



Impact of estrogen replacement therapy on outcomes following total shoulder arthroplasty: a propensity-matched retrospective cohort study of 1,779 patients

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Background: While estrogen is essential for bone remodeling, its impact on joint health is more nuanced. Previous studies suggest that high estrogen states, including those induced by estrogen replacement therapy (ERT), are associated with osteoarthritis and an increased risk of revisions after hip and/or knee arthroplasty. Given the rise in total shoulder arthroplasty (TSA) cases, it is important to investigate factors that may impact its outcomes. This study aimed to evaluate whether ERT use impacts TSA outcomes at 2, 4, and 10 years postoperatively.

Materials and methods: This was a retrospective cohort study of females aged ≥ 55 years who underwent TSA, using the TriNetX Research Network. Patients were stratified by ERT use for at least 1–5 years preoperatively. One-to-one propensity score matching was performed based on age, race, bone density, osteoarthritis, and other comorbidities. Primary outcomes were revision rates at 2, 4, and 10 years. Secondary outcomes included prosthetic joint infections, mechanical complications, and shoulder instability, as well as 90-day postoperative medical complications. Tests of significance and risk ratios (RR) were calculated to compare outcomes with an alpha of <0.05 .

Results: After matching, 1,779 patients were included in each group. At 90 days, the ERT cohort had a higher risk of deep vein thrombosis (RR = 1.91; $P = .012$). At 2 and 4 years postoperatively, the ERT group had a significantly higher risk of revisions (RR = 1.71 and 1.59, respectively), shoulder instability (RR = 1.81 and 1.80), and overall mechanical complications (RR = 1.60 and 1.67). At 10 years, the risk for revisions (RR = 1.59; $P = .002$) and mechanical complications (RR = 1.43; $P = .005$) persisted.

Conclusion: Our findings suggest that ERT is associated with long-term increased risk of revision procedures and mechanical complications following TSA. This demonstrates the complex relationship between estrogen and bone health, highlighting the need for future studies investigating the impact of ERT on implant survival and osseointegration.

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Estrogen plays a pivotal yet complex role in bone and joint health. In females, estrogen levels vary throughout the lifetime, peaking in the second decade of life and declining by up to 50% by age 50.¹⁹ Menopause, which occurs at the average of age 51 in the United States, decreases estrogen levels further and leads to symptoms such

as hot flashes and fatigue. In an estrogen-deficient state, an imbalance between bone formation and turnover occurs, as estrogen's modulatory effects on osteoclasts becomes limited.⁶ This leads to the high bone turnover rate characteristic of osteoporosis, a common condition in women over 50 years of age. In this context, “women” are defined here as individuals assigned female at birth.

The impact of estrogen on joint health, particularly in the context of osteoarthritis, reveals a more nuanced picture. Some studies suggest that high estrogen states, including those induced by use of estrogen replacement therapy (ERT), can exacerbate osteoarthritis and increase the risk of joint replacements, particularly in the knee and hip.^{3,8,14–16,22,30,31} The complex relationship

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Table I
Demographics and comorbidities of patients undergoing TSA before matching.

Variable	ERT (N = 1,853)	Non-ERT (N = 36,291)	P value	Std. diff.
Demographics				
Age at index (Mean ± SD)	70.2 ± 8.3	70.7 ± 8.3	.013	0.06
White	1,468 (82.4%)	29,761 (82.2%)	.888	0.003
Female	1,782 (100%)	36,184 (100%)	–	–
Black or African American	111 (6.2%)	2,485 (6.9%)	.297	0.026
Asian	10 (0.6%)	449 (1.2%)	.01	0.072
Comorbidities				
Diabetes mellitus	428 (23.9%)	8,657 (23.9%)	.928	0.002
BMI 30–39, adult	344 (19.3%)	5,697 (15.7%)	<.001	0.094
BMI ≥40, adult	163 (9.1%)	3,071 (8.5%)	.33	0.023
Essential hypertension	1,340 (75.2%)	24,806 (68.6%)	<.001	0.148
Chronic kidney disease	286 (16.0%)	4,479 (12.4%)	<.001	0.105
Alcohol related disorders	101 (5.7%)	1,114 (3.1%)	<.001	0.127
Nicotine dependence	222 (12.5%)	3,831 (10.6%)	.013	0.059
Chronic obstructive pulmonary disease	276 (15.5%)	4,497 (12.4%)	<.001	0.088
Atrial fibrillation and flutter	191 (10.7%)	3,262 (9.0%)	.015	0.057
Disorders of bone density and structure	849 (47.6%)	12,313 (34.0%)	<.001	0.28
Other rheumatoid arthritis	221 (12.4%)	3,311 (9.2%)	<.001	0.105
Iron deficiency anemia	273 (15.3%)	3,451 (9.5%)	<.001	0.176
Long-term steroid use	238 (13.4%)	2,443 (6.8%)	<.001	0.221
Primary osteoarthritis, shoulder	1,337 (75.0%)	33,607 (92.9%)	<.001	0.501
Generalized anxiety disorder	241 (13.5%)	2,325 (6.4%)	<.001	0.239
Major depressive disorder, recurrent	242 (13.6%)	2,509 (6.9%)	<.001	0.22

SD, standard deviation; BMI, body mass index; ERT, estrogen replacement therapy; Std Diff, standardized difference; TSA, total shoulder arthroplasty.

