Preoperative Statin Exposure Reduces Periprosthetic Fractures and Revisions following Total Knee Arthroplasty

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Abstract

The purpose of this study is to examine patients undergoing primary total knee arthroplasty (TKA) with and without prior history of statin use. We specifically evaluated (1) 90-day to 2-year periprosthetic fractures, (2) revisions, and (3) respective risk factors. We queried a national, all-payer database for patients undergoing primary TKA between 2010 and 2020. Chronic statin exposure was then identified and defined as more than three prescriptions filled within 1 year prior to TKA (statin users). A control cohort of patients undergoing TKA without the prior history of statin use was then created (statin naïve). Cohorts were matched 1:1 based on age range, Charlson Comorbidity Index, sex, diabetes, obesity, and tobacco use, yielding 579,136 patients. Multivariate logistic regression was performed to evaluate the risk factors for periprosthetic fractures and revisions, adjusted for demographics and comorbidities. Statin users had a lower incidence of periprosthetic fractures from 90 days to 2 years compared with the statin naïve ($p < 0.001$). Similarly, statin users had a lower incidence of revisions at 90 days to 2 years ($p < 0.001$). Using the statin-naïve cohort as a reference, statin use was independently associated with decreased odds of periprosthetic fractures and revisions. Statin use was associated with a reduced risk of periprosthetic fractures and revisions. These results may mitigate postoperative risks though statin therapy is currently not recommended for fracture-related benefits alone.

Keywords

- statin
- periprosthetic fracture
- total knee arthroplasty
- arthroplasty

The pleiotropic effects of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) extend beyond managing cardiovascular health. Statin use has been suggested to suppress osteoclast cell activity to strengthen the bone formation.[1–3] Thus, the statin use in the setting of total knee arthroplasty (TKA) may have a greater value than previously understood. As TKA continues to serve as one of the fastest-growing procedures, the cumulative incidence of postoperative fractures will theoretically rise as well.[4] Periprosthetic fractures have a reported incidence of 1.7% and 0.3 to 2.5% following primary total hip arthroplasty (THA) and TKA, respectively.[5–8] Further, periprosthetic fractures constitute a substantial proportion of patients requiring revision surgeries.[9,10] However, a large study specifically evaluating statin exposure and fracture risk following TKA is lacking.

Multiple studies have attempted to identify the role of statin in enhancing bone health by blocking osteoclastogenesis, thereby preserving bone mass.[1–3] Luckman et al[1] observed statin-induced apoptosis of specific macrophages and murine osteoclasts by a similar mechanism to nitrogen-containing

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bisphosphonates. Another study observed statin's inhibitory effect on the differentiation of osteoclasts.[3] Statins have also been suggested to attenuate fracture risk. Results from a Danish Hip Arthroplasty Registry demonstrated a significant risk reduction of periprosthetic fractures and revision following THA.[11] These results were similarly demonstrated among United States veterans where statin use was associated with reduced fracture risk when compared with nonlipid lowering agents.[12] Statin's potential to reduce fracture risk is promising, but further study with increased sample sizes may be warranted to corroborate previous findings.

The expansion of TKA in recent years to include more patients than ever directly translates to increased periprosthetic fracture risk incidence. Furthermore, a substantial proportion of TKA recipients receive statin therapy. The purpose of this study is to examine chronic statin users versus statin-naïve TKA recipients utilizing a national dataset. We specifically evaluated (1) 90-day to 2-year periprosthetic fractures, (2) revisions, and (3) respective risk factors.

Methods

Database Selection

We queried the "MKnee" dataset within a national, all-payer database (PearlDiver, Inc., Colorado Springs, CO). This database contains over 122 million Health Insurance Portability and Accountability Act compliant patient records spanning January 1, 2010 and April 31, 2020. Patient records across all payer categories are available, including commercial, Medicare, Medicaid, and cash payers. To date, this is one of the largest updated national databases with the ability to track a substantial number of patients longitudinally over a long time period. In effect, this reduces potential type II errors that may arise. Patient populations, outcomes, and complications were identified using International Classification of Diseases (ICD) nine and ten procedural and diagnoses codes, as well as Current Procedural Terminology (CPT) codes. Institutional review board approval was waived for this publicly available database study.

