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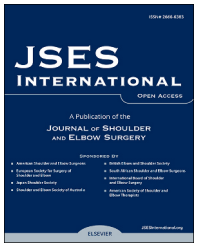

Prescription testosterone is associated with increased risk of infection-related and all-cause reoperations after primary total shoulder arthroplasty in male patients

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ABSTRACT

Background: Total shoulder arthroplasty (TSA) is an effective procedure for patients with progressive shoulder conditions, but complications like infection and reoperation remain common concerns. Testosterone therapy, often prescribed for hypogonadism, may impact immune function and wound healing, potentially increasing the risk of infections and reoperations. However, the association between testosterone use and reoperation after TSA remains unclear.

Methods: We performed a retrospective cohort study using the MarketScan Commercial Claims Database, including 54,850 primary TSAs from 2017 to 2021. Patients with testosterone prescriptions within 12 months before surgery were identified. After matching for demographic and clinical factors, 481 men prescribed testosterone were compared to 962 controls. Cumulative incidences of infection-related and all-cause reoperations at 1, 2, and 3 years postoperatively were analyzed using univariate and multivariate regression models. Data were summarized as odds ratios (ORs) and 95% confidence intervals (CIs). Statistical significance was set at $P < .05$.

Results: Demographic features were similar between men prescribed testosterone and those not prescribed testosterone. Men prescribed testosterone had statistically significantly higher cumulative incidences of both infection-related reoperations and all-cause reoperations at 1, 2, and 3 years. Multivariate analysis confirmed that testosterone use was an independent risk factor for both infection-related (OR = 4.1, 95% CI [1.0-16.4], $P = .049$) and all-cause reoperations (OR = 2.2, 95% CI [1.1-4.3], $P = .03$).

Conclusion: Our findings suggest that testosterone use is associated with a higher risk of both infection-related and all-cause reoperations after TSA. Future research is needed to determine whether this association is causal and deepen the understanding of testosterone's effects on wound healing and immune recovery.

Level of evidence: Level III; Retrospective Cohort Comparison using Large Database; Prognosis Study

Keywords: Total shoulder arthroplasty; Testosterone; Reoperation; Infection; Postoperative complications; Immunomodulation

This study was exempt from institutional review board approval.

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Total shoulder arthroplasty (TSA) has emerged as an effective procedure for patients with progressive shoulder arthritis, sequelae of fractures, and other debilitating conditions.[23] While TSA is generally associated with positive outcomes, complications such as infection and the need for reoperation remain significant concerns.[7,19] Reoperation, particularly due to infection, can negatively affect patient outcomes and quality of life, increasing health care costs and prolonging recovery times.[6,12]

Testosterone therapy, widely prescribed for hypogonadism and other conditions, affects various aspects of musculoskeletal and immune function.[1] However, its influence on surgical outcomes, particularly after TSA, remains uncertain.[4] Emerging evidence suggests that testosterone supplementation may impair immune responses and wound healing,[8-11] potentially increasing the risk of postoperative infection and reoperation. Elevated serum testosterone levels have been linked to higher dermal *Cutibacterium acnes* (*C. acnes*) loads,[24,26] and greater *C. acnes* colonization has been associated with periprosthetic joint infection.[21,22] Mechanistically, testosterone enhances sebaceous gland activity and sebum production,[15,17] creating lipid-rich conditions that favor *C. acnes* growth, while also altering the skin microbiome[5] and modulating local immune responses.[8,12] Systemically, androgens may downregulate key inflammatory mediators such as interleukin-1β, interleukin-6, tumor necrosis factor alpha, and C-reactive protein[28] and reduce macrophage and neutrophil activity.[8,11] Testosterone may also delay wound healing by suppressing keratinocyte proliferation and migration via inhibition of Wnt/β-catenin and transforming growth factor signaling,[27] limiting angiogenesis through vascular endothelial growth factor downregulation,[16] and disrupting fibroblast-mediated collagen synthesis through interference with the TGF-β/Smad3 pathway.[3] Despite these proposed mechanisms, the direct relationship between prescription testosterone use and postoperative infection or reoperation after TSA remains inadequately defined and warrants further investigation.[20,24,26]

The relationship between prescription testosterone use and the risk of periprosthetic infection or reoperation following TSA remains poorly defined, with existing evidence both limited and conflicting. Previous studies have been constrained by heterogeneous patient cohorts—often combining anatomic and reverse shoulder arthroplasty—insufficient adjustment for key confounding variables such as comorbidities and Charlson Comorbidity Index (CCI) scores, and a narrow focus on infection-related outcomes without accounting for broader reoperation risks over time. This study aims to fill that gap by specifically evaluating the association between prescription testosterone use and the odds of both infection-related and all-cause reoperation following primary TSA, while addressing the methodological limitations of earlier research. A retrospective cohort investigation was conducted utilizing the MarketScan Commercial Claims Database, which offers a robust platform for analyzing real-world data across a large population.[18] Through this study, we seek to better understand the impact of testosterone therapy on postoperative outcomes and to inform clinical decision-making in patients receiving TSA. We hypothesize that prescription testosterone use is associated with a higher risk of reoperation due to infection and all-cause reoperation after TSA.

