What Is the Impact of Anti-Estrogen Therapy on Total Joint Arthroplasty Outcomes? A View into Women's Health After Breast Cancer

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The purpose of this study is to determine if differences exist in patient-reported outcome measures (PROMs), revision rates, and postoperative health care utilization between individuals that have a history of taking anti-estrogen medication prior to total joint arthroplasty (TJA) and those who have not in matched cohorts. Patients undergoing primary TJA from 2015 to 2023 were reviewed retrospectively. Demographics, history of medication use, PROMs pre- and post-TJA, revision TJA history, and post-TJA hospital utilization were extracted from medical records. Propensity score matching was then performed at 10:1 control to patients with a history of taking anti-estrogen medication prior to TJA accounting for age, race, American Society of Anesthesiologists physical status classification, and body mass index. Patient PROMs, revision rate, and post-TJA hospital utilization were then compared. After applying exclusion criteria, stratifying the groups into total hip arthroplasty (THA) and total knee arthroplasty (TKA), and propensity score matching, the outcomes of 345 THAs and 549 TKAs were analyzed. Patients taking anti-estrogen medications who underwent THA had significantly higher Patient-Reported Outcome Measures Information System (PROMIS) Pain Interference scores; PROMIS Physical Function scores at 6 weeks, lower PROMIS Physical Function at 1 year; and higher rates of readmission at 90 days. There was no difference in PROMs or hospital utilization between groups in patients that underwent TKA. Patients with a history of taking anti-estrogen medications had meaningful improvement after THA and TKA. Although PROMs were similar between groups after TKA, PROMs suggest that patients taking anti-estrogen medication may have worse pain early after THA as well as worse overall function. (Journal of Surgical Orthopaedic Advances 34(3):142-151, 2025)

Key words: patient reported outcome measures, arthroplasty, anti-estrogen, breast cancer, women

The most common cancer in the female population is breast cancer, with most instances of cancer having estrogen receptor (ER) and/or progesterone receptor overexpression.[1-3] In many cases even after curative therapy, patients are started on anti-estrogen medication to prevent cancer recurrence.[4,5] Currently, aromatase inhibitors are the primary adjuvant therapy for postmenopausal women with ER+ breast cancer.[4,5] However, multiple drugs (i.e., tamoxifen,[6] letrozole,[7] raloxifene,[8] exemestane,[9] anastrozole,[10] and fulvestrant[11]) targeting estrogen or its receptor are credited with significant improvement in relapse-free survival.[4,5] Although these medications are critical for minimizing recurrence risk, they are associated with multiple musculoskeletal side effects such as myalgias, arthralgias, and fractures (Table 1).[12] Importantly, 36.5% of patients taking anti-estrogen medications discontinue their medication because of arthralgia.[5,13-15] Considering the importance of adhering to these medications for relapse-free survival, studies have been done to establish the best treatment modality for addressing arthralgia in these patients.

Total hip arthroplasty (THA) and total knee arthroplasty (TKA) have effectively treated patient pain and physical disability with progressively improving patient satisfaction.[16-19] Currently, studies investigating the role of THA and TKA in patients with a history of taking anti-estrogen medications are limited.[20] Although the pathophysiology of joint pain induced by estrogen suppression is not well understood, patients may experience these symptoms even in the absence of significant joint degeneration.[13,14] Recognizing the critical role of adherence to estrogen-suppressing medications for relapse-free survival in ER+ breast cancer patients, and considering the current limitations of available treatments for this pain,[14] it becomes imperative to gain a more comprehensive understanding of the outcomes of total joint arthroplasty (TJA) in this specific population.

The purpose of this study is to elucidate if differences exist in patient satisfaction (through patient-reported outcomes measures [PROMs]), revision rate, and postoperative health care utilization between individuals that have a history of taking anti-estrogen medication prior to TJA and those who have not. The authors hypothesized that patients with a history of taking anti-estrogen medications will have less PROM improvement after TJA.

Methods

Inclusion and Exclusion Criteria

At a tertiary referral academic center, patients ≥ 18 years old undergoing primary TJA between January 1, 2015, and August 1, 2023, were identified retrospectively with an institutional database. Exclusion criteria were male sex, < 1 year follow-up, or insufficient general (patient-reported outcome measurement information system [PROMIS] Pain Interference [PI], Physical Function [PF], or depression) or joint-spe-

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cific (hip disability and osteoarthritis outcome score for joint replacement [HOOS JR] and knee disability and osteoarthritis outcome score for joint replacement [KOOS JR]) PROMs.[21-24]

Data Collection

Preoperative demographics (i.e., patient age, weight, body mass index [BMI], race, ethnicity), American Society of Anesthesiologists (ASA) physical status classification, and patient comorbidities were collected. The reason for primary TKA, laterality, estimated blood loss (EBL), and length of stay (LOS) were also collected. In addition, general (i.e., PROMIS PI, PF, depression) and joint-specific (i.e., HOOS JR and KOOS JR) PROMs were collected preoperatively and at 6-weeks and 1-year postoperatively. Postoperative follow-up, need for revision TKA, all-cause emergency department (ED) visits, and all-cause readmissions were also collected.