Patient Selection

All patients who underwent primary TKA between January 1, 2010 and April 31, 2020 were identified ($n = 1{,}837{,}719$). Patients who were chronic statin users prior to surgery were then identified using the Universal System of Classification drug code (USC-32110). Chronic statin use was defined as filling more than three statin prescriptions in the year prior to receiving a TKA ($n = 603{,}326$). A control cohort of patients who never received a statin prescription prior to TKA was then identified (statin naïve), yielding 1,036,897 patients. Both cohorts were then matched 1:1 based on age range, sex, Charlson Comorbidity Index (CCI), diabetes, obesity, and tobacco use, yielding 579,136 patients.

Outcomes

Primary outcomes included 90-day, 1-year, and 2-year periprosthetic fractures and revision surgeries. Secondary outcomes included patient demographics such as age, sex, diabetes, obesity, and tobacco use.

Patient Demographics

Demographics and baseline characteristics were similar among both TKA cohorts. They had a mean age of 67 ± 7.8 years, female predominance (61.1%), diabetes (55.9%), obesity (53.2%), and tobacco use (22.9%). All p-values for these matched variables were 0.999 (see ►**Table 1**).

Statistical Analyses

Continuous variables including ages were compared using Student's t-tests. Categorical variables including demographics, comorbidities, periprosthetic fractures, revision surgeries, and other complications were compared using chi-square tests. Multivariate logistic regressions were conducted to evaluate risk factors for periprosthetic fractures and revision surgeries from 90 days to 2 years. Assessed variables included ages (<60; 60 to 70; 71 to 80; >80 years), female sex, alcohol abuse, body mass index (<25; 25 to 30; 30.1 to 40; >40), CCI > 3, diabetes, statin use, and tobacco use. The statin-naïve cohort served as the reference. All analyses were performed using R Studio (Statistics Department of the University of Auckland) with significance defined as $p < 0.05$.

Results

Periprosthetic Fractures and Revision Surgeries

The incidence and odds of periprosthetic fractures at 90 days were lower among statin users, compared with the statin naïve (0.10 vs. 0.13%, odds ratio [OR] 0.81 [0.72–0.89], $p < 0.001$; see ►**Tables 2** and **3**). These differences were

Table 1 Demographics and baseline characteristics

	TKA statin users (n = 579,136)	TKA statin naïve (n = 579,136)	p-Value
Age (SD)	67 (7.8)	67 (7.8)	0.999
Sex			0.999
Male	225,255 (38.9)	225,255 (38.9)	
Female	353,881 (61.1)	353,881 (61.1)	
Diabetes	323,675 (55.9)	323,675 (55.9)	0.999
Obesity	307,957 (53.2)	307,957 (53.2)	0.999
Tobacco use	132,838 (22.9)	132,838 (22.9)	0.999

Abbreviations: TKA: total knee arthroplasty; SD, Standard deviation.

Table 2 Postoperative periprosthetic fractures and revisions

	TKA statin users (n = 579,136)	TKA statin naïve (n = 579,136)	*p*-Value
90-d complications			
Periprosthetic fractures	599 (0.10)	747 (0.13)	<0.001
Revisions	2,795 (0.48)	3,266 (0.56)	<0.001
1-y complications			
Periprosthetic fractures	1,133 (0.20)	1,369 (0.24)	<0.001
Revisions	6,596 (1.14)	7,518 (1.30)	<0.001
2-year complications			
Periprosthetic fractures	1,842 (0.32)	2,158 (0.37)	<0.001
Revisions	12,636 (2.18)	13,808 (2.38)	<0.001

Abbreviation: TKA, total knee arthroplasty.

Table 3 Odds ratios for periprosthetic fractures and revisions

	TKA odds ratios (95% CI)	
90-d complications		
Periprosthetic fractures	0.81	0.72–0.89
Revisions	0.86	0.81–0.90
1-y complications		
Periprosthetic fracture	0.83	0.77–0.90
Revision	0.88	0.85–0.91
2-y complications		
Periprosthetic fracture	0.85	0.80–0.91
Revision	0.91	0.89–0.94

Abbreviations: CI, confidence interval; TKA, total knee arthroplasty.

more pronounced at 1 year (0.20 vs. 0.24%, OR 0.83 [0.77–0.90], $p < 0.001$) and 2 years (0.20 vs. 0.24%, OR 0.85 [0.80–0.91], $p < 0.001$). The incidence and odds of revision surgeries at 90 days were lower among statin users compared with the statin naïve (0.48 vs. 0.56%, OR 0.86 [0.81–0.90], $p < 0.001$). Revision surgery rate differences continued at 1 year (1.14 vs. 1.30%, OR 0.88 [0.85–0.91], $p < 0.001$) and 2 years (2.18 vs. 2.38%, OR 0.91 [0.89–0.94], $p < 0.001$).