Materials and methods

After approval from our institutional review board, a retrospective cohort study was conducted using the MarketScan Commercial Claims Database (Merative, Ann Arbor, MI, USA).[18] A total of 54,850 primary TSAs were identified between January 1, 2017, and December 31, 2021, based on specified Current Procedural Terminology (CPT) and International Classification of Diseases, Tenth Edition (ICD-10) procedure codes.

Patients were excluded if their primary TSA was performed for a diagnosis of malignancy or infection. Gender dysphoria was identified using the relevant ICD-10 codes. Patients were considered testosterone users if they had a prescription for testosterone within 1 year prior to TSA. Claims were further excluded based on the criteria shown in Fig. 1, resulting in a final study population of 10,017 TSAs.

All outcomes were identified using relevant CPT and ICD-10 codes (Supplemental Table 1). Ipsilateral TSA reoperations were determined based on procedure codes, with laterality established using CPT modifiers and diagnosis code indicators. Reoperations attributed to infection were defined by the presence of infection-related diagnosis codes at the time of surgery. Patients were followed for up to three years postoperatively or until December 31, 2022, to assess the occurrence of ipsilateral reoperation.

Comorbidities, such as diabetes mellitus, hypertension, hyperlipidemia, obesity, smoking, and alcohol use within 30 days of TSA, were defined using the relevant ICD-10 codes. The CCI, including each category, was calculated within 30 days of TSA using the ICD-10 codes and criteria described by Glasheen et al.[13]

Patients were then matched 2:1 based on age, setting of TSA (inpatient or outpatient), comorbidities (diabetes, hypertension, hyperlipidemia, obesity, smoking, and alcohol use), and CCI score using Mahalanobis nearest-neighbor matching. This matching resulted in a final analysis cohort of 481 men prescribed testosterone and 962 men not prescribed testosterone.

Matching was performed using R (R Core Team, Vienna, Austria), and cumulative incidences of infection-related and all-cause reoperation at 1, 2, and 3 years postoperatively were