Baseline demographic characteristics and comorbidities of patients in the ERT and non-ERT, cohorts are presented as mean ± standard deviation for continuous variables and as counts (%) for categorical variables.

Bold indicates P-value < .05.

Table II
Demographics and comorbidities of patients undergoing TSA after matching.

Variable	ERT (N = 1,779)	Non-ERT (N = 1,779)	P value	Std. diff.
Demographics				
Age at index (Mean ± SD)	70.2 ± 8.3	70.4 ± 8.3	.562	0.019
White	1,466 (82.4%)	1,487 (83.6%)	.349	0.031
Female	1,779 (100%)	1,779 (100%)	–	–
Black or African American	110 (6.2%)	113 (6.4%)	.836	0.007
Asian	10 (0.6%)	11 (0.6%)	.827	0.007
Comorbidities				
Diabetes mellitus	426 (23.9%)	409 (23.0%)	.501	0.023
BMI 30–39, adult	343 (19.3%)	322 (18.1%)	.366	0.03
BMI ≥40, adult	163 (9.2%)	162 (9.1%)	.954	0.002
Essential hypertension	1,337 (75.2%)	1,345 (75.6%)	.756	0.01
Chronic kidney disease	284 (16.0%)	271 (15.2%)	.548	0.02
Alcohol related disorders	100 (5.6%)	97 (5.5%)	.826	0.007
Nicotine dependence	209 (12.5%)	222 (11.7%)	.504	0.022
Chronic obstructive pulmonary disease	275 (15.5%)	216 (12.1%)	.004	0.096
Atrial fibrillation and flutter	191 (10.7%)	183 (10.3%)	.662	0.015
Disorders of bone density and structure	847 (47.6%)	873 (49.1%)	.383	0.029
Other rheumatoid arthritis	220 (12.4%)	196 (11.0%)	.211	0.042
Iron deficiency anemia	272 (15.3%)	235 (13.2%)	.076	0.06
Long-term steroid use	236 (13.3%)	233 (13.1%)	.882	0.005
Primary osteoarthritis, shoulder	1,337 (75.2%)	1,327 (74.6%)	.699	0.013
Generalized anxiety disorder	238 (13.4%)	240 (13.5%)	.922	0.003
Major depressive disorder, recurrent	239 (13.4%)	210 (11.8%)	.143	0.049

SD, standard deviation; BMI, body mass index; ERT, estrogen replacement therapy; Std Diff, standardized difference; TSA, total shoulder arthroplasty.

Baseline characteristics are shown as mean ± standard deviation for continuous variables and as counts (%) for categorical variables.

Bold indicates P-value < .05.

between estrogen, bone density, and joint health raises important questions about the broader impact of ERT on orthopedic surgical outcomes. Only two retrospective studies have explored this relationship with a focus on total hip and knee replacements.^{10,23} These studies demonstrated that preoperative use of ERT may lead to increased orthopedic complications and revision procedures. With expanding indications and advancements in shoulder replacements,¹¹ the role of ERT use on total shoulder arthroplasty (TSA) outcomes should be explored. This study sought to address this gap by analyzing the effects of ERT on TSA medical and surgical

outcomes at 90 days as well as at 2, 4, and 10 years postoperatively. We hypothesized that patients on ERT have higher risk of revision procedures at 2-, 4-, and 10-years post TSA procedures.

Methods

This was a retrospective matched cohort study using the TriNetX Research Network encompassing over 138 million patients across 100 healthcare organizations, which include hospitals and clinics. Clinical variables are derived directly from clinical documents

Table III
Ninety-day complications post-TSA in ERT vs. non- ERT cohorts.