Stratification

Patients that met inclusion criteria were stratified into THA and TKA groups. Within each cohort, if a patient had a history of taking anti-estrogen medication (i.e., tamoxifen, raloxifene, letrozole, anastrozole, exemestane, bazedoxifene, toremifene, or fulvestrant) before their primary THA or TKA, they were included in the respective anti-estrogen group for that procedure (Table 2). There were a total 818 THAs and 1,201 TKAs. A total of 37 THA and 59 TKA patients were taking anti-estrogen medications at the time of surgery. Both the THA and the TKA cohorts had a mean follow-up > 2 years.

Propensity Score Matching

Due to sample size limitations in the anti-estrogen group, control cohorts were expanded through propensity score matching at 10:1 control to anti-estrogen. This ratio maximized power from the large number of available controls while maintaining balance for age, race, BMI, and ASA. The included variables for the matching process were chosen because of their potential influence on the outcomes of interest.

Outcome Variables

The primary objective of this study was to evaluate PROMs between patients that underwent TJA with and without a history of taking anti-estrogen medication. T-scores[25] were used to report PROMIS score. HOOS JR raw scores on a zero (perfect hip health) to 24 (total hip disability) point scale were reported, and raw scores on a zero (perfect knee health) to 28 (total knee disability) were used to report KOOS JR score.[26] Secondarily, revision rates after primary TJA and overall all-cause emergency department visits and readmissions were compared between those who took anti-estrogen medications and those who did not.

Statistical Analysis

Mean with standard deviation (SD) or median with interquartile range was used to summarize normal and non-normal continuous variables, respectively. These were then compared using *t*-test or Mann-Whitney *U* test, respectively. Categorical variables were summarized using frequency and proportion, and subsequently compared using Chi-squared test. Significance for statistical tests was set to a *p*-value of ≤ 0.05. Standardized mean differences (SMD) measured effect size with values ≥ 0.2 suggesting a small effect, ≥ 0.5 suggesting a medium effect, and $\geq$ suggesting 0.8 a large effect. Statistical analysis was performed using R statistical programming language (version 4.1; Vienna, Austria).[27] Institutional Review Board approval was received, and this study adhered to Strengthening of the Reporting of Observational Studies in Epidemiology guidelines.[28]

TABLE 1. Anti-estrogen medications

	MOA	Uses	Side effects
SERMs			
Tamoxifen	- Estrogen receptor agonist at the bone and endometrium - Estrogen antagonist in the breast	- Adjuvant breast cancer therapy - Palliative treatment in metastatic breast cancer - Risk reduction in ductal carcinoma in situ	- Thromboembolism - Hypercalcemia - Hot flashes
Raloxifene	- Acts as an estrogen agonist at the bone - Estrogen antagonist in breast and uterine tissue	- Osteoporosis in postmenopausal women - Glucocorticoid-induced osteoporosis - Breast cancer risk reduction in postmenopausal women	- Thromboembolism - Arthralgia - Hot flashes
AIs			
Letrozole	- Inhibits the conversion of androgens to estrogens	- Adjuvant early-stage breast cancer therapy for pre- and postmenopausal women	- Reduction in bone mineral density - Arthralgia - Bone pain - Musculoskeletal effects
Anastrozole	- Inhibits the conversion of androgens to estrogens	- Adjuvant early-stage breast cancer therapy for pre- and postmenopausal women	- Reduction in bone mineral density - Fracture - Arthralgia - Arthritis
Exemestane	- Inhibits aromatase through "suicide" inhibition	- Adjuvant early-stage breast cancer therapy for pre- and postmenopausal women	- Reduction in bone mineral density - Arthralgia
ER degraders			
Fulvestrant	- Estrogen receptor antagonist - Estrogen receptor down-regulator	- Second-line treatment in postmenopausal women with ER+ metastatic breast cancer	- Bone pain - Musculoskeletal pain - Arthralgia

MOA, mechanism of action; SERMS, Selective estrogen receptor modulators; AIs, aromatase inhibitors; ER, estrogen receptor

TABLE 2. Unmatched demographics total hip arthroplasty and total knee arthroplasty

