22,39] With specific regard to testosterone, basic science animal research has found that testosterone levels were correlated with greater ACL strength in a load-to-failure and ultimate stress model in rats.[28,29] In humans, the literature has been mixed, with results in female populations demonstrating decreased levels of testosterone as a potential risk factor for ACL rupture, whereas in male populations, increased levels of testosterone were associated with an increased risk for ACL rupture.[34] While the results of these studies are difficult to translate to the clinical setting, they provide foundational information denoting the significance

TABLE 2
Rate of Reconstruction Failure After Anterior Cruciate Ligament Reconstruction in Patients With and Without Testosterone Replacement Therapy Within the 2 to 5 Years After Their Surgery[a]

	No. of Tears		Unadjusted Analysis		Adjusted Analysis	
Population and Timeline	Prior Testosterone Use	Control	OR (95% CI)	*P*	OR (95% CI)	*P*
Total	818	818				
2 y	14 (1.71)	11 (1.34)	1.28 (0.58-2.83)	.687	0.95 (0.33-2.72)	.931
3 y	19 (2.32)	12 (1.47)	1.60 (0.77-3.31)	.277	1.30 (0.51-3.33)	.583
4 y	23 (2.81)	13 (1.59)	1.79 (0.90-3.56)	.129	1.53 (0.64-3.68)	.336
5 y	25 (3.06)	13 (1.59)	1.95 (0.99-3.84)	.071	1.58 (0.67-3.77)	.295

[a]Data are given as n (%) unless otherwise indicated.

of testosterone as a hormone that likely affects the health status of the ACL. Taken together, there is likely a complex relationship between ACL health and sex hormone levels, with testosterone a key player in this equation for both men and women.

Hamlet et al[11] investigated the biological significance of sex hormones and the presence of androgen receptors in the human ACL by conducting primary immunolocalization of androgen target cells within the ACL. Their study revealed the existence of androgen receptors within stromal fibroblasts and synoviocytes of ACL tissue in young male participants. Interestingly, these male athletes exhibited augmented collagen content in comparison with their female counterparts. The presence of androgen receptors hints at the potential influence of androgens on the structural composition of the ACL. Subsequent studies have lent support to this hypothesis, demonstrating that women also harbor androgen receptors within the ACL, albeit to a lesser extent than men. Lovering and Romani[21] corroborated the presence of androgen receptors in the ACLs of young women by conducting an in-depth analysis to ascertain the correlation between testosterone, the free androgen index (FAI), estrogen, and ACL stiffness at 3 distinct stages of the menstrual cycle in healthy, active women. The authors found that participants with higher concentrations of FAI or testosterone near ovulation demonstrated heightened ACL stiffness, whereas participants with higher estrogen-to-testosterone or estrogen-to-FAI ratios exhibited lower ACL stiffness near ovulation and during the luteal phase. This finding underscores the pivotal role of the dynamic balance between estrogen and testosterone in mediating ACL stiffness.

Such noteworthy findings lend insight to the observations discerned in our present study. Despite foundational scientific investigations suggesting that natural testosterone is associated with augmented ACL strength, our current study's results indicate an elevated risk of ACL injury among patients receiving exogenous TRT. A plausible explanation for this discrepancy may lie within the altered relationship between endogenous levels of testosterone and estrogen. Alternatively, this effect may be mediated by the well-documented adverse effect of increased estrogen levels in men undergoing TRT given the aromatization of testosterone into estrogen.[3] It is conceivable that the surplus of estrogen exerts a detrimental effect on the mechanical properties of the ACL, a phenomenon that is the result of reduced lysyl oxidase activity, and results in detrimental augmentations to collagen and elastin cross-linking in ligamentous structures.[20] While this explanation provides a biochemical perspective, it is essential to acknowledge that the relationship between testosterone and ligament integrity is multifactorial and may be subject to confounding factors that account for the observed elevated risk of native ACL injury in patients undergoing TRT.

Beyond the physiological interplay of testosterone and the balance of the testosterone-to-estrogen ratio, the risk for ACL injury is substantially influenced by additional risk factors such as the type and volume of physical activity a patient may pursue. Patients seeking TRT are often interested in enhancing their longevity and physical fitness. Specifically, these patients have been shown to self-report improvements in energy, focus/cognition, sociability, and overall well-being after initiating TRT.[35] These subjective measures in conjunction with objective measurements such as improvements in body composition and fitness capacity may result in increased participation in activities that place patients at increased risk for sustaining ACL injuries.[3,8,13,19,40] Therefore, it is prudent that future basic science and clinical studies further elucidate the influence of testosterone on ligament health and seek to minimize confounding variables related to ACL injury risk.

