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Insulin Dependence Heralds Adverse Events After Hip And Knee Arthroplasty

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INSULIN DEPENDENCE HERALDS ADVERSE EVENTS AFTER HIP AND KNEE ARTHROPLASTY

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ABSTRACT

INSULIN DEPENDENCE HERALDS ADVERSE EVENTS AFTER HIP AND KNEE ARTHROPLASTY

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Total hip arthroplasty (THA) and total knee arthroplasty (TKA) are two of the most frequently performed orthopaedic procedures. As the prevalence of diabetes mellitus (DM) continues to increase the burden of its sequelae and associated surgical complications has also increased. More patients with DM are candidates for total joint arthroplasty (TJA) than ever before. For these reasons, it is important to understand the associations between DM and the rates of perioperative adverse events in patients with DM who will undergo TJA.

The American College of Surgeons National Surgical Quality Improvement Program database (ACS NSQIP) records perioperative adverse events and patient factors including demographics and comorbidities. Patients who underwent TJA between 2005

and 2014 were identified and characterized as having either insulin dependent diabetes mellitus (IDDM), non-insulin dependent diabetes mellitus (NIDDM), or neither. Multivariate Poisson regression was used to assess the relative risk of multiple adverse events in the initial 30 postoperative days while controlling for demographic and comorbid factors.

A total of 71,733 patients who underwent THA were identified (1,920 IDDM (2.7%), 6,305 NIDDM (8.8%), and 63,508 without DM (88.5%)), and 114,102 patients who underwent TKA were identified (4,881 IDDM (4.3%), 15,367 NIDDM (13.5%), and 93,854 (82.2%) without DM). Relative to patients without diabetes, patients with NIDDM who underwent THA were shown to be at an increased relative risk for 3 of 17 adverse events studied while those who underwent TKA were at increased risk for 2 of 17. Patients with NIDDM who underwent THA were at greater risk for sepsis or septic shock, readmission to hospital within 30 days, and extended postoperative length of stay (LOS) while those who underwent TKA were at greater risk of myocardial infarction (MI) and extended postoperative length of stay (LOS) (greater than 5 days). Patients with IDDM who underwent THA were shown to be at an increased relative risk for 11 of 17 adverse events studied. These were death, sepsis or septic shock, myocardial infarction, wound-related infection, unplanned intubation, renal insufficiency, return to the operating room, readmission, pneumonia, urinary tract infection, and extended LOS. Similarly, patients with IDDM who underwent TKA were found to be at an increased relative risk for 12 of 17 adverse events studied. These were sepsis or septic shock, MI, renal failure,

ventilator time great than 48 hours, unplanned intubation, renal insufficiency, return to the operating room, wound dehiscence, readmission to hospital within 30 postoperative days, pneumonia, urinary tract infection, and extended LOS.

Compared to patients with NIDDM, patients with IDDM are at greater risk for many more perioperative adverse events relative to patients without DM. This association between insulin dependence and risks of adverse events after TJA has important implications for patient selection, preoperative risk stratification, surgical planning, postoperative expectations, and patient counseling. These data will be useful to medical and surgical teams so that they may better anticipate or prevent these adverse events in these at-risk populations.

ACS NSQIP DISCLAIMER

The ACS NSQIP and the hospitals participating in the ACS NSQIP are the source of the data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors. These studies do not represent the views of plans of the ACS or the ACS NSQIP.

CONTENTS

PURPOSE

These studies evaluate the null hypotheses that patients with insulin dependent diabetes mellitus (IDDM) and patients with non-insulin dependent diabetes mellitus (NIDDM) do not have greater risks of perioperative adverse events following total joint arthroplasty (TJA) relative to patients without diabetes mellitus (DM).

The study presented in the first chapter evaluates the above hypotheses in cohort of patients who underwent total hip arthroplasty (THA). This study used the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database between the years 2005 and 2014 to collect this cohort. The study presented in the second chapter evaluates the same hypotheses in a total knee arthroplasty (TKA) cohort using the ACS NSQIP database.

Specifically, this thesis compares the rates of the following adverse events for patients with IDDM or NIDDM to patients without DM following THA or TKA. The adverse events studied are: death, cardiac arrest, stroke or cerebrovascular accident, sepsis or septic shock, myocardial infarction, renal failure, thrombotic event, wound-related infection, ventilator time greater than 48 hours, unplanned intubation, renal insufficiency, return to the operating room, wound dehiscence, readmission, pneumonia, urinary tract infection, and extended length of stay (greater than five days) for patients with IDDM or NIDDM to patients without DM following THA or TKA.