THA	Control (n = 781)	Anti-estrogen (n = 37)	*p*-Value***	SMD
Demographics				
Follow-up (years) (mean [SD])*	2.1 (0.9)	2.0 (1.0)	0.66	0.07
Female	781 (100.0)	37 (100.0)	NA	< 0.001
Age (years) (mean [SD])*	63.9 (11.2)	67.1 (8.9)	0.09	**0.31**
Race (n [%])**			0.17	**0.49**
White	615 (78.7)	34 (91.9)		
Black	141 (18.1)	2 (5.4)		
Asian	6 (0.8)	1 (2.7)		
Other	11 (1.4)	0 (0.0)		
NR	8 (1.0)	0 (0.0)		
Ethnicity (n [%])**			0.42	**0.31**
Hispanic	15 (1.9)	0 (0.0)		
Not Hispanic	746 (95.5)	37 (100.0)		
NR	20 (2.6)	0 (0.0)		
Weight (kg) (mean [SD])*	76.6 (20.2)	75.5 (21.1)	0.75	0.05
BMI (mean [SD])*	28.5 (7.6)	28.5 (6.6)	0.99	0.002
ASA classification (n [%])**				
0	2 (0.3)	0 (0.0)	1.00	0.07
1	23 (2.9)	0 (0.0)	0.58	**0.25**
2	445 (57.0)	19 (51.4)	0.61	0.11
3	304 (38.9)	18 (48.6)	0.31	**0.20**
4	7 (0.9)	0 (0.0)	1.00	0.13
Procedure specifics				
Laterality (n [%])**			0.87	0.10
Bilateral	1 (0.1)	0 (0.0)		
Left	348 (44.6)	15 (40.5)		
Right	432 (55.3)	22 (59.5)		
EBL (mL) (mean [SD])*	207.0 (144.9)	210.8 (174.1)	0.88	0.02
LOS (days) (mean [SD])*	2.6 (1.8)	2.5 (1.8)	0.75	0.05
Comorbidities (n [%])**				
Diabetes	208 (26.6)	7 (18.9)	0.40	0.19
Cancer history	157 (20.1)	35 (94.6)	**< 0.001**	**2.29**
Breast cancer history	71 (9.1)	33 (89.2)	**< 0.001**	**2.68**
Indication (n [%])**				
OA	735 (94.1)	37 (100.0)	0.25	**0.35**
Inflammatory arthritis	1 (0.1)	0 (0.0)	1.00	0.05
AVN	22 (2.8)	0 (0.0)	0.61	**0.24**
Posttraumatic OA	2 (0.3)	0 (0.0)	1.00	0.07
Hip dysplasia	8 (1.0)	0 (0.0)	1.00	0.14
DJD	3 (0.4)	0 (0.0)	1.00	0.09
Fracture	21 (2.7)	0 (0.0)	0.63	**0.24**
Pain	43 (5.5)	6 (16.2)	0.02	**0.35**
Other	3 (0.4)	0 (0.0)	1.00	0.09
Multifactorial	56 (7.2)	6 (16.2)	0.09	**0.28**
Medication history (n [%])**				
Anastrozole	0 (0.0)	9 (24.3)	**< 0.001**	**0.80**
Letrozole	0 (0.0)	20 (54.1)	**< 0.001**	**1.53**
Raloxifene	0 (0.0)	5 (13.5)	**< 0.001**	**0.56**
Exemestane	0 (0.0)	7 (18.9)	**< 0.001**	**0.68**
Tamoxifen	0 (0.0)	10 (27.0)	**< 0.001**	**0.86**
Fulvestrant	0 (0.0)	1 (2.7)	**0.03**	**0.24**
Multiple	0 (0.0)	10 (27.0)	**< 0.001**	**0.86**

TABLE 2. Continued.

TKA	Control (n = 1142)	Anti-estrogen (n = 59)	*p*-Value	SMD
Demographics				
Follow up (years) (mean [SD])*	2.0 (1.0)	2.0 (0.9)	0.74	0.05
Female	1142 (100.0)	59 (100.0)	NA	NA
Age (years) (mean [SD])*	67.0 (9.0)	69.9 (7.9)	**0.01**	**0.35**
Race (n [%])**			0.26	**0.39**
White	830 (72.7)	50 (84.7)		
Black	256 (22.4)	9 (15.3)		
Asian	28 (2.5)	0 (0.0)		
Other	23 (2.0)	0 (0.0)		
NR	5 (0.4)	0 (0.0)		
Ethnicity (n [%])**			0.61	0.18
Hispanic	24 (2.1)	1 (1.7)		
Not Hispanic	1100 (96.3)	58 (98.3)		
NR	18 (1.6)	0 (0.0)		
Weight (kg) (mean [SD])*	83.9 (17.6)	84.3 (15.5)	0.86	0.03
BMI (mean [SD])*	31.6 (6.8)	31.0 (5.6)	0.50	0.10
ASA classification (n [%])**				
1	9 (0.8)	0 (0.0)	1.00	0.13
2	624 (54.6)	27 (45.8)	0.23	0.18
3	505 (44.2)	32 (54.2)	0.17	**0.20**
4	4 (0.4)	0 (0.0)	1.00	0.08
Procedure specifics				
Laterality (n [%])**			0.37	0.19
Bilateral	1 (0.1)	0 (0.0)		
Left	551 (48.2)	23 (39.0)		
Right	590 (51.7)	36 (61.0)		
EBL (mL) (mean [SD])*	91.0 (78.0)	87.4 (65.8)	0.73	0.05
LOS (days) (mean [SD])*	2.6 (1.5)	2.8 (2.3)	0.29	0.11
Comorbidities (n [%])**				
Diabetes	330 (28.9)	21 (35.6)	0.34	0.14
Cancer history	219 (19.2)	43 (72.9)	**< 0.001**	**1.28**
Breast cancer history	119 (10.4)	49 (83.1)	**< 0.001**	**2.12**
Indication (n [%])**				
OA	1130 (98.9)	59 (100.0)	0.90	0.15
Inflammatory arthritis	5 (0.4)	0 (0.0)	1.00	0.09
AVN	2 (0.2)	0 (0.0)	1.00	0.06
Posttraumatic OA	4 (0.4)	0 (0.0)	1.00	0.08
DJD	12 (1.1)	0 (0.0)	0.90	0.15
Fracture	1 (0.1)	0 (0.0)	1.00	0.04
Pain	16 (1.4)	1 (1.7)	1.00	0.02
Other	1 (0.1)	0 (0.0)	1.00	0.04
Multifactorial	27 (2.4)	1 (1.7)	1.00	0.05
Medication history (n [%])**				
Anastrozole	0 (0.0)	14 (23.7)	**< 0.001**	**0.79**
Letrozole	0 (0.0)	30 (50.8)	**< 0.001**	**1.44**
Raloxifene	0 (0.0)	8 (13.6)	**< 0.001**	**0.56**
Exemestane	0 (0.0)	10 (16.9)	**< 0.001**	**0.64**
Tamoxifen	0 (0.0)	21 (35.6)	**< 0.001**	**1.05**
Fulvestrant	0 (0.0)	1 (1.7)	**0.04**	**0.19**
Multiple	0 (0.0)	20 (33.9)	**< 0.001**	**1.01**