Complication	ERT cohort	Non-ERT cohort	P value	RR [95% CI]
DVT	42 (2.4%)	22 (1.2%)	.012	1.909 [1.145, 3.184]
PE	30 (1.7%)	18 (1.0%)	.081	1.667 [0.933, 2.979]
SSTI	29 (1.6%)	21 (1.2%)	.255	1.381 [0.791, 2.412]
Prosthetic joint infection	29 (1.6%)	17 (1.0%)	.075	1.706 [0.941, 3.093]
Sepsis	23 (1.3%)	13 (0.7%)	.094	1.769 [0.899, 3.481]
MI	12 (0.7%)	10 (0.6%)	.669	1.200 [0.520, 2.770]
AKI	37 (2.1%)	26 (1.5%)	.162	1.423 [0.866, 2.340]
Dehiscence	10 (0.6%)	10 (0.6%)	1.000	1.000 [0.417, 2.397]
Anemia	70 (3.9%)	49 (2.8%)	.050	1.429 [0.998, 2.046]
Blood transfusion	21 (1.2%)	22 (1.2%)	.878	0.955 [0.527, 1.729]
Heart failure	10 (0.6%)	13 (0.8%)	.534	0.771 [0.339, 1.754]
ED use	229 (12.9%)	207 (11.6%)	.261	1.106 [0.928, 1.319]
Hospital readmission	96 (5.4%)	103 (5.8%)	.610	0.932 [0.711, 1.221]
All mechanical complications	28 (1.6%)	22 (1.2%)	.393	1.273 [0.731, 2.216]
Mechanical loosening	≤10 (0.6%)	≤10 (0.6%)	1.000	1.000 [0.417, 2.397]
Periprosthetic fracture	136 (7.6%)	114 (6.4%)	.149	1.193 [0.938, 1.517]
Prosthetic dislocation	18 (1.0%)	≤10 (0.6%)	.129	1.800 [0.833, 3.888]
Aseptic revision	13 (0.7%)	≤10 (0.6%)	.530	1.300 [0.572, 2.957]
All revisions	20 (1.1%)	16 (0.9%)	.503	1.250 [0.650, 2.404]
Instability	37 (2.1%)	24 (1.3%)	.093	1.542 [0.926, 2.566]

RR, risk ratios; CI, confidence intervals; TSA, total shoulder arthroplasty; ERT, estrogen replacement therapy; DVT, deep vein thrombosis; PE, pulmonary embolism; SSTI, superficial soft tissue infection; MI, myocardial infarction; AKI, acute kidney injury; ED, emergency department. These include medical events such as myocardial infarction, pulmonary embolism, etc. as well as orthopedic complications such as infections, mechanical complications and revision procedures. Data are presented as incidence (%) and P-values with corresponding RR and 95% CI. Bold indicates P-value < .05.

through an established natural language processing system within TriNetX. The advantages of this database are access to both insured and uninsured patients, as well as the ability for long-term follow-ups. Diagnoses and procedures were gathered using Current Procedural Terminology, International Classification of Diseases, 10th Revision (ICD-10) clinical modification and procedure coding system, which are automatically mapped to their corresponding ICD, ninth Revision codes. Information regarding medications was gathered through RxNorm by National Library of Medicine and the Anatomical Therapeutic Chemical classification system.

All cohorts consisted of female patients aged 55 or older undergoing TSA procedures, including anatomic and reverse TSAs from 2004 to 2024 (Supplementary Appendix S1). Patients were further stratified based on having a prescription for ERT at least 1-5 years prior to their procedure to ensure that there was adequate time for the drug to exert its effects on bone.²⁸ Patients with a prescription for progesterone only, or estrogen and progesterone combination products, were excluded as the inclusion of progesterone can have a varying impact on bone.^{22,25} Vaginal route of administration for ERT was also excluded due to concern for not reaching adequate blood concentration levels; however, other routes, including oral, transdermal, and injectable forms, were included.¹⁷

A one-to-one (1:1) propensity score matching was performed with scores generated using greedy nearest neighbor algorithms with a caliper width of 0.1 pooled SD. An absolute value >0.1 for standardized mean difference was used to assess for residual imbalance. Variables chosen for matching included age at surgery, race, osteoarthritis of the shoulder, disorders of bone density and structure (includes osteoporosis with and without pathologic fracture), diabetes mellitus, body mass index (BMI) 30-39 and 40 and greater, rheumatoid arthritis, alcohol related disorders, nicotine dependence, essential hypertension, iron deficiency anemia, long term use of steroids, chronic obstructive pulmonary disease, atrial fibrillation and flutter, generalized anxiety disorder, major depressive disorder, and chronic kidney disease (Supplementary Appendix S1).^{2,5,7,9,13,18,20,21,29}

The primary outcomes were 2-, 4-, and 10-year revision rates (Supplementary Appendix S1). Secondary outcomes were orthopedic complications at 90 days, 2, 4-, and 10-years post-TSA,

Table IV
Two-year outcomes post-TSA in ERT vs. non-ERT cohorts.