Risk Factors for Periprosthetic Fractures

Statin use was associated with decreased odds of periprosthetic fractures, when referencing the statin-naïve cohort (ORs ≤ 0.82; see ►**Table 4**). Age from 71 to 80 years was the most significant age-related risk factor for periprosthetic fractures (TKA: ORs ≥3.01). BMI > 40 kg/m^2 was the most significant body-mass-related risk factor for periprosthetic fractures (TKA: ORs ≥1.54).

Risk Factors for Revision Surgeries

Statin use was associated with decreased odds of revision surgeries, when referencing the statin-naïve cohort (ORs ≤0.90; see ►**Table 5**). Age >80 years was the most significant age-related risk factor for revision surgeries (ORs ≥ 1.66). BMI >40 kg/m^2 was the most significant body-mass-related risk factor for revision surgeries (ORs ≥1.35).

Discussion

Over 35 million people in the United States are prescribed statin therapy to manage cardiovascular health, trending higher since past few years.[13] Over the past two decades, numerous experimental and clinical studies have associated statin use with improved bone health, with potential consequences in patients undergoing TKA. Periprosthetic fracture remains a feared complication following TKA, and rates are likely to rise along with the concomitant increases in TKA.[14] However, the relationship between statin use and fracture healing in a national dataset is yet to be examined. We compared chronic statin users versus statin-native patients prior to TKA using a national, all-payer database. Ninety-day to two-year periprosthetic fracture rates were decreased among statin users. Similar findings were demonstrated for 90-day to 2-year revision rates.

The limitations of this study come from the use of a database. Study cohorts were assessed using medical and billing codes, both subject to misclassification and improper billing. However, an independent party formally audits patient information contained within the used database, mitigating these potential errors. Furthermore, specific patient, social, and, surgical factors could not be

Table 4 Multivariate logistic regression for periprosthetic fractures

	TKA		
	Odds ratio	**Confidence interval**	**p-Value**
90-d complications			
Age <60	1.39	1.10–1.74	0.005
Age 60–70	2.01	1.62–2.45	<0.001
Age 71–80	3.24	2.61–3.99	<0.001
Age >80	1.07	0.61–2.09	0.821
Female sex	2.94	2.62–3.31	<0.001
Alcohol abuse	1.95	1.63–2.30	<0.001
BMI <25 kg/m^2	1.34	1.11–1.61	0.002
BMI 25–30 kg/m^2	0.93	0.80–1.07	0.326
BMI 30.1–40 kg/m^2	1.00	0.90–1.10	0.994
BMI >40 kg/m^2	1.87	1.68–2.07	<0.001
CCI > 3	1.71	1.53–1.91	<0.001
Diabetes mellitus	1.01	0.92–1.11	0.875
Statin users	0.77	0.69–0.85	<0.001
Tobacco use	1.19	1.09–1.31	<0.001
1-y complications			
Age <60	1.82	1.54–2.13	<0.001
Age 60–70	2.06	1.77–2.38	<0.001
Age 71–80	3.01	2.57–3.50	<0.001
Age >80	1.28	0.81–2.16	0.326
Female sex	2.10	1.94–2.27	<0.001
Alcohol abuse	1.88	1.66–2.12	<0.001
BMI <25 kg/m^2	1.37	1.19–1.56	<0.001
BMI 25–30 kg/m^2	0.94	0.85–1.04	0.261
BMI 30.1–40 kg/m^2	1.02	0.95–1.09	0.646
BMI >40 kg/m^2	1.67	1.54–1.80	<0.001
CCI > 3	1.63	1.50–1.77	<0.001
Diabetes mellitus	1.06	0.99–1.13	0.117
Statin users	0.80	0.74–0.86	<0.001
Tobacco use	1.20	1.12–1.28	<0.001
2-y complications			
Age <60	2.32	2.05–2.61	<0.001
Age 60–70	2.49	2.23–2.77	<0.001
Age 71–80	3.70	3.30–4.14	<0.001
Age >80	0.74	0.55–1.02	0.053
Female sex	1.95	1.84–2.08	<0.001
Alcohol abuse	1.84	1.67–2.03	<0.001
BMI <25 kg/m^2	1.49	1.34–1.65	<0.001
BMI 25–30 kg/m^2	0.94	0.87–1.02	0.156
BMI 30.1–40 kg/m^2	1.02	0.96–1.08	0.481
BMI >40 kg/m^2	1.54	1.44–1.64	<0.001
CCI > 3	1.70	1.59–1.81	<0.001
Diabetes mellitus	1.09	1.03–1.15	0.002
Statin users	0.82	0.77–0.87	<0.001
Tobacco use	1.19	1.13–1.25	<0.001