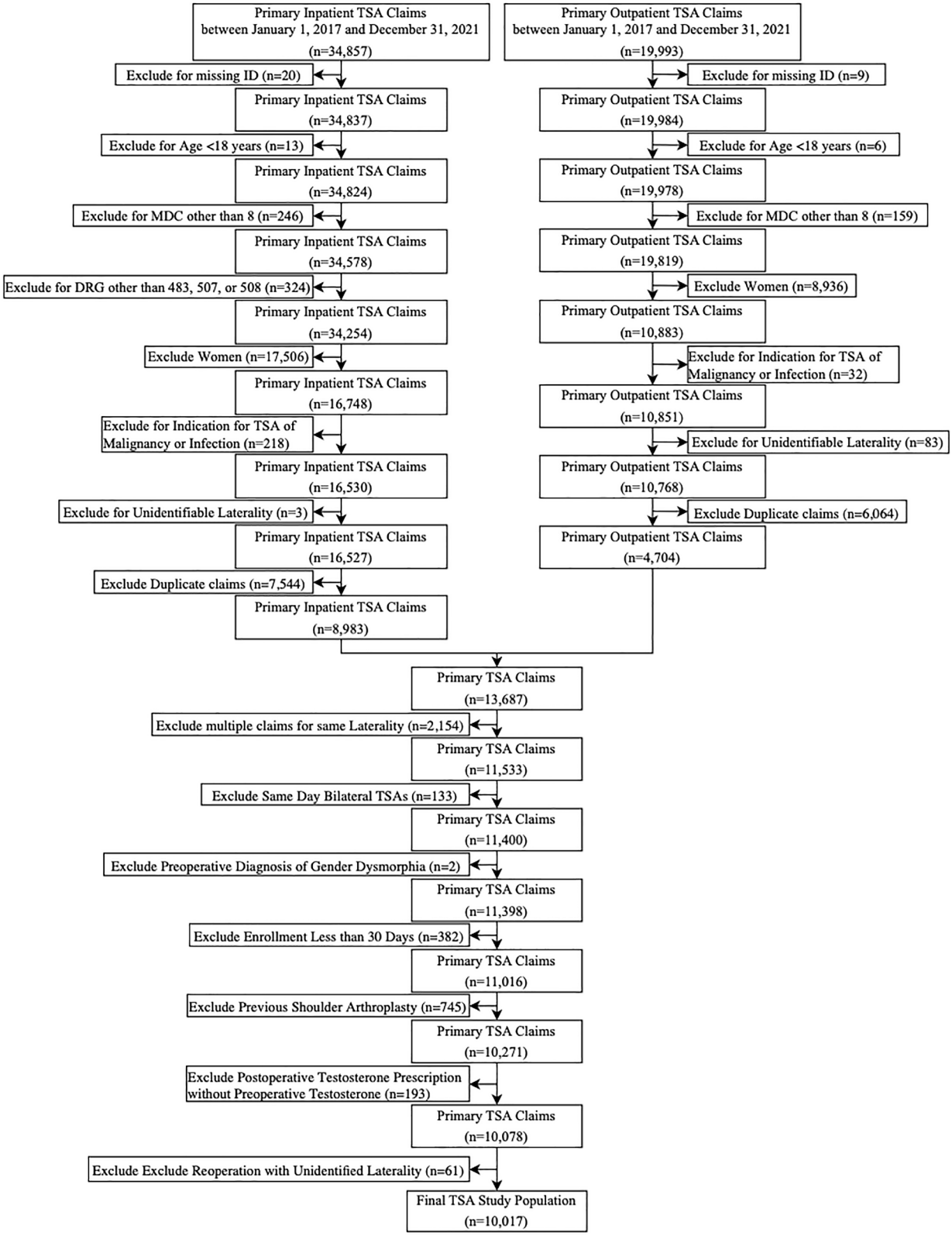

Figure 1 — Flowchart of the selected patient cohort. *TSA*, total shoulder arthroplasty; *DRG*, diagnosis related group; *MDC*, major diagnostic category.

Table I – The baseline demographics of the analyzed cohort.

Demographic and clinical variables	No prescription testosterone n = 962	Prescription testosterone n = 481	Total n = 1,443	*P* value
Age (yr), mean (range)	60.6 (31-89)	60.5 (34-88)	60.5 (31-89)	.9*
Laterality, n (%)				.1†
Left	419 (43.6)	232 (48.2)	651 (45.1)	
Right	543 (56.4)	249 (51.8)	792 (54.9)	
Diabetes mellitus, n (%)	202 (21.0)	101 (21.0)	303 (21.0)	1.0†
Hypertension, n (%)	604 (62.8)	302 (62.8)	906 (62.8)	1.0†
Hyperlipidemia, n (%)	442 (45.9)	221 (45.9)	663 (45.9)	1.0†
Obesity, n (%)	250 (26.0)	125 (26.0)	375 (26.0)	1.0†
Smoking, n (%)	128 (13.3)	64 (13.3)	192 (13.3)	1.0†
Alcohol, n (%)	10 (1.0)	5 (1.0)	15 (1.0)	1.0†
CCI score, mean (range)	2.4 (0-12)	2.4 (0-11)	2.4 (0-12)	.9*
Setting of TSA, n (%)				1.0†
Inpatient	618 (64.2)	309 (64.2)	927 (64.2)	
Outpatient	344 (35.8)	172 (35.8)	516 (35.8)	
Length of stay (d), mean (range)	0.9 (0-27)	0.9 (0-28)	0.9 (0-28)	.9*
Follow-up (yr), mean (range)	2.1 (0.1-6.0)	1.9 (0.1-5.9)	2.1 (0.1-6.0)	.02*

CCI, Charlson Comorbidity Index; *TSA*, total shoulder arthroplasty.
* *P* values for numerical variables were calculated using a two-tailed independent samples *t*-test.
† *P* values for categorical variables were calculated using a two-tailed chi-square test.

estimated using the Kaplan–Meier survival method. Statistical analysis was conducted using Python (Python Software Foundation, Beaverton, OR). Chi-square tests and independent samples *t*-tests were used to compare the matched cohort of men with and without prescription testosterone. Univariate and multivariate logistic regression models were employed to evaluate risk factors for all-cause reoperation and reoperation for infection. Firth's correction in R was applied to calculate odds ratios (ORs) and 95% confidence intervals (CIs) when zero instances of a condition were observed.[9] Statistical significance was set at $P < .05$. The detailed coding information is available in Supplemental Table 1.

