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## Hypothyroidism Increases 90-Day Complications and Costs Following Primary Total Knee Arthroplasty

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### Abstract

**Background:** Thyroid disease is common and often remains undetected in the US population. Thyroid hormone has an array of metabolic, immunologic, and musculoskeletal functions crucial to well-being. The influence of thyroid disease on perioperative outcomes following primary total knee arthroplasty (TKA) is poorly understood. We hypothesized that hypothyroidism was associated with a higher risk of postoperative complications and 90-day costs following primary TKA.

**Methods:** The Medicare standard analytical files were queried using International Classification of Disease codes between 2005 and 2014 to identify patients undergoing primary TKA. Patients with a diagnosis of hypothyroidism were matched by age and gender on a 1:1 ratio. Ninety-day postoperative complication rates, day of surgery, and 90-day global period charges and reimbursements were compared between matched cohorts.

**Results:** A total of 2,369,594 primary TKAs were identified between 2005 and 2014. After age and gender matching, each cohort consisted of 98,555 patients. Hypothyroidism was associated with greater odds of postoperative complications compared to matched controls (odds ratio 1.367, 95% confidence interval 1.322–1.413). The 90-day incidence of multiple postoperative medical and surgical complications, including periprosthetic joint infection, was higher among patients with hypothyroidism. Day of surgery and 90-day episode of care costs were significantly higher in the hypothyroidism cohort.

**Conclusion:** This study demonstrated an increased risk of multiple postoperative complications and higher costs among patients with hypothyroidism following primary TKA. Surgeons should

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counsel patients on these findings and seek preoperative optimization strategies to reduce these risks and lower costs in this patient population.

## Keywords

hypothyroidism; thyroid disease; total joint arthroplasty; total knee arthroplasty; risk factors

Total knee arthroplasty (TKA) is a cost-effective [1,2] option for reducing pain and improving function among patients with end-stage knee arthritis [3]. Not surprisingly, it is one of the most frequently performed procedures in the United States [4–6], imposing an enormous economic burden on the healthcare system [7]. Although complications following TKA are rare [8], the personal and fiscal costs can be overwhelming [9–12]. Attention has recently focused on identifying risk factors associated with adverse events [13–20], and worse clinical outcomes [21–24], following TKA, presuming the identification of modifiable variables may allow for preoperative intervention, potentially improving outcomes and decreasing cost.

Between 4.6% and 12% of the US population are affected by thyroid disease [25,26]. Thyroid hormone has a number of systemic and musculoskeletal functions including bone remodeling and maintaining articular cartilage health [27,28]. Research suggests an increased risk of osteoarthritis among people with thyroid disease [29,30]. The reported prevalence of hypothyroidism in the total joints population is up to 18%, which is significantly higher than in the general population [31]. Hypothyroidism has previously been associated with an increased risk of periprosthetic joint infection (PJI) in a retrospective, single center study [32]. However, no prior research has evaluated the influence of thyroid disease on post-operative outcomes or cost following primary TKA. Therefore, we sought to evaluate the influence of hypothyroidism on complication rates and cost of primary TKA using a large national database. We hypothesized that, following primary TKA, hypothyroidism was associated with a higher risk of postoperative complication as well as an increase in the 90-day episode of care cost compared to patients without thyroid disease.

## Materials and Methods

A retrospective, case-control study was performed to investigate the effects of hypothyroidism on 90-day complications and costs following TKA. The PearlDiver Supercomputer (Warsaw, IN) was utilized to query the entire Medicare sample from 2005 to 2014 by way of the standard analytical files. Medicare releases 100% of their inpatient and outpatient hospital billing data across all service locations nationwide. These data are deidentified and cohorts less than 11 are removed and these data are sent to PearlDiver for distribution subscribers. The dataset used for this study is composed of 100% of the records of Medicare patients from 2005 to 2014 without any patient identifiers. This publically and commercially available HIPAA compliant server provides the ability to identify and track patient information based on International Classification of Disease (ICD) and Current Procedural Terminology (CPT) codes. The ICD and Current Procedural Terminology codes utilized in this search have been previously used in the literature [33,34]. Patients with ICD-9 codes for hypothyroidism were identified based on codes 2440 (postsurgical