Abbreviations: BMI, Body mass index; CCI, Charles Comorbidity Index; TKA, total knee arthroplasty.
Note: Referent cohort: Statin naive control cohort.

Table 5 Multivariate logistic regression for revision surgeries

	TKA		
	Odds ratio	**Confidence interval**	**p-Value**
90-d complications			
Age <60	2.58	2.32–2.85	<0.001
Age 60–70	2.08	1.89–2.29	<0.001
Age 71–80	1.96	1.77–2.17	<0.001
Age >80	4.30	2.50–8.32	<0.001
Female sex	0.77	0.74–0.80	<0.001
Alcohol abuse	1.73	1.61–1.86	<0.001
BMI <25 kg/m^2	1.26	1.14–1.39	<0.001
BMI 25–30 kg/m^2	0.88	0.82–0.94	<0.001
BMI 30.1–40 kg/m^2	0.98	0.93–1.02	0.304
BMI >40 kg/m^2	1.75	1.67–1.84	<0.001
CCI > 3	1.36	1.29–1.44	<0.001
Diabetes mellitus	1.26	1.20–1.31	<0.001
Statin users	0.85	0.81–0.89	<0.001
Tobacco use	1.23	1.18–1.28	<0.001
1-y complications			
Age <60	3.31	3.10–3.53	<0.001
Age 60–70	2.11	1.98–2.25	<0.001
Age 71–80	1.73	1.62–1.85	<0.001
Age >80	3.72	2.63–5.50	<0.001
Female sex	0.82	0.80–0.84	<0.001
Alcohol abuse	1.51	1.44–1.58	<0.001
BMI <25 kg/m^2	1.23	1.16–1.31	<0.001
BMI 25–30 kg/m^2	0.99	0.94–1.03	0.603
BMI 30.1–40 kg/m^2	1.06	1.03–1.09	<0.001
BMI >40 kg/m^2	1.42	1.37–1.46	<0.001
CCI > 3	1.19	1.15–1.24	<0.001
Diabetes mellitus	1.27	1.24–1.31	<0.001
Statin users	0.88	0.85–0.91	<0.001
Tobacco use	1.24	1.21–1.28	<0.001
2-y complications			
Age <60	4.54	4.34–4.74	<0.001
Age 60–70	2.81	2.70–2.93	<0.001
Age 71–80	2.23	2.13–2.33	<0.001
Age >80	1.66	1.37–2.03	<0.001
Female sex	0.88	0.86–0.89	<0.001
Alcohol abuse	1.35	1.30–1.40	<0.001
BMI <25 kg/m^2	1.26	1.20–1.32	<0.001
BMI 25–30 kg/m^2	1.10	1.06–1.13	<0.001
BMI 30.1–40 kg/m^2	1.15	1.12–1.17	<0.001
BMI >40 kg/m^2	1.35	1.32–1.39	<0.001
CCI > 3	1.30	1.26–1.33	<0.001

(*Continued*)

Table 5 (*Continued*)

	TKA		
	Odds ratio	Confidence interval	p-Value
Diabetes mellitus	1.22	1.20–1.25	<0.001
Statin users	0.90	0.88–0.92	<0.001
Tobacco use	1.26	1.23–1.29	<0.001

Abbreviations: BMI, body mass index; CCI, Charles Comorbidity Index; TKA, total knee arthroplasty.
Note: Referent cohort: statin naive control cohort.

evaluated such as race, ethnicity, discharge status, operative time, or surgical volume. However, patient cohorts were specifically identified using ICD and CPT codes, as well as USC codes to determine statin status. This enabled proper evaluation of two large and distinct patient cohorts. Another limitation lies within how statin therapy was defined. We could not assess the specific dose of statin use or the therapy strength for each patient. However, we specifically defined chronic statin use as filling more than three statin prescriptions within the year of undergoing a TKA. These potential limitations should not be disqualifying given this database's unique strength to identify a large sum of distinct patients to track over a relatively long time period.