While TRT was observed to be associated with an increased risk of native ACL injury, our study did not observe any statistically significant difference in the risk of reinjury among patients undergoing ACLR. One potential explanation for the absence of a statistical difference may be in relation to the use of allografts in ACLR. As the median age of our cohort was 48 years, it is possible that allografts were routinely used.[6] Given the known biochemical alterations in tissue composition associated with allograft processing, it could be that this process alters androgen and estrogen receptor density. It is therefore plausible that these changes may influence one's risk for rerupture while undergoing TRT.[31] Furthermore, previous research has suggested that TRT may have a protective effect when administered in the perioperative period before and after ACLR. For instance, a study conducted by Thompson et al[37] revealed a significant disruption of the hypothalamic-pituitary axis, the primary regulator of testosterone levels, after ACLR. The authors reported

a substantial decrease in both total and free testosterone levels in patients undergoing ACLR. Notably, patient-reported outcomes (PROs) mirrored these trends in testosterone levels, with an observed increase in PROs as testosterone levels returned to baseline after surgery. Such findings pose a concern, as a postsurgery decline in testosterone can exacerbate the loss of muscle mass and strength commonly observed in the postoperative setting, potentially leading to delayed recovery and impaired functional outcomes. Consequently, researchers have delved into investigating the potential benefits of TRT in the phase after ACLR. In a recent randomized controlled trial conducted by Wu et al,[40] patients were randomized to receive either TRT or a placebo after ACLR. The study revealed a significant increase in lean muscle mass among those receiving TRT, while patients in the placebo group experienced a decrease in postoperative lean muscle mass. Although no significant differences in long-term PROs were observed, it is essential to note that this study was limited by its relatively small sample size of only 13 patients. Nevertheless, these preliminary findings, which suggest an accelerated recovery after ACLR with supplemental testosterone, underscore the need for future studies to further elucidate the potential benefits of hormonal supplementation after ACLR, particularly in elite athletes who require an expedited return to play.

The results of our study provide important improvements to the existing body of literature. Our findings demonstrated an increased risk of a primary ACL rupture after various early time points of consecutive exogenous testosterone use ranging from 6 months to 2 years in both male and female cohorts. These results are further strengthened by the fact that both cohorts far exceeded sample size calculations, confirming that appropriate power was achieved. Interestingly, no significant differences were found in regard to risk for revision ACLR at up to 5 years postoperatively. While both groups had acceptable revision rates of <5%, the relatively low total number of revisions precluded appropriate powering for this cohort, and these results should be interpreted with caution.[23] Notably, the administration of exogenous testosterone may lead to important increases in physical activity in patients as a result of improved energy levels, which may present a difficult-to-study risk factor for ligamentous and tendon injury. As a result, a causal relationship between ACL rupture and testosterone supplementation cannot be definitively made. However, these important findings provide a useful counseling point when caring for patients prescribed testosterone supplementation, particularly those who take part in contact and/or pivoting activities or have other risk factors for cruciate ligament rupture. Another highly relevant point when considering testosterone supplementation could be its potential utility in the rehabilitation of patients who have ACL injuries. As testosterone has been shown to increase the caliber of the ACL in a rat model as well as increase lean muscle mass and does not show an increased risk of rerupture requiring revision per our findings, TRT may be useful in the rehabilitation process after ACL tear and reconstruction.[4,18,28,32] There are currently no long-term studies showing improved clinical outcomes in such a group, but this represents an important topic for future research.

Limitations

There are several limitations to the present study. First, the retrospective nature of this database-claims study heavily relies on consistent and accurate recording of both ICD-10 codes and TRT prescription records to generate the desired cohorts. Second, our results regarding risk for revision reconstruction are limited by the fact that the cohort was underpowered, which may represent the presence of type 2 error. Additionally, the inability to identify concomitant injuries, graft choice, and rehabilitation protocols limits the interpretability of these results, as they can contribute to ACLR failure. This limitation may have been impacted by whether patients elected to undergo revision surgery as well as the reliance on appropriate coding practices identifying laterality. Third, we were unable to identify the indication for TRT initiation, dosing regimen, and serum testosterone levels at the time of injury. Similarly, we were unable to ascertain activity levels of individual patients before their initial injury and after reconstruction. We aimed to minimize the effect of these variables through identification of TRT treatment timing in relation to injury as well as patient demographics such as age and medical comorbidities. Logically, more active patients may have greater exposure to injury, and our inability to quantify this exposure may confound our results. Last, although the patients in this study represent a sizable cohort, the data were generated using a single insurance provider, which may not be a representative sample of patients with other insurance providers such as Medicare or Medicaid.

CONCLUSION

Patients receiving TRT were significantly more likely to sustain a primary ACL rupture but were not at a statistically significant increased risk of reconstruction failure.

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