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INTRODUCTION TO CHAPTERS

Total joint arthroplasty (TJA) is a common procedure to relieve pain from osteoarthritis (OA). Globally, the prevalence of OA is projected to continue increasing[1] and the rates of total hip arthroplasty (THA) and total knee arthroplasty (TKA) in the United States (US) are also projected to continue to increase through the decade.[2] Diabetes mellitus (DM) is one of the most common medical morbidities among candidates for TJA. The prevalence of DM in the TJA population ranges from 6% in the United Kingdom[3] and 12% in Western China[4] to 20% in New York City[5] and 19-20% in the US generally,[6,7] and the prevalence of DM globally[8] and in the US continues to increase.[9] According to a recent study of the National Health Interview Survey, the lifetime risk of being diagnosed with DM in the US is 40% and this estimate is 13 to 20 percentage points greater than it was two decades previously.[10] Likewise, a study from the Centers for Disease Control and Prevention that uses current US census data estimates that the prevalence of DM in the US will increase from 14% in 2010 to 25-28% by 2050.[11]

The associations between DM, obesity, and OA are complex. There are many conditions comorbid with DM, and some of the most common of these are hypertension (76%), coronary artery disease (28%), renal disease (18%), cerebrovascular disease (16%),

diabetic eye disease (15%), and heart failure (13%). OA is second only to hypertension among these and is comorbid in the majority of patients with DM (55%).[12] Obesity is a known risk factor for DM[13-17] and obesity is also a risk factor for OA[18-22] at least partly related to increased mechanical load[23] but also due to other non-biomechanical factors associated with obesity.[24] Furthermore OA has been shown to be a barrier to physical activity in the obese,[25] and low physical activity levels have been shown to be correlated with risks of DM.[14,26] DM itself may also be a risk factor for OA independent of obesity,[27] perhaps related to an effect that hyperglycemia may have on joint tissues including collagen.[28] Clearly, the association between DM and OA is multifactorial and complex.

The association between DM, OA, and TJA is also very strong. The Centers for Disease Control and Prevention has reported that the prevalence of OA in the US is greater in adults with DM (52%) compared to adults without DM (29%).[29] Furthermore, studies have found that patients with DM are more likely to undergo TJA than patients without DM independent of age and body mass index,[27] and patients with DM have greater rates of TJA than patients without DM at all ages younger than 66.[30] Overall, 1 in 5 patients who undergo TJA in the US have DM,[6,7] so it is important to investigate how DM is related to perioperative adverse events after TJA.

DM is defined by a fasting glucose greater than or equal to 126mg/dl, or a 2 hour glucose tolerance test greater than 200mg/dl, or a random glucose greater than

200mg/dl, or a glycated hemoglobin (hemoglobin A1c, HbA1c) value greater than 6.5%.[31] DM is often described as type 1 or type 2 in non-gestational individuals. The pathogenesis of DM type 1 is related to autoimmune destruction of the insulin secreting beta cells of the pancreas,[32] and the pathogenesis of DM type 2 is related to acquired insulin resistance. Individuals with DM type 1 are always insulin dependent. DM type 2 can be managed with lifestyle modifications or oral hypoglycemic agents, but patients with recalcitrant disease may become insulin dependent.[32,33] This thesis categorizes patients with DM by pharmacologic treatment regimen. For the purposes of this thesis, patients with IDDM are any patients who use daily insulin therapy to control hyperglycemia, and patients with NIDDM are patients who use pharmacologic agents other than insulin to control hyperglycemia. For the purposes of this thesis, patients without DM either do not have diabetes or use diet and lifestyle modifications alone to control hyperglycemia.

Although numerous recent studies have reported an association between DM and adverse events following TJA,[4,6,7,34-52] relatively few studies have investigated associations between these adverse events and identifiable subpopulations of patients with DM such as patients with DM type 1 versus DM type 2[53-55] or patients with insulin dependent diabetes mellitus (IDDM) versus non-insulin dependent diabetes mellitus (NIDDM).[53,55-57] A few studies have found that patients who use insulin are at greater risk for particular perioperative adverse events – most notably cardiac complications after elective major noncardiac surgery[58] – and one surgical risk calculator uses insulin

dependence as one of many risk factors to compute the absolute risks of particular adverse events,[59] but no studies have found that patients with IDDM are at relatively greater risk for particular adverse events other than infection[57] after TJA.

Whether patients with DM undergo THA or TKA, it is important to determine whether particular subpopulations are at greater risk for adverse events, and determining the particular adverse events for which they are at risk is also important. Although glycemic control as measured by glycated hemoglobin and perioperative blood glucose as measured by postoperative blood glucose level are well recognized risk factors for adverse events,[60] the association between insulin dependence and the risks of adverse events has not been well appreciated. This information will be useful for patient counseling and expectations, preoperative risk stratification, and postoperative management. Identifying particular adverse events for which subpopulations are at greater risk could also encourage the implementation of appropriate preventative and monitoring measures.