The role of statins on bone metabolism has been explored in several studies within the past two decades. Grasser et al[15] studied the influence of lovastatin's inhibitory effect on osteoclast development via blocking a key protein involved in bone resorption. Moon et al[16] assessed the inhibitory effects of simvastatin and highlighted its suppression of reactive oxygen species formed from osteoclast differentiating signaling pathways. They also found decreased expression of tartrate-resistant acid phosphatase, a marker of osteoclast differentiation. Actual bone formation following statin use is not as well understood. In a comparative study of hydrophobic and hydrophilic statins in animal models, Hughes et al[17] did not observe increased bone formation rates with statin treatment. In contrast, an impactful study by Mundy et al[18] highlighted statin's effect on increasing the expression of bone morphogenic protein-2 gene in bone cells, thereby increasing bone formation and cancellous bone volume. Another study showed increased bone formation and resorption when high-dose statin was administered.[19] Despite some varied reporting, statins are primarily suggested to influence the resorptive properties of osteoclasts as opposed to the regenerative capacity of other cell-mediated pathways. These experimental studies have laid the groundwork for further clinical study and its potential applications in arthroplasty, such as postoperative fracture prevention.

The association between statin use and fracture prevention has been explored in patients who have osteoporosis. In a large cross-sectional study of over 1,300 women in Australia, Pasco et al[20] demonstrated that the OR for fracture associated with statin use was 0.45 at the femoral neck, when adjusting for bone mineral density (BMD). The dramatic fracture reduction observed with statin use, they concluded, is substantially higher than expected from BMD changes alone. In a Scandinavian randomized trial of simvastatin versus placebo in patients with coronary heart disease, no differences were found in fracture risk between cohorts.[21] However, fracture incidence was not a predefined study endpoint, possibly influencing the actual fracture incidence. In a more recent randomized study with fracture incidence as a secondary outcome, Peña et al[22] reported a fracture incidence of 1.20 and 1.14 per 100 person-years for the statin and placebo cohort, respectively ($p = 0.53$). Statin's influence on fracture risk has been explored, despite varied reports available over the past two decades. However, arthroplasty procedures may confer a greater risk for fracture though statin's effect has not been thoroughly examined in this setting.

Few studies assess the role of statins following THA; however, they corroborate the present findings of decreased postoperative periprosthetic fracture and revision surgeries. Thillemann et al[11] identified over 2,300 matched patients from the Danish Hip Arthroplasty Registry who underwent revision THA. Compared with no use of statin, postoperative statin use was associated with reduced revision rates due to periprosthetic fractures (adjusted relative risk 0.12 [0.04 to 0.33]). Another study by Zhang et al[2] examined 42 patients treated with postoperative statin for 1 year versus no statins following primary THA. They reported significantly less BMD percentage loss among statin users ($p < 0.05$). The aforementioned studies evaluated statin use only in the postoperative setting; however, the present studies' methodology identified preoperative chronic statin use versus statin-naïve patients. We felt that this comparison has the potential to better elucidate differences in statin versus no statin use. Despite this difference, our findings of reduced periprosthetic fractures and revision surgeries up to 2 years are corroborated by previous literature. Furthermore, the present study is unique in that it examines statin use among a national dataset in the setting of TKA. Although the reported periprosthetic fracture incidence is under 2.5%, they continue to be difficult to manage.[5–8] As more orthopaedic surgeons shift to an alternative payment model, the postoperative complication profile will be of keener interest. Thus, statin therapy has the potential to play an influential role in fracture reduction, thereby reducing cost expenditures. Current guidelines limit statin's use in managing cardiovascular health, and they are not recommended in the setting of arthroplasty for their reported fracture-related benefits. However, the present findings are encouraging and

may provide a framework for future examination of statin's role on fracture risk. Statin use is associated with a reduced periprosthetic fracture risk and revision surgery rate following TKA; however, the small, yet significant, differences between cohorts warrant further long-term examination.

Conclusion

Chronic statin exposure is associated with a reduced risk of 90-day,1-year, and 2-year periprosthetic fracture and revision surgery following TKA, as compared with the statin naïve. These findings are corroborated by a majority of the relevant experimental and clinical studies available; however, future high-level research is warranted for validation. The authors do not recommend administering statin therapy prior to TKA on the basis of its purported fracture reduction benefits alone, though these findings may guide postoperative patient expectations.

Conflict of Interest
None declared.

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