Complication	ERT cohort	Non-ERT cohort	P value
Prosthetic joint infection	69 (3.9%)	52 (2.9%)	.116
Mechanical loosening	22 (1.2%)	≤10 (0.6%)	.033
Periprosthetic fracture	184 (10.3%)	146 (8.2%)	.028
Dislocation	43 (2.4%)	24 (1.3%)	.019
Aseptic revision	46 (2.6%)	28 (1.6%)	.034
All mechanical complications	91 (5.1%)	57 (3.2%)	.004
All revisions	75 (4.2%)	44 (2.5%)	.004
Instability	64 (3.6%)	33 (1.9%)	.001

TSA, total shoulder arthroplasty; ERT, estrogen replacement therapy. A comparison of prosthetic joint infection, mechanical complications, instability, and revision rates are made. Data are presented as incidence (%) with associated P-values. Bold indicates P-value < .05.

including periprosthetic joint infection (PJI), mechanical loosening, periprosthetic fracture, prosthetic dislocation, shoulder instability, and any mechanical complications. Other medical outcomes investigated at 90 days included deep vein thrombosis (DVT), pulmonary embolism, pneumonia, superficial soft tissue infection, sepsis, acute kidney failure, wound dehiscence, iron deficiency anemia, blood transfusion, and heart failure. All statistical analyses were conducted using TriNetX's analytic tool package. Continuous variables were assessed via a two-tailed Student's t-test, presented as mean ± standard deviation. Chi-square test was used for categorical values presented as frequency and percentage. An alpha level of 0.05 was used to determine statistical significance.

TriNetX is compliant with the Health Insurance Portability and Accountability Act and certified to the International Standards Organization 27001:2013 standard, ensuring the security and privacy of healthcare data through its Information Security Management System. All data were accessed and analyzed on December 16th, 2024. No identifiable patient-level information or healthcare organization-specific data were disclosed, and all results are presented in aggregated form. Outcomes older than 20 years are not reported and cohorts with 10 or fewer patients is shown as ≤10 to protect patient privacy. Given that this study involved secondary analysis of deidentified data, our institution deemed it institutional review board exempt.

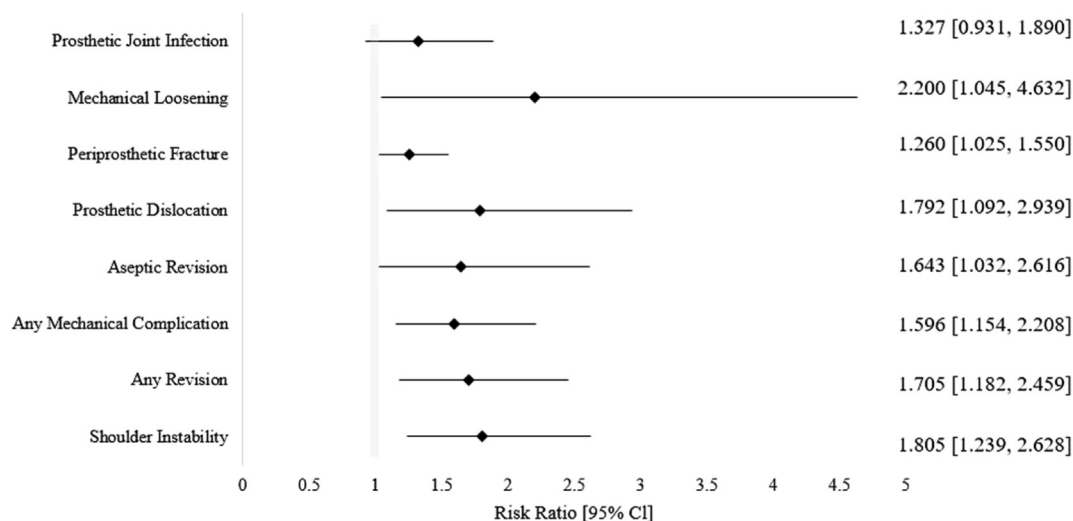


Figure 1 A forest plot depicting RR with 95% CI for 2-year postoperative complications in ERT vs. non-ERT cohorts. Outcomes include revision surgery, mechanical complications, prosthetic dislocation, and shoulder instability. A RR >1.0 indicates a higher risk in the ERT cohort. RR, risk ratios; CI, confidence intervals; ERT, estrogen replacement therapy.

Table V

Four-year outcomes post-TSA in ERT vs. non-ERT cohorts.

Complication	ERT cohort	Non-ERT cohort	P value
Prosthetic joint infection	90 (5.1%)	67 (3.8%)	.060
Mechanical loosening	32 (1.8%)	16 (0.9%)	.020
Periprosthetic fracture	191 (10.7%)	161 (9.1%)	.092
Prosthetic dislocation	52 (2.9%)	29 (1.6%)	.010
Aseptic revision	56 (3.1%)	35 (2.0%)	.026
All mechanical complications	115 (6.5%)	69 (3.9%)	.000
All revisions	97 (5.5%)	61 (3.4%)	.003
Instability	74 (4.2%)	41 (2.3%)	.002

TSA, total shoulder arthroplasty; ERT, estrogen replacement therapy.