hypothyroidism), 2441 (other/postablative hypothyroidism), 2442 (iodine hypothyroidism), 2443 (iatrogenic hypothyroidism), and 2448 (acquired hypothyroidism not elsewhere classifiable/other specified acquired hypothyroidism). Patients with a diagnosis of hyperthyroidism (ICD-9 codes 242.0–242.3 and 242.9) were excluded. No other exclusion criteria were utilized. All diagnosis slots were used to identify a diagnosis of hyperthyroidism or hypothyroidism. A comparison of the Charlson Comorbidity Index (CCI), a measurement of morbidity and mortality risk shown to be associated with worse outcomes following orthopedic surgery [33], was performed to determine the similarity between cohorts. Following the creation of the cohorts, the server performs a random selection of patients to match 2 cohorts with the same age and gender distribution with the only differentiating factor being the presence or absence of hypothyroidism. This also provides a method to randomize each cohort to match the same criteria, which allows confounders to be randomly present in both cohorts. Patients were matched based on age, gender, and CCI at a 1:1 ratio prior to cost and outcome analysis (Table 1).

Ninety-day complication rates were tracked through ICD-9 coding. Day of surgery and 90-day global period charges and reimbursements were analyzed as markers of costs, using previously described techniques [33,35]. We selected a 90-day global period to represent the most common time period for bundle payment initiatives as depicted in the Comprehensive Care for Joint Reconstruction model.

Given that the data were extracted from a HIPAA compliant server, the current study did not require Institutional Review Board approval. Odds ratios (ORs) and 95% confidence intervals were calculated. Independent samples 2-tailed t-tests were performed for the comparison of means. A *P*-value of <.05 was used to define statistical significance [36]. All data were analyzed using the software Statistical Package for Social Sciences [SPSS] version 23 (Chicago, IL). No external funding source was used for the conduct of this study.

## Results

A total of 2,369,594 primary TKAs were identified as having been performed between 2005 and 2014. During the same time period, within the database, a total of 1,277,014 patients had a diagnosis of hypothyroidism. After age and gender matching and randomization, each cohort comprised 98,555 patients (Table 1). Due to the matching process, the gender and age distributions among both cohorts were the same. Comparison of CCI scores between cohorts revealed no statistically significant difference ( $P=.892$ ). Analysis of the cumulative 90-day outcomes demonstrated that following primary TKA, patients with a diagnosis of hypothyroidism were at increased odds of medical and surgical complications (9.7% vs 7.09%, OR 1.367, 95% CI 1.322–1.413) compared to the matched cohort. Additionally, patients with a diagnosis of hypothyroidism experienced a significantly higher rate of many individual medical complications compared to the matched cohort (Table 2). Similarly, postoperative infections were significantly more frequent among patients with hypothyroidism (Table 3). Compared to the matched cohort, patients with hypothyroidism incurred significantly greater day of surgery (\$54,459.39 standard deviation (SD): \$36,026.99 vs \$52,181.17 SD: \$33,476.67) and 90-day episode of care (\$61,622.39 SD:

\$47,900.80 vs \$57,871.69 SD: \$42,333.69) charges and reimbursements ( $P < .001$ ) (Table 4).

## Discussion

Although the prevalence of thyroid disease among patients undergoing total joint arthroplasty is reportedly high [32], previous evaluation of its influence on outcomes following primary TKA is limited. This study found hypothyroidism to be a significant risk factor for postoperative medical and surgical complications and that it is associated with increased episode of care costs following primary TKA.

Patients with hypothyroidism were found to have significantly greater odds of thromboembolic disease including deep venous thrombosis (OR 1.252) and pulmonary embolism (OR 1.206) compared to matched controls. Additionally, hypothyroidism was associated with greater odds of acute postoperative anemia (OR 1.326) requiring a blood transfusion (OR 1.428). These findings may be explained by the direct and indirect effects of thyroid hormone on platelet maturation and function, the synthesis and action of coagulation factors, and the maintenance of blood viscosity [37].