This table shows the demographics, follow-up time, procedure laterality, blood loss, length of stay, indication, comorbidities, and medication history of the unmatched cohort that underwent primary THA and TKA. The cohort was stratified into a control cohort with no history of taking anti-estrogen medications and those with a history of taking anti-estrogen medication.

* *t*-test.

** Chi-squared test.

*** $p < 0.05$.

Bold indicates statistical significance.

THA, total hip arthroplasty; SMD, standardized mean difference ≥ 0.2; SD, standard deviation; NA, not applicable; BMI, body mass index; ASA, American Society of Anesthesiologists; EBL, estimated blood loss; LOS, length of stay; OA, osteoarthritis; AVN, avascular necrosis; TKA, total knee arthroplasty; DJD, degenerative joint disease; NR, not reported

Matched Demographics

After 10:1 propensity score matching, a total of 345 THAs and 549 TKAs were analyzed (Table 3). Both groups had similar distributions of demographics. The most common indication for TJA was osteoarthritis (OA) for both the control and the anti-estrogen group. Of the patients with a history of anti-estrogen who underwent THA, 89.2% (33/37) had a history of breast cancer, and of those who underwent TKA, 82.8% (48/58) had a history of breast cancer. The most common anti-estrogen medications used in both cohorts were letrozole, anastrozole, and tamoxifen.

Results

Pre- to Postoperative Patient-reported Outcomes Measures

Total hip arthroplasty

Median PROMIS PI, PROMIS PF, depression, and HOOS JR scores preoperatively were similar for both groups (Table 4). At 6-week follow up, median PROMIS PF, depression, and HOOS JR scores were not statistically different. However, median PROMIS PI at 6 weeks was significantly higher in the anti-estrogen group (60.0 [54.0, 63.0] vs. 56.0 [52.8, 61.0]; p = 0.03; SMD = 0.51). This difference in median PROMIS PI was no longer present at the 1-year time point (56.0 [51.5, 62.0] vs. 54.0 [50.0, 60.0]; p = 0.41; SMD = 0.19). In addition, median HOOS JR scores were similar between groups at 1 year. Outcome scores at 1 year for PROMIS PF (41.0 [35.0, 47.0] vs. 44.0 [39.0, 50.0]; p = 0.03; SMD = 0.39) and PROMIS depression (50.0 [44.8, 54.0] vs. 46.0 [34.0, 51.0]; p = 0.04; SMD = 0.38) were statistically worse in the anti-estrogen group.

Total knee arthroplasty

Median preoperative PROMIS PI, PROMIS PF, depression, and KOOS JR scores were similar between groups (Table 5). At 6-week follow up, median PROMIS PI, PROMIS PF, depression, and KOOS JR scores were not statistically different. Similarly, PROM scores at 1 year for median PROMIS PI, PROMIS PF, depression, and KOOS JR showed no statistically significant difference between groups.