A comparison of prosthetic joint infection, mechanical complications, instability, and revision rates are made. Data are presented as incidence (%) with associated P-values. Bold indicates P-value < .05.

Results

Demographics and characteristics before matching

Before propensity score matching, a total of 1,853 patients in the ERT cohort and 36,291 patients in the non-ERT cohort undergoing TSA were identified (Table I). Prior to matching, patients in the ERT cohort were slightly older (70.2 ± 8.3 years vs. 70.7 ± 8.3 years; $P = .013$; Std diff = 0.060), and had a higher proportion of White patients (82.4% vs. 82.2%; $P = .888$; Std diff = 0.003) compared to those in the non-ERT cohort. In the ERT cohort, the proportion of Black or African American patients was higher (6.2% vs. 6.9%; $P = .297$; Std diff = 0.026), while the proportion of Asian patients was lower (0.6% vs. 1.2%; $P = .010$; Std diff = 0.072) than the non-ERT cohort. Regarding comorbidities, the ERT cohort had a higher prevalence of obese adults with BMI 30–39 (19.3% vs. 15.7%; $P < .001$; Std diff = 0.094). Patients in the ERT cohort were more likely to have a concurrent diagnosis of disorders of bone density and structure (47.6% vs. 34.0%; $P < .001$; Std diff = 0.280) and osteoarthritis of the shoulder (75.0% vs. 92.9%; $P < .001$; Std diff = 0.501).

Demographics and characteristics after matching

After propensity score matching, a total of 1,779 patients were included in both the ERT and non-ERT cohorts (Table II). The mean

age was 70.2 ± 8.3 years in the ERT cohort and 70.4 ± 8.3 years in the non-ERT cohort ($P = .562$; Std diff = 0.019). The proportion of White patients (82.4% vs. 83.6%; $P = .349$; Std diff = 0.031), Black or African American patients (6.2% vs. 6.4%; $P = .836$; Std diff = 0.007), and Asian patients (0.6% vs. 0.6%; $P = .827$; Std diff = 0.007) were comparable after matching. Diabetes mellitus was present in 23.9% of the ERT cohort compared to 23.0% in the non-ERT cohort ($P = .501$; Std diff = 0.023). Rates of obesity were also similar between the cohorts (BMI 30–39: $P = .366$; Std diff = 0.030 & BMI ≥ 40 : $P = .954$; Std diff = 0.002). Similarly, after matching there was no difference in prevalence of disorders of bone density and structure (47.6% vs. 49.1%; $P = .383$; Std diff = 0.029) and osteoarthritis of the shoulder (75.2% vs. 74.6%; $P = .699$; Std diff = 0.013). There was a significant difference in preoperative diagnosis of chronic obstructive pulmonary disease (15.5% vs. 12.1%; $P = .004$; Std diff = 0.096) and atrial fibrillation and flutter (10.7% vs. 10.3%; $P = .662$; Std diff = 0.015). However, the standardized difference was <0.1 for both.

Ninety-day postoperative outcomes

At 90 days postoperatively, patients on ERT had an approximately 90% higher risk of developing DVT (incidence 42 [2.4%] vs. 22 [1.2%], risk ratio [RR] = 1.91, 95% confidence interval [CI]: [1.145, 3.184]; $P = .012$) (Table III). The incidence and risk of developing other medical complications were not significantly different between the groups. Rates of pulmonary embolism (30 [1.7%] vs. 18 [1.0%]; RR = 1.667 [0.933–2.979]; $P = .081$), superficial soft tissue infection (29 [1.6%] vs. 21 [1.2%]; RR = 1.381 [0.791–2.412]; $P = .255$), and blood transfusions (21 [1.2%] vs. 22 [1.2%]; RR = 0.955 [0.527, 1.729]; $P = .955$) were similar in both cohorts. Similarly, emergency department use (229 [12.9%] vs. 207 [11.6%]; RR = 1.106 [0.928–1.319]; $P = .261$) and hospital readmissions (96 [5.4%] vs. 103 [5.8%]; RR = 0.932 [0.711, 1.221]; $P = .610$) occurred at similar rates.

Rates of orthopedic-specific complications also did not differ significantly between the two cohorts at 90 days postoperatively (Table III). Rates of developing any mechanical complication (28 [1.6%] vs. 22 [1.2%]; RR = 1.273 [0.731–2.216]; $P = .393$), periprosthetic fracture (136 [7.6%] vs. 114 [6.4%]; RR = 1.193 [0.938–1.517]; $P = .149$), and aseptic revision (13 [0.7%] vs. 10 [0.6%]; RR = 1.300 [0.572–2.957]; $P = .530$) were similar.