The results of this study are also consistent with previously reported results regarding the influence of hypothyroidism on PJI. Similar to the 2.46 higher odds of PJI reported in the study by Tan et al [32], this study also found hypothyroidism to be associated with a significantly greater odds of postoperative PJI compared to matched controls. The increased risk of PJI may be related to the role of thyroid hormone in modulating cell-mediated immunity and cellular metabolism [38,39]. These roles of thyroid hormone may also explain the finding that patients with hypothyroidism had significantly higher odds of postoperative pneumonia (OR 1.579) and intubation (OR 1.524) compared to the matched controls.

Patients with hypothyroidism were also found to have incurred significantly higher charges following primary TKA when compared to matched controls. Although the results of this study do not identify hypothyroidism as an independent risk factor of increased cost, per se, it does associate a diagnosis of hypothyroidism with higher costs overall. Perhaps the main contributor to the increased cost identified in this study is the higher complication rates. For instance, the average cost of a PJI has been reported to be \$116,383 per episode [11]. Similarly, thromboembolic disease is associated with significantly increased cost [9], estimated at \$18,000 if identified during the index hospitalization and nearly \$6000 when diagnosed after discharge and causing a readmission [10]. These findings help explain the fact that 94% of American Association of Hip and Knee Surgeons members express concerns regarding the financial disincentive of operating on high-risk patients [40]. Consequently, seeking to optimize underlying metabolic abnormalities associated with hypothyroidism may not only improve outcomes, but may also decrease episode of care costs following primary TKA.

Although utilization of large, national databases for epidemiological research has numerous strengths [41], limitations of this study include those inherent in any analysis of data from administrative databases [42]. For instance, the Medicare standard analytical files may be

subject to coding error or errors in data entry [42]. Additionally, the prevalence of comorbid conditions and adverse events may be underreported [36]. Moreover, the retrospective nature might cause retrospective bias as well as selection bias. Both types of bias are diminished here as the server allowed randomization of patients and thus the investigators involved in the study did not ultimately decide which patients to exclude, which might occur in a traditional retrospective chart review process. Although selection bias might have occurred because of the ICD codes utilized, we believe that the coding for these is very accurate as hospitals invest great effort into their coding teams, as they are responsible for the billing to Medicare. Finally, the statistical methodology chosen for this study involves associating hypothyroidism with higher cost and increased complications following primary TKA. This study does not demonstrate a causal relationship between hypothyroidism and the observed complications because this study did not control potential confounders that may affect the outcomes of interest. Adjusting for covariates that affect the outcomes of interest would provide greater confidence with our conclusions and future studies performing multivariable logistic regression analysis should be designed now that this association has been made.

## Conclusions

This study demonstrates an increased risk of a multiple perioperative complication and higher cost. The results of this study may improve surgeons' ability to preoperatively counsel patients regarding their specific risks associated with TKA. These findings imply that the increased risk of a patient with hypothyroidism can be reduced through normalization of thyroid function. However, future prospective studies need to be conducted evaluating whether correction of hypothyroidism results in improved outcomes and reduced cost compared to patients with abnormal thyroid function.

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**Table 1**

Matched Medicare Beneficiaries Undergoing TKA During the Study Period With and Without a Diagnosis of Hypothyroidism.

Patient Demographics	Number of Patients (%)
Age group	
64 and under	11,513 (11.7)
65–69	28,730 (29.2)
70–74	24,142 (24.5)
75–79	19,543 (19.8)
80–84	11,160 (11.3)
85 and over	3467 (3.5)
Gender	
Female	81,306 (82.5)
Male	17,249 (17.5)

Patient age and gender demographics for the control (n = 98,555) and hypothyroid (n = 98,555) cohorts.



**Table 2**  
 Comparison Between the Incidence of Postoperative Medical Complications Among Medicare Beneficiaries Undergoing TKA During the Study Period With and Without a Diagnosis of Hypothyroidism Between Hypothyroid (n = 98,555) and Euthyroid (n = 98,555) Using Pearson Chi-Squared Test.