TABLE 3. Matched demographics total hip arthroplasty and total knee arthroplasty

THA	Control (n = 308)	Anti-estrogen (n = 37)	*p*-Value***	SMD
Demographics				
Follow up (years) (mean [SD])*	2.1 (0.9)	2.0 (1.0)	0.78	0.05
Female	308 (100.0)	37 (100.0)	NA	< 0.001
Age (years) (mean [SD])*	66.3 (8.5)	67.1 (8.9)	0.61	0.09
Race (n [%])**			0.19	**0.20**
White	287 (93.2)	34 (91.9)		
Black	20 (6.5)	2 (5.4)		
Asian	1 (0.3)	1 (2.7)		
Ethnicity (n [%])**			0.47	**0.29**
Hispanic	5 (1.6)	0 (0.0)		
Not Hispanic	296 (96.1)	37 (100.0)		
NR	7 (2.3)	0 (0.0)		
Weight (kg) (mean [SD])*	76.0 (17.5)	75.5 (21.1)	0.88	0.02
BMI (mean [SD])*	28.4 (6.6)	28.5 (6.6)	0.94	0.01
ASA Classification (n [%])**				
2	181 (58.8)	19 (51.4)	0.49	0.15
3	127 (41.2)	18 (48.6)	0.49	0.15
Procedure specifics				
Laterality (n [%])**				
Left	143 (46.4)	15 (39.5)	0.61	0.12
Right	165 (53.6)	22 (59.5)	0.61	0.12
EBL (mL) (mean [SD])*	199.1 (108.0)	210.8 (174.1)	0.56	0.08
LOS (days) (mean [SD])*	2.5 (1.5)	2.5 (1.8)	1.00	0.001
Comorbidities (n [%])**				
Diabetes	74 (24.0)	7 (18.9)	0.63	0.13
Cancer history	71 (23.1)	35 (94.6)	**< 0.001**	**2.12**
Breast cancer history	25 (8.1)	33 (89.2)	**< 0.001**	**2.77**
Indication (n [%])**				
OA	298 (96.8)	37 (100.0)	0.55	**0.26**
Pain	15 (4.9)	6 (16.2)	0.02	**0.38**
DJD	2 (0.6)	0 (0.0)	1.00	0.11
AVN	4 (1.3)	0 (0.0)	1.00	0.16
Dysplasia	1 (0.3)	0 (0.0)	1.00	0.08
Fracture	5 (1.6)	0 (0.0)	0.96	0.18
Other	2 (0.6)	0 (0.0)	1.00	0.11
Multifactorial	19 (6.2)	6 (16.2)	0.06	**0.32**
Medication history (n [%])**				
Anastrozole	0 (0.0)	9 (24.3)	**< 0.001**	**0.80**
Letrozole	0 (0.0)	20 (54.1)	**< 0.001**	**1.53**
Raloxifene	0 (0.0)	5 (13.5)	**< 0.001**	**0.56**
Exemestane	0 (0.0)	7 (18.9)	**< 0.001**	**0.68**
Tamoxifen	0 (0.0)	10 (27.0)	**< 0.001**	**0.86**
Fulvestrant	0 (0.0)	1 (2.7)	0.20	**0.24**
Multiple	0 (0.0)	10 (27.0)	**< 0.001**	**0.86**

All-cause Revision Rate and Postoperative Hospital Utilization

Total hip arthroplasty

There was no statistically significant difference between groups regarding all-cause ED visits, mortality, and all-cause revision (see Table 5). Overall, 8.1% (3/37) patients in the anti-estrogen group required revision ($p = 0.19$; SMD = 0.25). At 90 days, patients in the anti-estrogen group had a higher rate of readmission compared with control (5 [13.5%] vs. 14 [4.5%]; $p = 0.04$; SMD = 0.27). Breakdown of these readmissions showed that the most common surgery-related reasons patients with history of taking anti-estrogen medications were readmitted was for wound care (1 [2.7%]), dislocation (2 [5.4%]), and post-operative pain (1 [2.7%]) (Table 6). The most common surgery-related reasons patients in the control group were readmitted was for periprosthetic joint infection (5 [1.6]), wound care (1 [0.3%]), and periprosthetic fracture (1 [0.3%]).

Total knee arthroplasty

There was no statistically significant difference between groups regarding all-cause ED visits, readmission, mortality, and all-cause revision (Table 5). Notably, 0% (0/58) patients in the anti-estrogen group required revision for their TKA.

TABLE 3. Continued.

TKA	Control (n = 491)	Anti-estrogen (n = 58)	*p*-Value	SMD
Demographics				
Follow up (years) (mean [SD])*	2.1 (1.0)	2.0 (0.9)	0.83	0.03
Female	491 (100.0)	58 (100.0)	NA	< 0.001
Age (years) (mean [SD])*	68.8 (8.0)	69.7 (7.8)	0.43	0.11
Race (n [%])**			0.97	0.03
White	409 (83.3)	49 (84.5)		
Black	82 (16.7)	9 (15.5)		
Ethnicity (n [%])**			0.83	0.11
Hispanic	10 (2.0)	1 (1.7)		
Not Hispanic	478 (97.4)	57 (98.3)		
NR	3 (0.6)	0 (0.0)		
Weight (kg) (mean [SD])*	82.2 (17.1)	84.4 (15.6)	0.35	0.14
BMI (mean [SD])*	31.1 (6.5)	31.0 (5.7)	0.88	0.02
ASA Classification (n [%])**				
2	246 (50.1)	27 (46.6)	0.71	0.07
3	245 (49.9)	31 (53.4)	0.71	0.07
Procedure specifics				
Laterality (n [%])**			0.23	0.19
Left	232 (47.3)	22 (37.9)		
Right	259 (52.7)	36 (62.1)		
EBL (mL) (mean [SD])*	92.8 (79.0)	88.4 (65.8)	0.69	0.06
LOS (days) (mean [SD])*	2.5 (1.2)	2.8 (2.3)	0.12	0.16
Comorbidities (n [%])**				
Diabetes	134 (27.3)	20 (34.5)	0.32	0.16
Cancer history	104 (21.2)	42 (72.4)	**< 0.001**	**1.20**
Breast cancer history	56 (11.4)	48 (82.8)	**< 0.001**	**2.04**
Indication (n [%])**				
OA	486 (99.0)	58 (100.0)	0.97	0.14
Pain	6 (1.2)	1 (1.7)	1.00	0.04
DJD	6 (1.2)	0 (0.0)	0.86	0.16
Inflammatory	1 (0.2)	0 (0.0)	1.00	0.06
AVN	1 (0.2)	0 (0.0)	1.00	0.06
Multifactorial	9 (1.8)	1 (1.7)	1.00	0.01
Medication history (n [%])**				
Anastrozole	0 (0.0)	14 (24.1)	**< 0.001**	**0.80**
Letrozole	0 (0.0)	30 (51.7)	**< 0.001**	**1.46**
Raloxifene	0 (0.0)	8 (13.8)	**< 0.001**	**0.57**
Exemestane	0 (0.0)	10 (17.2)	**< 0.001**	**0.65**
Tamoxifen	0 (0.0)	20 (34.5)	**< 0.001**	**1.03**
Fulvestrant	0 (0.0)	1 (1.7)	0.20	0.19
Multiple	0 (0.0)	20 (34.5)	**< 0.001**	**1.03**