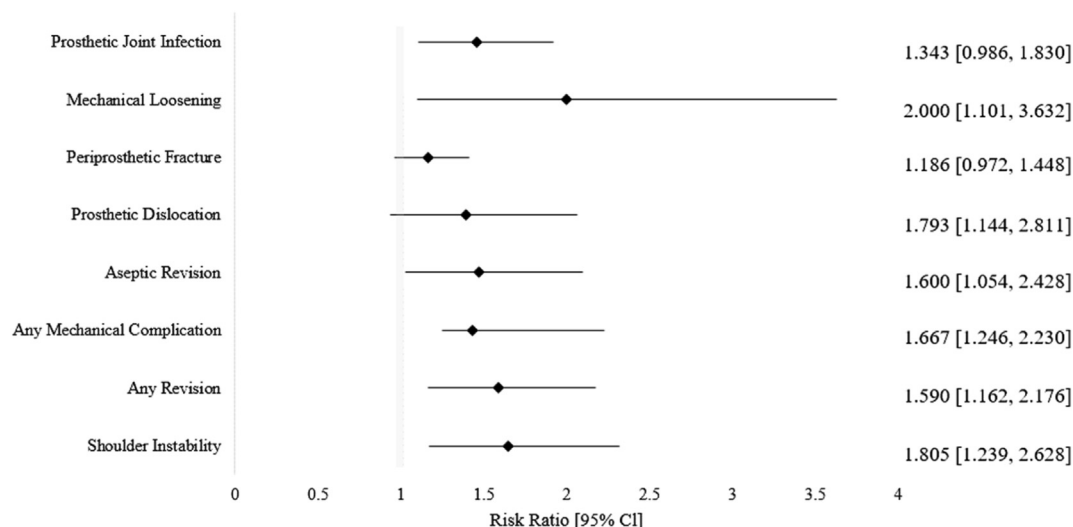


Figure 2 A forest plot depicting RR with 95% CI for 4-year postoperative complications in ERT vs. non-ERT cohorts. Outcomes include revision surgery, mechanical complications, prosthetic dislocation, and shoulder instability. A RR >1.0 indicates a higher risk in the ERT cohort. RR, risk ratios; CI, confidence intervals; ERT, estrogen replacement therapy.

Table VI

Ten-year outcomes post-TSA in ERT vs. non-ERT cohorts.

Complication	ERT cohort	Non-ERT cohort	P value
Prosthetic joint infection	118 (6.6%)	81 (4.6%)	.007
Mechanical loosening	39 (2.2%)	26 (1.5%)	.104
Periprosthetic fracture	199 (11.2%)	171 (9.6%)	.124
Prosthetic dislocation	57 (3.2%)	41 (2.3%)	.101
Aseptic revision	72 (4.0%)	49 (2.8%)	.033
All mechanical complications	139 (7.8%)	97 (5.5%)	.005
All revisions	125 (7.0%)	81 (4.6%)	.002
Instability	84 (4.7%)	41 (2.3%)	.004

TSA, total shoulder arthroplasty; ERT, estrogen replacement therapy.

A comparison of prosthetic joint infection, mechanical complications, instability, and revision rates are made. Data are presented as incidence (%) with associated *P*-values. Bold indicates *P*-value < .05.

Two-year postoperative outcomes

At 2-years post-TSA, those taking ERT had 65% higher risk of aseptic revision procedures (46 [2.6%] vs. 28 [1.6%], RR = 1.64 [1.03–2.62]; *P* = .034) and 71% higher risk of all revisions (75 [4.2%] vs. 44 [2.5%], RR = 1.71 [1.18–2.46]; *P* = .004) (Table IV & Fig. 1). The ERT group was also at higher risk of experiencing mechanical loosening (22 [1.2%] vs. 10 [0.6%], RR = 2.20 [1.05–4.63]; *P* = .033), periprosthetic fractures (184 [10.3%] vs. 146 [8.2%], RR = 1.26 [1.03–1.55]; *P* = .028), and prosthetic dislocations (43 [2.4%] vs. 24 [1.3%], RR = 1.79 [1.09–2.94]; *P* = .019). Patients in the ERT group also had a higher risk of developing any mechanical complications (91 [5.1%] vs. 57 [3.2%], RR = 1.60 [1.15–2.21]; *P* = .004), and shoulder instability (64 [3.6%] vs. 33 [1.9%], RR = 1.81 [1.24–2.63]; *P* = .001) compared to the non-ERT cohort. There were no significant differences in rates of prosthetic joint infection (69 [3.9%] vs. 52 [2.9%], RR = 1.33 [0.93–1.89]; *P* = .116) between the two groups at this time point.