Results

Demographics

Demographic and clinical characteristics were similar between men prescribed testosterone (n = 481) and those not prescribed testosterone (n = 962) (Table I). The mean age was comparable between groups (60.5 years [range, 34-88] vs. 60.6 years [range, 31-89]; $P = .9$). Laterality distribution was similar, with left-sided procedures in 232 (48.2%) testosterone users and 419 (43.6%) nonusers ($P = .1$). Comorbidities were also comparable, including diabetes mellitus (101 [21.0%] vs. 202 [21.0%], $P = 1.0$), hypertension (302 [62.8%] vs. 604 [62.8%], $P = 1.0$), hyperlipidemia (221 [45.9%] vs. 442 [45.9%], $P = 1.0$), obesity (125 [26.0%] vs. 250 [26.0%], $P = 1.0$), and smoking (64 [13.3%] vs. 128 [13.3%], $P = 1.0$). Mean CCI scores were identical between groups (2.4, $P = .9$). The majority of procedures were performed in inpatient settings (309 [64.2%] vs. 618 [64.2%], $P = 1.0$), and mean length of stay was the same (0.9 days, $P = .9$). However, patients not prescribed testosterone had a slightly longer mean follow-up duration (2.1 years [range, 0.1-6.0] vs. 1.9 years [range, 0.1-5.9]; $P = .02$).

Risk factors for reoperation for infection

Men prescribed testosterone had a significantly higher cumulative incidence of reoperation for infection at 1 year (1.4%, 0%, $P < .001$), 2 years (1.4% vs. 0.2%, $P = .003$), and 3 years (1.4% vs. 0.7%, $P = .03$) postoperatively compared to those not prescribed testosterone (Fig. 2). In the univariate analysis, testosterone use was a risk factor for reoperation for infection (OR = 4.0, 95% CI [1.0-16.2], $P = .049$). Other factors, including age, laterality, comorbidities (diabetes mellitus, hypertension, hyperlipidemia, obesity, smoking, alcohol), CCI score, inpatient TSA, and length of stay were not significant risk factors (Table II). The multivariate analysis confirmed that only prescription testosterone (OR = 4.1, 95% CI [1.0-16.4], $P = .049$) was a risk factor for reoperation for infection (Table III).

Risk factors for all-cause reoperation

Men prescribed testosterone had a higher cumulative incidence of all-cause reoperation at 1 year (3% vs. 1.2%, $P = .03$), 2 years (4.3% vs. 1.6%, $P = .01$), and 3 years (4.3% vs. 2.5%, $P = .02$) postoperatively compared to those not prescribed testosterone (Fig. 3). In the univariate analysis, testosterone use increased the risk for reoperation (OR = 2.2, 95% CI [1.1-4.3], $P = .03$). Other factors, for example, age, comorbidities, and TSA-related factors, were not associated with reoperation risk (Table IV). The multivariate analysis showed that prescription testosterone (OR = 2.2, CI = 1.1-4.3, $P = .03$) was the only significant risk factor for all-cause reoperation (Table V).

Discussion

This investigation was designed to assess the relationship between prescription testosterone use and the risk of reoperation for infection and all-cause reoperation following primary TSA.

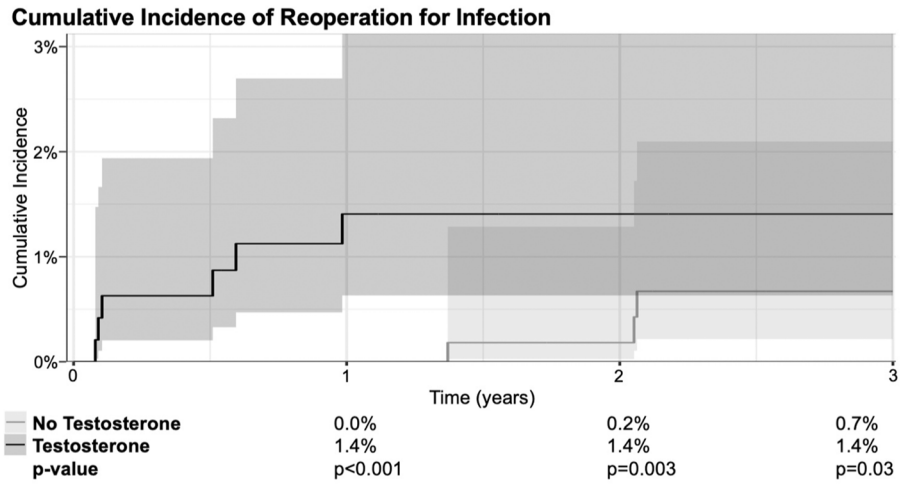

Figure 2 – Cumulative incidence of reoperation for infection. Men prescribed testosterone had a significantly higher cumulative incidence for reoperation for infection at 1, 2, and 3 years postoperatively.

Table II – Univariate analysis of risk factors for reoperation for infection.