This table shows the demographics, follow-up time, procedure laterality, blood loss, length of stay, indication, comorbidities, medication history of the matched cohort that underwent primary THA and TKA. The cohort was stratified into a control cohort with no history of taking anti-estrogen medications and those with a history of taking anti-estrogen medication.

* *t*-test.

** Chi-squared test.

*** $p < 0.05$.

Bold indicates statistical significance.

THA, total hip arthroplasty; SMD, standardized mean difference ≥ 0.2; SD, standard deviation; NR, not reported; EBL, estimated blood loss; LOS, length of stay; OA, osteoarthritis; DJD, degenerative joint disease; AVN, avascular necrosis; BMI, body mass index; ASA, American Society of Anesthesiologists; TKA, total knee arthroplasty

Discussion

The aim of this study was to assess pre- to post-TJA PROMs, revision rate, and postoperative hospital utilization in patients with a history of taking anti-estrogen medications compared with a matched control that accounted for age, race, ASA physical status classification, and BMI. The results of this study suggested that patients with a history of using anti-estrogen medications undergoing THA tended to have more pain in the early postoperative period, worse physical function, and depression at 1 year, and higher 90-day readmission rates. Patients undergoing TKA had no statistically significant difference in outcomes from control.

TABLE 4. Total hip arthroplasty and total knee arthroplasty patient-reported outcomes preoperatively to postoperatively (medians)

THA	Control (n = 308)	Anti-estrogen (n = 37)	*p*-Value***	SMD
PROMIS PI (median [IQR])*				
Preoperatively	67.0 [63.0, 71.0]	67.0 [63.8, 72.2]	0.28	**0.27**
6 weeks	56.0 [52.8, 61.0]	60.0 [54.0, 63.0]	**0.03**	**0.51**
Δ at 6 weeks	−11.0 [−16.0, −7.0]	−8.0 [−13.0, −6.0]	0.16	**0.32**
1 year	54.0 [50.0, 60.0]	56.0 [51.5, 62.0]	0.41	0.19
Δ at 1 year	−13.0 [−19.0, −7.0]	−11.0 [−16.5, −8.0]	0.64	0.12
PROMIS PF (median [IQR])*				
Preoperatively	35.0 [31.0, 39.0]	34.0 [29.0, 38.2]	0.84	0.11
6 weeks	41.0 [35.0, 45.0]	39.0 [33.0, 46.0]	0.30	**0.21**
Δ at 6 weeks	6.0 [2.0, 11.0]	4.0 [0.0, 11.0]	0.56	0.001
1 year	44.0 [39.0, 50.0]	41.0 [35.0, 47.0]	**0.03**	**0.39**
Δ at 1 year	11.0 [5.0, 14.5]	7.0 [4.5, 13.0]	0.34	**0.21**
PROMIS depression (median [IQR])*				
Preoperatively	53.0 [48.0, 59.0]	54.0 [49.5, 58.5]	0.33	**0.28**
6 weeks	46.0 [34.0, 50.0]	49.0 [42.0, 53.0]	0.09	**0.34**
Δ at 6 weeks	−8.0 [−14.0, −3.0]	−6.0 [−9.8, −3.8]	0.64	0.03
1 year	46.0 [34.0, 51.0]	50.0 [44.8, 54.0]	**0.04**	**0.38**
Δ at 1 year	−6.0 [−12.5, −2.0]	−6.0 [−9.8, −1.2]	0.60	0.10
HOOS JR (median [IQR])*				
Preoperatively	13.0 [10.0, 16.0]	14.0 [11.5, 16.0]	0.52	0.04
6 weeks	6.0 [3.0, 9.5]	3.5 [2.8, 4.2]	0.33	**0.89**
Δ at 6 weeks	−7.5 [−10.8, −5.0]	−13.0 [−14.0, −12.0]	0.07	**0.50**
1 year	5.0 [2.0, 9.0]	3.5 [2.8, 4.2]	0.59	**0.68**
Δ at 1 year	−7.0 [−11.0, −4.0]	NA [NA, NA]	NA	NA
TKA	**Control (n = 491)**	**Anti-estrogen (n = 58)**	***p*-Value**	**SMD**
PROMIS PI (median [IQR])*				
Preoperatively	65.0 [62.0, 68.0]	64.0 [62.2, 67.0]	0.80	0.02
6 weeks	56.0 [53.0, 62.0]	56.0 [50.0, 62.0]	0.69	0.13
Δ at 6 weeks	−9.0 [−14.5, −5.0]	−9.0 [−14.5, −5.0]	0.93	0.04
1 year	54.0 [50.0, 59.0]	56.0 [50.0, 61.0]	0.45	0.09
Δ at 1 year	−11.0 [−17.0, −6.0]	−10.0 [−18.8, −5.2]	0.65	0.001
PROMIS PF (median [IQR])*				
Preoperatively	35.0 [31.0, 40.0]	35.0 [31.5, 38.0]	0.20	**0.20**
6 weeks	41.0 [36.0, 46.0]	41.0 [34.0, 45.0]	0.43	0.17
Δ at 6 weeks	6.0 [2.0, 11.8]	6.0 [1.0, 11.0]	0.75	0.17
1 year	44.0 [39.0, 49.0]	43.0 [38.8, 48.5]	0.47	0.13
Δ at 1 year	8.5 [4.0, 13.0]	10.0 [5.0, 15.5]	0.40	0.16
PROMIS depression (median [IQR])*				
Preoperatively	52.0 [48.0, 57.0]	54.0 [48.0, 56.0]	0.83	0.06
6 weeks	45.0 [34.0, 50.0]	41.0 [34.0, 50.0]	0.22	**0.28**
Δ at 6 weeks	−7.0 [−13.0, −2.0]	−12.5 [−16.8, −2.2]	0.15	**0.30**
1 year	46.0 [34.0, 50.0]	44.0 [34.0, 49.0]	0.39	0.08
Δ at 1 year	−7.0 [−13.0, −2.0]	−9.5 [−14.8, −5.2]	0.15	**0.29**
KOOS JR (median [IQR])*				
Preoperatively	15.0 [12.0, 18.0]	15.0 [12.5, 17.5]	0.56	**0.24**
6 weeks	7.0 [3.0, 12.0]	10.0 [6.0, 14.5]	0.56	**0.39**
Δ at 6 weeks	−9.0 [−12.2, −6.0]	−7.0 [−10.5, −3.5]	0.87	**0.24**
1 year	7.0 [4.0, 12.0]	6.0 [2.0, 13.8]	0.80	0.04
Δ at 1 year	−7.0 [−11.5, −4.0]	−7.0 [−12.2, −3.5]	0.94	0.04