Four-year postoperative outcomes

At the 4-year time point, patients in the ERT group had a 60% higher risk of aseptic revision procedures (56 [3.1%] vs. 35 [2.0%], RR = 1.60 [1.05–2.43]; *P* = .026) and a 59% higher risk of all revisions (97 [5.5%] vs. 61 [3.4%], RR = 1.59 [1.16–2.18]; *P* = .003) (Table V & Fig. 2). Risks for mechanical loosening and prosthetic dislocation

persisted, with the ERT cohort having two times the risk of mechanical loosening (32 [1.8%] vs. 16 [0.9%], RR = 2.00 [1.10–3.63]; *P* = .02) and a 79% higher risk of prosthetic dislocations (52 [2.9%] vs. 29 [1.6%], RR = 1.79 [1.14–2.81]; *P* = .01). Furthermore, patients on ERT had a higher incidence of experiencing any mechanical complication (115 [6.5%] vs. 69 [3.9%], RR = 1.67 [1.25–2.23]; *P* < .001) and shoulder instability (74 [4.2%] vs. 41 [2.3%], RR = 1.81 [1.24–2.63]; *P* = .002) compared to the non-ERT cohort. There were no statistically significant differences in periprosthetic fractures (191 [10.7%] vs. 161 [9.1%], RR = 1.19 [0.97–1.45]; *P* = .092) and PJI at the 4-year time point.

Ten-year postoperative outcomes

At the 10-year time point, the risks for aseptic revision (72 [4.0%] vs. 49 [2.8%], RR = 1.469 [1.028–2.100]; *P* = .033) and all revisions (125 [7.0%] vs. 81 [4.6%], RR = 1.590 [1.162–2.176]; *P* = .002) persisted (Table VI & Fig. 3). The ERT cohort had a 43% higher risk of developing any mechanical complications (139 [7.8%] vs. 97 [5.5%], RR = 1.433 [1.246–2.230]; *P* = .005) and a 65% higher risk of developing shoulder instability (84 [4.7%] vs. 41 [2.3%], RR = 1.647 [1.170–2.318]; *P* = .004) compared to the non-ERT cohort. The incidence of PJI was also significantly greater in the ERT cohort (118 [6.6%] vs. 81 [4.6%], RR = 1.457 [1.106, 1.918]; *P* = .007). However, incidence and risk of mechanical loosening, periprosthetic fracture, and prosthetic dislocation were not significantly different at 10 years.

Discussion

This study's most significant finding was that women aged 55 years and older taking ERT who undergo TSA have a higher relative risk for revision procedures at 2-, 4-, and 10-years postoperatively as compared to the cohort not taking ERT, consistent with our hypothesis. Patients in the ERT cohort also had a higher risk of developing mechanical complications and shoulder instability at these time points. At 2- and 4-years post-TSA, mechanical loosening and prosthetic dislocations also occurred at higher rates in patients taking ERT compared to those not taking ERT. Interestingly, we also found that the ERT group had higher rates of DVTs at 90 days postoperatively.

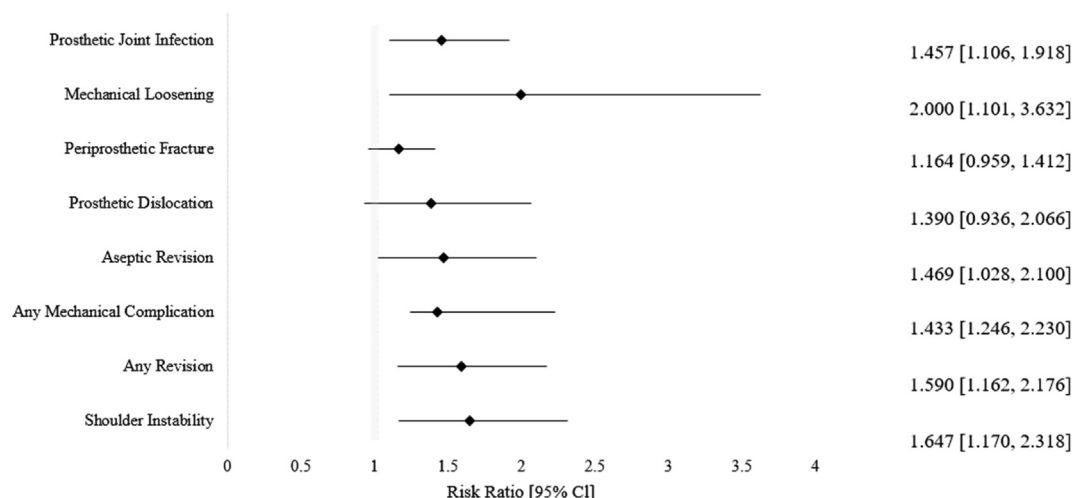


Figure 3 A forest plot depicting RR with 95% CI for 10-year postoperative complications in ERT vs. Non-ERT cohorts. Outcomes include revision surgery, mechanical complications, prosthetic dislocation, and shoulder instability. A RR >1.0 indicates a higher risk in the ERT cohort. RR, risk ratios; CI, confidence intervals; ERT, estrogen replacement therapy.