Risk factor	No reoperation for infection n = 1,434	Reoperation for infection n = 9	Total n = 1,443	*P* value*	OR (95% CI)
Age (yr), mean (range)	60.5 (31-89)	63.1 (46-86)	60.5 (31-89)	.3	1.0 (1.0-1.1)
Laterality, n (%)					
Left	645 (45.0)	6 (66.7)	651 (45.1)	.2	2.4 (0.6-9.8)
Right	789 (55.0)	3 (33.3)	792 (54.9)	Ref	Ref
Prescription testosterone, n (%)					
No prescription testosterone	959 (66.9)	3 (33.3)	962 (66.7)	Ref	Ref
Prescription testosterone	475 (33.1)	6 (66.7)	481 (33.3)	.049	4.0 (1.0-16.2)
Diabetes mellitus, n (%)	302 (21.1)	1 (11.1)	303 (21.0)	.5	0.5 (0.1-3.8)
Hypertension, n (%)	901 (62.8)	5 (55.6)	906 (62.8)	.7	0.7 (0.2-2.8)
Hyperlipidemia, n (%)	662 (46.2)	1 (11.1)	663 (45.9)	.1	0.1 (0.0-1.2)
Obesity, n (%)	373 (26.0)	2 (22.2)	375 (26.0)	.8	0.8 (0.2-3.9)
Smoking, n (%)	191 (13.3)	1 (11.1)	192 (13.3)	.8	0.8 (0.1-6.5)
Alcohol, n (%)	15 (1.0)	0 (0.0)	15 (1.0)	.4	4.8 (0.04-41.1)
CCI Score, mean (range)	2.4 (0-12)	3.0 (0-10)	2.4 (0-12)	.3	1.2 (0.9-1.5)
Setting of TSA, n (%)					
Inpatient	921 (64.2)	6 (66.7)	927 (64.2)	.9	1.1 (0.3-4.5)
Outpatient	513 (35.8)	3 (33.3)	516 (35.8)	Ref	Ref
Length of stay (d), mean (range)	0.9 (0-28)	1.3 (0-4)	0.9 (0-28)	.4	1.1 (0.9-1.3)

CCI, Charlson Comorbidity Index; *TSA*, total shoulder arthroplasty; *Ref*, reference; *OR*, odds ratio; *CI*, confidence interval.
* OR and corresponding *P* values were derived from univariate logistic regression.

Our findings suggest that prescription testosterone may be associated with an increased risk of both infection-related and all-cause reoperations after TSA, which was supported by univariate and multivariate analyses. In addition, men prescribed testosterone had a significantly higher cumulative incidence of infection-related and all-cause reoperations at 1, 2, and 3 years postoperatively, highlighting the potential long-term impact of testosterone on reoperation risk. Although the overall sample size of this study was large, the absolute number of infection-related reoperations was small, resulting in wide CIs and limited statistical power. This low event rate not only contributes to borderline statistical significance but also raises the potential for type I error. Consequently, these findings should be interpreted with caution and considered hypothesis-generating, pending confirmation in future studies with larger event counts and prospective validation.

These findings are consistent with previous studies suggesting that testosterone therapy can negatively impact immune function and wound healing,[8,11] potentially increasing the risk of infection and complications following surgical procedures.[24,26] Su et al[26] analyzed the PearlDiver database (PearlDiver Technologies, Colorado Springs, CO, USA) to evaluate the influence of testosterone use on prosthetic joint infection frequencies after TSA. Among 43,997 patients, 2,285 used testosterone. They demonstrated that testosterone use within 6 months of TSA was connected to a higher infection rate (3.4%) compared to nonusers (2.4%) [OR = 1.44, 95% CI: 1.03-2.01, *P* = .042]. No increased risk was observed for those

Table III – Multivariate analysis of risk factors for reoperation for infection.

Risk factor	P value*	OR (95% CI)
Age (yr)	.5	1.0 (0.9-1.1)
Prescription testosterone	.049	4.1 (1.0-16.4)
Diabetes mellitus	.4	0.4 (0.0-3.6)
Hypertension	.9	1.1 (0.3-4.3)
Hyperlipidemia	.1	0.1 (0.0-1.1)
Obesity	1.0	1.0 (0.2-5.4)
Smoking	.8	0.8 (0.1-6.7)
CCI score	.5	1.2 (0.8-1.7)
Inpatient setting of TSA	1.0	1.0 (0.2-4.6)

CCI, Charlson Comorbidity Index; *TSA*, total shoulder arthroplasty; *OR*, odds ratio; *CI*, confidence interval.
* OR and corresponding *P* values were derived from multivariate logistic regression.