This table shows the preoperative PROM score and postoperative PROM score at 6 weeks and 1 year for patients without a history of anti-estrogen medications compared with those with a history of anti-estrogen medications.

* Mann-Whitney *U* test.

** Chi-squared test.

*** $p < 0.05$.

Bold indicates statistical significance.

THA, total hip arthroplasty; SMD, standardized mean difference ≥ 0.2; PROMIS, patient-reported outcomes measurement information system; PI, pain interference; PF, physical function; HOOS JR, hip dysfunction and osteoarthritis outcome score for joint replacement; TKA, total knee arthroplasty; KOOS JR, knee dysfunction and osteoarthritis outcome score for joint replacement; PROM, patient-reported outcomes measurement

Anti-estrogens, such as letrozole and anastrozole, are the gold-standard adjuvant therapy for ER+ breast cancer in postmenopausal women.[4,5,29-33] However, most anti-estrogen medications have musculoskeletal side effects.[5-11,33] Studies have shown that over half of patients taking these medications develop new or worsening joint pain,[33-35] which in turn results in over 30% of women discontinuing these medications. Discontinuation of adjuvant therapy has been shown to increase the risk of breast cancer recurrence and mortality.[33-35] Consequently, managing patient pain is vitally important. Currently, management with both pharmacologic and nonpharmacologic options has been largely ineffective, and given that knees are among the most common joints affected, arthroplasty can play a significant role.[5]

Although the pathophysiology behind how these medications manifest in joint pain is poorly understood, studies have shown that women who develop anti-estrogen–induced joint pain tend to have lower levels of estrogen compared with their asymptomatic counterparts.[36] Considering that estrogen not only helps to preserve bone but also prevents extracellular breakdown of chondrocytes, it is possible these factors play a role in the development of joint pain symptoms and/or progression of OA in these patients.[36,37] However, prospective research comparing hip and knee films before and after starting these anti-estrogen medications would be needed to better understand this relationship.

TABLE 5. Emergency department visits, readmissions, mortality, and revisions

THA	Control (n = 308)	Anti-estrogen (n = 37)	*p*-Value***	SMD
ED visits (n [%])*				
90 days	29 (9.4)	5 (13.5)	0.52	0.09
180 days	42 (13.6)	6 (16.2)	0.76	0.04
Readmissions (n [%])*				
90 days	14 (4.5)	5 (13.5)	**0.04**	**0.27**
180 days	28 (9.1)	7 (18.9)	0.15	**0.20**
Mortality (n [%])*				
90 days	0 (0.0)	0 (0.0)	NaN	< 0.001
180 days	0 (0.0)	0 (0.0)	NaN	< 0.001
All-cause revisions				
Revisions **(n [%])***	8 (2.6)	3 (8.1)	0.19	**0.25**
Years to revision **(mean [SD])***	0.6 (0.7)	0.2 (0.1)	0.68	**0.36**
TKA	**Control (n = 491)**	**Anti-estrogen (n = 58)**	***p*-Value**	**SMD**
ED visits (n [%])*				
90 days	3 (8.8)	3 (5.2)	0.43	0.13
180 days	3 (12.8)	5 (8.6)	0.46	0.12
Readmissions (n [%])*				
90 days	43 (4.1)	0 (0.0)	0.16	**0.27**
180 days	39 (7.9)	4 (6.9)	0.79	0.04
Mortality (n [%])*				
90 days	1 (0.2)	0 (0.0)	0.73	0.06
180 days	1 (0.2)	0 (0.0)	0.73	0.06
All-cause revisions				
Revisions **(n [%])***	12 (2.4)	0 (0.0)	0.47	**0.22**
Years to revision **(mean [SD])***	1.6 (1.1)	NaN (NA)	NA	NA