Our findings align with previous literature demonstrating an association between ERT and orthopedic complications following joint replacement. Collins et al investigated the effects of ERT use on postoperative outcomes of THA and total knee arthroplasty.¹⁰ They found that at 2-years postoperatively, patients taking ERT exhibited higher risk of aseptic loosening and combined joint complications after THA, as well as revision procedures and combined joint complications following total knee arthroplasty. The authors discussed that their findings could be due to inclusion of patients who took ERT for 6 months before or after their procedure, which may not provide sufficient time for ERT to impact bone health. In this study, we ensured that patients had a prescription for ERT at least 1–5 years before their procedure but still observed similar results. A related study by McCormick et al demonstrated that patients on ERT for at least a year had higher odds of revision procedures, including all-cause revision and acetabular and/or femoral component revisions.²³

The exact mechanism for these findings remains unknown. Previous studies have demonstrated that the effect of estrogen on bone depends on bone quality, disease stage, and the underlying pathophysiology of joint disease.^{28,30,31} A meta-analysis by Sinha et al found that patients on ERT had a significant detrimental effect on dental implant osseointegration.²⁷ Moreover, depending on the ratio between bone formation and resorption, subchondral bone remodeling can present in either sclerotic or osteoporotic patterns. Estrogen can be potentially harmful to the sclerotic phenotype, while being beneficial to the osteoporotic phenotype.³¹ Thus, our findings together with reports in the literature, indicate that estrogen therapy cannot be uniformly classified as protective or detrimental to bone health. Instead, its ultimate effect likely depends on the clinical context, timing, dosage, and biological milieu—emphasizing the significance of a personalized approach when considering ERT in patients undergoing joint replacement. Screening for prolonged ERT usage before proceeding with TSA may be helpful for patient counseling.

Our study also found an increase in risk of DVT within 90 days of TSA in patients taking ERT. The association of ERT in postmenopausal women and idiopathic DVT has been established, particularly with orally administered ER.^{4,12,24} Estrogen treatment results in a prothrombotic state by elevating levels of Von Willebrand factor and factor VII, while decreasing levels of antithrombin

III, thereby influencing hemostasis at various points.^{1,26} However, increased risk of DVT after total joint replacement in patients taking ERT has not previously been demonstrated.²³ Future research should investigate whether a more aggressive or prolonged regimen of DVT prophylaxis after TSA is needed in patients on ERT.

This study has several strengths and limitations. Selection bias, attributable to the retrospective design, limits the ability of this study design to assign causal relationships. The accuracy of current procedural terminology and ICD codes may introduce biases or confounding variables associated with the use of claims databases. In addition, dosages and duration of ERT treatment, as well as use of thromboprophylaxis agents could not be established, potentially over- or underestimating the impact of ERT on TSA outcomes. Finally, this manuscript includes estrogen-only products due to the limited literature regarding the variable impact of progesterone on bone health. While this allowed for a more focused initial analysis, future research should investigate the effects of combination therapies and other contemporary hormonal treatments. To mitigate the impact of these biases, variables such as age, race, BMI, presence of osteoporosis with or without pathologic fracture, osteoarthritis, and other comorbidities were controlled by matching our cohorts; however, readers should still consider these limitations when interpreting the results of this investigation. Our study also excluded transvaginal routes of administration and ensured that patients were on longer durations of ERT treatment (as compared to other studies) to ensure adequate timing for impact on bone health. Future research should be conducted to examine mechanisms behind the impact of ERT on TSA outcomes and bone health.

Conclusion

Our findings suggest that ERT is associated with a long-term increased risk of revision procedures and mechanical complications following TSA. This demonstrates the complex relationship between estrogen and bone health, highlighting the need for orthopedic surgeons to pay special attention to this patient population and counsel patients regarding potential risks. Future studies investigating the impact of ERT on implant survival, as well as osseointegration, should be conducted to improve the prognosis of arthroplasty in these populations.

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Conflicts of interest: Dr. Srikumaran serves as a board or committee member for AAOS, American Shoulder and Elbow Surgeons, and IASES; reports stock or stock options from ROM3, Sonogen, and Tigon Medical; is a paid consultant for, and receives intellectual property royalties from, Fx Shoulder and Tigon Medical; receives other financial or material support from Arthrex, DePuy—a Johnson & Johnson Company, and Thieme; and has been a paid presenter or speaker for, and received research support from, Fx Shoulder. The remaining authors declare no conflicts of interest.

Supplementary Data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jseint.2025.04.022>.

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