who stopped testosterone 6-12 months prior. Multivariate analysis identified younger age and diabetes mellitus as independently associated. The authors recommend screening for testosterone use and considering cessation before surgery to reduce infection risk.[26] Schiffman et al[24] examined the relationship between testosterone concentrations and skin *Cutibacterium* loads in 51 patients receiving TSA. They found that both total serum testosterone and free testosterone levels measured in the clinic were strongly correlated with higher *Cutibacterium* loads on the skin in the clinic, operating room, and wound edge during surgery. Multivariate analysis showed that serum testosterone independently predicted high skin *Cutibacterium* loads, even when accounting for age and sex. The results of this study suggest that patients receiving supplementary testosterone have a higher dermal *Cutibacterium* load, mediated by higher serum testosterone, highlighting a potential role for testosterone supplementation in the risk of developing periprosthetic joint infection following TSA.[24]

In contrast, Parmar et al[20] conducted a retrospective cohort study utilizing the PearlDiver database (2010-2022) to investigate the impact of supplementary testosterone therapy on outcomes following reverse total shoulder arthroplasty (rTSA) specifically. A cohort of 1,906 rTSA patients who used supplementary testosterone therapy within 90 days of surgery was matched with a control group of 1,906 patients based on CCI, age, and gender. This study found no significant differences in revision rates (12.01% vs. 11.02%, $P = .335$) or prosthetic joint infection rates (1.42% vs. 1.63%, $P = .597$). These findings suggest that, unlike the results seen by Su et al[26] and Schiffman et al,[24] supplementary testosterone therapy does not seem to amplify the likelihood of infection or other complications following rTSA.

Our findings align with prior studies, reinforcing the consistency and reliability of the observed association between testosterone therapy and postoperative outcomes following TSA.[26] However, this study contributes several important strengths to the existing literature. Unlike previous research that often included mixed cohorts or focused on rTSA, our analysis specifically examines primary TSA, a population with distinct indications, outcomes, and risk profiles. The 2:1 matched cohort design, controlling for key demographic and clinical variables, including comorbidities and CCI scores, enhances internal validity and allows for more precise risk estimation. In addition, we report cumulative incidence of all-cause reoperation at 1, 2, and 3 years, extending beyond the infection-related outcomes commonly evaluated in earlier work. Finally, the study contextualizes these results within clinical practice by addressing implications for preoperative planning, testosterone management, immune function, and patient counseling, thereby providing valuable guidance for clinicians.

The proposed biological mechanisms linking testosterone to increased dermal *C. acnes* load through enhanced sebaceous activity,[5] altered skin microbiota,[8] and local immune modulation[8,11] are based on prior studies and should be interpreted as hypothesis-generating. Because our database does not contain microbiologic data, these mechanisms cannot be confirmed within the present analysis and instead

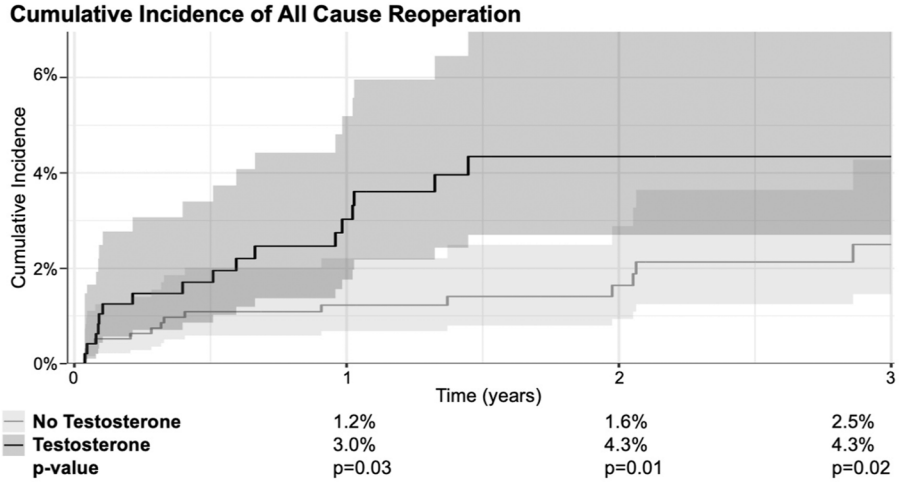

Figure 3 – Cumulative incidence of all cause reoperation. Men prescribed testosterone had a significantly higher cumulative incidence for all cause reoperation at 1, 2, and 3 years postoperatively.

Table IV – Univariate analysis of risk factors for all-cause reoperation.