This table shows the ED visits, readmissions, mortality, and all-cause revisions of the matched cohort that underwent primary THA and TKA. The cohort was stratified into a control cohort with no history of taking anti-estrogen medications and those with a history of taking anti-estrogen medication.

* *t*-test.

** Chi-squared test.

*** $p < 0.05$.

Bold indicates statistical significance.

THA, total hip arthroplasty; SMD, standardized mean difference ≥ 0.2; ED, emergency department; TKA, total knee arthroplasty; NaN, not a number; NA, not applicable

TABLE 6. 90-day readmission break down for total hip arthroplasty

THA	Control (n = 308)	Anti-estrogen (n = 37)
90-day readmissions (n [%])*	14 (4.5)	5 (13.5)
Nonsurgery related	7 (2.3)	1 (2.7)
Surgery related	7 (2.3)	4 (10.8)
Wound care	1 (0.3)	1 (2.7)
Dislocation	0 (0.0)	2 (5.4)
Postoperative pain	0 (0.0)	1 (2.7)
PPF	1 (0.3)	0 (0.0)
PJI	5 (1.6)	0 (0.0)

This table shows the breakdown of readmission after THA for the control and anti-estrogen groups.
THA, total hip arthroplasty; PPF, periprosthetic fracture; PJI, periprosthetic joint infection

PROMs were of interest in this study to discern if patients taking these anti-estrogen medications had different pain, function, and depression at presentation and after TJA compared with the typical TJA patient. Although there were differences in PROMs in the THA groups and no statistically significant differences in the TKA group, both groups had meaningful improvement in general and joint-specific PROMs.[38] In addition, for both THA and TKA procedures, both control and anti-estrogen groups had median PROMIS PI that improved from moderate pain to mild or within normal limits. Similarly, PROMIS PF improved from moderate disability to mild disability in both groups.

Given the mounting evidence that pain, depression, and perceived patient outcome are all related, PROMIS depression scores were assessed. Results from the THA cohort showed that patients had similar preoperative depression scores, but the anti-estrogen group had significantly higher depression scores than control at 1 year. However, the median PROMIS depression score was improved from baseline for both groups. For patients undergoing TKA, results showed pre- and postoperative PROMIS depression was similar between groups as well as overall a trend toward improvement after surgery. Although this improvement in depression scores is a good outcome and likely related to improved pain and physical function, depression scores were within normal limits both pre- and postoperatively.

In addition to PROMs, this study investigated revision rates as well as postoperative hospital utilization. Revision rates for THA and TKA were similar between groups; however, additional studies are needed to better understand implant survival in this patient population, as estrogen suppression effects on bone quality could impact this outcome. Hospital utilization was also investigated, as ED visits, readmissions, and mortality are often metrics hospital systems monitor for overall value-based care. Although this study did find a statistically significant difference in 90-day readmissions between groups in THA, the number of events was minimal, and the indications for readmissions were highly variable. A recent study by Ledford et al. noted that patients with a history of breast cancer tend to be at higher risk for fracture and deep vein thrombosis after THA.[20] This cohort of patients with a history of taking anti-estrogen medications did not have these complications; however, there is a difference in the study cohort of interest, which may account for why this finding was not also present in this study.

Limitations

This study has several notable limitations. Although this is a propensity score-matched study, causality cannot be inferred because this is a retrospective study. In addition, although the institutional database was queried from 2015 to 2023, PROM reporting was not mandated until 2019 at the sourcing institution. As a result, many patients were excluded due to missing data leading to a small sample size of patients with a history of taking anti-estrogen medications. A matching ratio of 10:1 was used in the attempt to mitigate this limitation given the substantial available controls. However, although using the nearest neighbor method for propensity score matching minimizes this, it can be acknowledged that higher matching ratio introduces some bias. As with all retrospective studies, this study is also limited by the quality and accuracy of the data available in the electronic medical record.

Future Directions

Future retrospective studies addressing this subset of patients should be multicentered to provide additional statistical power for determining if differences in PROMs exist as well as postoperative complication rate. Furthermore, with a larger sample size, regression analyses assessing specific medications as well as the duration of treatment to determine associations with PROMs would be advised. Also, studies with larger sample sizes can investigate TJA survivorship. Prospective studies assessing radiographic progression of OA before and after initiation of anti-estrogen medications would be valuable in demystifying the timeline of and relationship between the side effect from these medications and OA.

Conclusion

Patients with a history of taking anti-estrogen medications had meaningful improvement after THA and TKA; however, expectations should be discussed with these patients prior to TJA, as their overall outcomes may not be equivalent to the average arthroplasty patient. Additional studies are required to better understand PROMs in this population.

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