Medical Complications	ICD Code	Hypothyroid and TKA (n = 98,555)	Non-Hypothyroid and TKA (n = 98,555)	Odds Ratio	95% CI	P Value
Acute postoperative anemia	285.1	1.93%	1.45%	1.326	1.237–1.422	<.001
Thrombocytopenia	287.4–287.5	0.28%	0.17%	1.577	1.303–1.910	<.001
Intubation	96.xx	0.10%	0.07%	1.524	1.114–2.084	.008
Pulmonary embolism	415.1	0.28%	0.23%	1.206	1.012–1.437	.036
Deep venous thrombosis	453.4	0.66%	0.53%	1.252	1.115–1.406	<.001
Pneumonia	480–486	0.54%	0.34%	1.579	1.377–1.810	<.001
Transfusion of blood	99.x	1.23%	0.86%	1.428	1.307–1.561	<.001
Acute renal failure	584	0.59%	0.45%	1.304	1.152–1.477	<.001
Postoperative bleeding	998.1	0.41%	0.32%	1.252	1.080–1.451	.003
Cardiac complication	997.1	0.04%	0.04%	0.897	0.569–1.416	.642
Peripheral vascular complication	997.2	0.02%	0.03%	0.92	0.522–1.621	.773
Urinary complication	997.5	0.02%	0.02%	1	0.561–1.783	1
Pulmonary insufficiency	518.5	0.02%	0.03%	0.75	0.426–1.321	.317
Acute myocardial infarction	410	0.14%	0.11%	1.217	0.946–1.564	.126

CI, confidence interval.

**Table 3**

Comparison Between the Incidence of Postoperative Surgical Complications Among Medicare Beneficiaries Undergoing TKA During the Study Period With and Without a Diagnosis of Hypothyroidism Between Hypothyroid (n = 98,555) and Euthyroid (n = 98,555) Using Pearson Chi-Squared Test.

Surgical Complications	ICD-9 Code	Hypothyroid and TKA (n = 98,555)	Non-Hypothyroid and TKA (n = 98,555)	Odds Ratio	95% CI	P Value
Acute postoperative infection	998.5	0.48%	0.35%	1.383	1.203–1.589	<.001
Osteomyelitis	730	0.04%	0.02%	1.824	1.054–3.221	.029
Infection of orthopedic device	996.66	0.35%	0.23%	1.502	1.271–1.775	<.001
Mechanical complication of orthopedic device	996.4	0.89%	0.69%	1.288	1.164–1.424	<.001
Unspecified mechanical complication of internal orthopedic device, implant, and graft	99640	0.06%	0.02%	2.811	1.708–4.625	<.001
Dislocation of prosthetic joint	99642	0.46%	0.36%	1.258	1.095–1.446	.001
Other mechanical complication of prosthetic joint implant	99647	0.06%	0.04%	1.6	1.078–2.376	.019
Other complications due to other internal prosthetic device, implant, and graft	996.79	0.01%	0.01%	1	0.416–2.403	1
Other mechanical complication of other internal orthopedic device, implant, and graft	99649	0.04%	0.03%	1.286	0.785–2.107	.317
Mechanical loosening of prosthetic joint	99641	0.07%	0.06%	1.119	0.787–1.590	.531
Accidental puncture	998.2	0.01%	0.01%	1	0.416–2.403	1
Broken prosthetic joint implant	99643	0.02%	0.02%	1.05	0.569–1.937	.876
Peri-prosthetic fracture around prosthetic joint	99644	0.18%	0.15%	1.153	0.927–1.434	.202

**Table 4**  
 Comparison Between the Mean Day of Surgery and 90-Day Global Charges and Reimbursements Among Medicare Beneficiaries Undergoing TKA During the Study Period With and Without a Diagnosis of Hypothyroidism Between Hypothyroid (n = 98,555) and Euthyroid (n = 98,555) Patients Using Student's T-Test.

	Hypothyroid and TKA (n = 98,555)	Non-Hypothyroid and TKA (n = 98,555)	P Value
Day of surgery			
Charges			
Mean (SD)	\$54,459.39 (\$36,026.99)	\$52,181.17 (\$33,476.67)	<.001
Reimbursements			
Mean (SD)	\$14,019.16 (\$7361.99)	\$13,173.51 (\$7367.44)	<.001
90-d global period			
Charges			
Mean (SD)	\$61,622.39 (\$47,900.80)	\$57,871.69 (\$42,333.69)	<.001
Reimbursements			
Mean (SD)	\$16,008.53 (\$10,166.29)	\$14,782.41 (\$9712.24)	<.001