Risk factor	No reoperation n = 1,410	Reoperation n = 33	Total n = 1,443	*P* value*	OR (95% CI)
Age (yr), mean (range)	60.6 (31-89)	59.9 (42-86)	60.5 (31-89)	.6	1.0 (0.9-1.0)
Laterality, n (%)					
Left	637 (45.2)	14 (42.4)	651 (45.1)	.8	0.9 (0.4-1.8)
Right	773 (54.8)	19 (57.6)	792 (54.9)	Ref	Ref
Prescription testosterone, n (%)					
No prescription testosterone	946 (67.1)	16 (48.5)	962 (66.7)	Ref	Ref
Prescription testosterone	464 (32.9)	17 (51.5)	481 (33.3)	.03	2.2 (1.1-4.3)
Diabetes mellitus, n (%)	298 (21.1)	5 (15.2)	303 (21.0)	.4	0.7 (0.3-1.7)
Hypertension, n (%)	887 (62.9)	19 (57.6)	906 (62.8)	.5	0.8 (0.4-1.6)
Hyperlipidemia, n (%)	652 (46.2)	11 (33.3)	663 (45.9)	.1	0.6 (0.3-1.2)
Obesity, n (%)	365 (25.9)	10 (30.3)	375 (26.0)	.6	1.2 (0.6-2.6)
Smoking, n (%)	189 (13.4)	3 (9.1)	192 (13.3)	.5	0.6 (0.2-2.1)
Alcohol, n (%)	15 (1.1)	0 (0.0)	15 (1.0)	.8	1.3 (0.01-10.4)
CCI Score, mean (range)	2.4 (0-12)	2.4 (0-10)	2.4 (0-12)	.9	1.0 (0.8-1.2)
Setting of TSA, n (%)					
Inpatient	909 (64.5)	18 (54.5)	927 (64.2)	.2	0.7 (0.3-1.3)
Outpatient	501 (35.5)	15 (45.5)	516 (35.8)	Ref	Ref
Length of stay (d), mean (range)	0.9 (0-28)	0.9 (0-5)	0.9 (0-28)	1.0	1.0 (0.8-1.3)

CCI, Charlson Comorbidity Index; *TSA*, total shoulder arthroplasty, *Ref*, reference; *OR*, odds ratio; *CI*, confidence interval.
* OR and corresponding *P* values were derived from multivariate logistic regression.

serve to contextualize our findings within existing experimental and clinical literature. Indeed, while the meta-analytic study by Foo et al[11] suggested that testosterone largely has immunosuppressive functions, the impact on immune function remains ambiguous, as it depends on the specific aspects of immunity being studied and whether testosterone's influence is direct or indirect. In line with these hypotheses, our study identified a statistically significant connection between testosterone usage and a higher risk of infection and reoperation postsurgery. However, the exact mechanisms through which testosterone may contribute to infection remain unclear, warranting further research to explore this relationship.

In this study, it was also found that men prescribed testosterone had a significantly higher cumulative incidence of all-cause reoperation at 1, 2, and 3 years postoperatively. This finding suggests that testosterone may have broader negative effects on postoperative outcomes following TSA, potentially increasing the need for reoperation, although the specific reasons for these additional surgeries remain unclear.

Table V – Multivariate analysis of risk factors for all-cause reoperation.

Risk factor	*P* value*	OR (95% CI)
Age (yr)	.7	1.0 (0.9-1.0)
Prescription Testosterone	.03	2.2 (1.1-4.3)
Diabetes mellitus	.3	0.6 (0.2-1.7)
Hypertension	1.0	1.0 (0.5-2.2)
Hyperlipidemia	.2	0.6 (0.3-1.3)
Obesity	.4	1.4 (0.6-3.1)
Smoking	.6	0.7 (0.2-2.4)
CCI Score	.5	1.1 (0.9-1.4)
Setting of TSA	.3	0.6 (0.3-1.4)

CCI, Charlson Comorbidity Index; *TSA*, total shoulder arthroplasty; *OR*, odds ratio; *CI*, confidence interval.
* OR and corresponding *P* values were derived from multivariate logistic regression.

These data also contrasts previously published data which suggests testosterone supplementation may be associated with improved postoperative outcomes. Flynn et al[10] reviewed five randomized controlled trials to evaluate the impact of perioperative testosterone supplementation on orthopedic surgical outcomes. Their study concluded that testosterone supplementation was positively linked to enhanced clinical metrics, body configuration, and bone mineral density. However, the influence of perioperative testosterone on the risk of infection-related and all-cause reoperations was not specifically assessed.[10] There are several possible explanations for the increased rate of all cause reoperation amongst these patients. Although the underlying reason and specific type of testosterone could not be obtained from the MarketScan database, a subset of these patients were likely taking supplemental testosterone for hypogonadism. Although testosterone supplementation can improve bone mineral density, some of these patients may have had lower bone mineral density at baseline due to underlying hormone deficiency, which is a known risk factor for osteoporosis.[14] Casp et al[2] also demonstrated that while the prevalence of osteoporosis was high amongst patients undergoing shoulder arthroplasty, it was also associated with a significantly elevated risk for reoperation within 2 years of both anatomic and reverse shoulder arthroplasty, which may explain our findings. Another possible explanation is that patients who opt to use testosterone supplementation for elective reasons may be more active and could potentially be putting more stress on their implants. Ultimately, more information regarding the indication for and type of testosterone supplementation would help provide more granularity to help elucidate the reason for the increased rate of all-cause revision.

Interestingly, established risk factors commonly associated with postoperative complications, such as age, comorbidities (eg, diabetes, hypertension), laterality, and length of stay,[25] did not significantly contribute to the hazard of reoperation for infection or all-cause reoperation in this

analysis. These findings suggest that testosterone therapy may represent an independent risk factor for adverse outcomes following TSA, regardless of other established risk factors.

The clinical implications of concurrent testosterone use in patients undergoing TSA warrant careful consideration. Identification of testosterone use during preoperative evaluation is important, as our study demonstrates an association between exogenous testosterone and an increased risk of reoperation. However, testosterone therapy alone should not be considered a contraindication to surgery. Rather, its presence should inform individualized risk stratification and shared decision-making, especially in elective cases.

The strength of this study lies in its large sample size and the use of a robust real-world database (the MarketScan Commercial Claims Database) to assess the effects of testosterone therapy on primary TSA outcomes. Matching patients based on various demographic and clinical factors also reduced potential biases and confounders, increasing the reliability of our results.

Several limitations should be considered. As a claims-based database, MarketScan lacks important clinical granularity, including infection severity, microbiologic confirmation, surgical approach, and details of conservative management prior to reoperation. Consequently, causal relationships between testosterone use and postoperative infection or reoperation cannot be definitively established. These inherent limitations underscore the need for future prospective studies with richer clinical data to confirm and expand upon our findings. Our definition of testosterone exposure—based on having a prescription within 12 months before surgery—does not capture adherence, dosage, formulation, indication, or treatment duration. These unmeasured factors may introduce heterogeneity and potential misclassification bias, limiting precision and insight into patient-specific factors that contribute to infection risk and revision surgery. Although reoperations were identified using ICD-10 and CPT codes associated with postoperative infection, the database does not provide pathogen-specific information, symptom severity, or whether conservative treatments were attempted. The low number of infection-related reoperations contributed to wide CIs and limited statistical power, so these results should be interpreted with caution. While matching controlled for several demographic and clinical variables, other relevant confounders—such as baseline testosterone levels, nutritional status, immunosuppressive or corticosteroid use, and prior shoulder procedures—were unavailable, potentially introducing residual confounding. Claims data may also be subject to coding inaccuracies across health care centers. In addition, the influence of other medications interacting with testosterone therapy was not assessed. Finally, this study included only male patients undergoing primary anatomic TSA, so findings may not generalize to women, patients undergoing rTSA, or those receiving other orthopedic implants. Further research in these populations is needed to determine whether similar associations exist.

Future research should focus on prospective studies with detailed data on testosterone dosage and treatment regimens and indications for supplementation in order to clarify its impact on postoperative outcomes. Studies should also aim to collect granular clinical information, including microbiologic data, infection severity, and conservative treatment strategies prior to reoperation, to address key limitations of claims-based analyses. Investigating the biological mechanisms of testosterone's effect on immune function and healing is also needed. Expanding research to other orthopedic procedures and exploring interactions with comorbid conditions could further inform clinical decision-making. Also, studies on gender-specific effects of testosterone therapy should be conducted to assess its impact across both men and women. Lastly, there is a need for future studies with richer clinical data to explore whether underlying conditions driving testosterone use (eg, hypogonadism, endocrine disorders, elective performance enhancement) may differentially affect postoperative outcomes.

Conclusion

This study investigated the association between prescription testosterone use and reoperation risk following primary TSA. Our results suggest that testosterone use may be linked to a higher risk of both infection-related and all-cause reoperations, as indicated by both univariate and multivariate analyses. Men prescribed testosterone demonstrated a significantly higher cumulative incidence of reoperations at 1, 2, and 3 years, highlighting a potential long-term impact. These findings should be interpreted with caution due to the small number of infection events, wide CIs, reliance on prescription data without dosing information, and inherent limitations of the retrospective database design. Nonetheless, the results underscore a clinically relevant association that warrants further investigation. Future prospective studies incorporating detailed clinical, pharmacologic, and microbiologic data are needed to confirm these associations, clarify potential biological mechanisms, and inform perioperative management strategies for patients receiving testosterone therapy.

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Supplementary Data

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