Furthermore, it has been found that patients with DM incur higher resource utilization and costs following TJA than patients without DM[61] at least partly due to their greater risk of postoperative adverse events, and some authors suggest that if providing TJA for patients with DM is not reimbursed at a greater rate than for patients without DM than a disparity in care may develop.[7] Likewise, it may be known or assumed by some providers that particular subpopulations of patients with DM will incur greater costs

than others, and for this reason identifying the particular adverse events for which particular subpopulations are at risk could contribute to amelioration of disparities in provision of TJA.

The American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database is uniquely useful for investigating these associations. In general, the statistical power afforded by the large sample size of national databases is helpful for investigating infrequent events and rare patient populations. ACS NSQIP differs from many national databases because it tracks the occurrence of adverse events that occur up to 30 days following hospital discharge, and it is unique among databases with outpatient follow-up because the data included in ACS NSQIP is gathered by specially trained medical professionals. In contrast to administrative databases that are based on reimbursement claims and have been shown to be limited,[62] inconsistent,[63] and fraught with errors,[64] ACS NSQIP data are chart-abstracted and prospectively collected, and high-quality data is ensured by routine auditing. This is demonstrated by an agreement rate between clinical reviewers of greater than 98%.[65] This reliability and internal validity is particularly important for studies that define cohort subpopulations based upon clinical parameters.

For the reasons outlined above, this study will use the ACS NSQIP database to compare the adverse event rates of patients without DM to patients with IDDM or NIDDM after THA and after TKA. THA and TKA will be treated independently. THA will be considered

in the first chapter, and in the second chapter TKA will be considered in a similar manner. These chapters will be organized as if they were distinct manuscripts meant for publication in a peer-reviewed journal, and an additional conclusion section will be added to summarize the thesis.

COMPARISON OF PERIOPERATIVE ADVERSE EVENT RATES FOLLOWING TOTAL HIP ARTHROPLASTY IN PATIENTS WITH DIABETES: INSULIN DEPENDENCE MAKES A DIFFERENCE.

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ABSTRACT

Background – Total hip arthroplasty (THA) is one of the most frequently performed orthopaedic procedures. As the prevalence of diabetes mellitus (DM) continues to increase the burden of its sequelae and associated surgical complications have also increased. For these reasons, it is important to understand the associations between DM and the rates of perioperative adverse events in patients with DM who will undergo THA.

Methods – The American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database records perioperative adverse events as well as patient factors including demographics and comorbidities. Patients who underwent THA between 2005 and 2014 were identified and characterized as having insulin dependent diabetes mellitus (IDDM), non-insulin dependent diabetes mellitus (NIDDM), or neither. Multivariate Poisson regression was used to assess the relative risk of multiple adverse events in the initial 30 postoperative days while controlling for demographic and comorbid factors.

Results – A total of 71,733 patients who underwent THA were identified (1,920 IDDM, 6,305 NIDDM, and 63,508 without DM). Relative to patients without diabetes, patients with NIDDM were at an increased relative risk for 3 of 17 adverse events studied. These were sepsis or septic shock, readmission to hospital within 30 days, and extended postoperative length of stay (LOS) (greater than 5 days). Patients with IDDM were at an increased relative risk for 11 of 17 adverse events studied. These included death, sepsis or septic shock, myocardial infarction, wound-related infection, unplanned intubation, renal insufficiency, return to the operating room, readmission, pneumonia, urinary tract infection, and extended LOS. Patients with IDDM and NIDDM were both at greater risk for sepsis or septic shock, readmission, and extended LOS. Patients with IDDM were at greater risk for all of these adverse events (sepsis or septic shock: relative risk [RR] = 3.53 versus 1.90, for IDDM and NIDDM respectively, readmission: RR = 2.11 vs. 1.28, and extended LOS: RR = 2.26 vs. 1.35).

Conclusions – Compared to patients with NIDDM, patients with IDDM are at greater risk for many more perioperative adverse events relative to patients without diabetes. These findings have important implications for patient selection, preoperative risk stratification, and postoperative expectations.

INTRODUCTION

The associations between diabetes mellitus (DM) and surgical outcomes is being scrutinized to a greater degree as the prevalence of DM increases in the US.[9-11] The correlation between DM and risks of complications following many orthopaedic procedures has been well established.[55,61,66,67] In regard to total hip arthroplasty (THA), previous retrospective studies have shown that patients with DM have a greater risk of infection of the surgical site, urinary tract, or lower respiratory tract,[38] and have greater risks of periprosthetic joint infection,[39,40] or any surgical site infection.[41] And patients with DM are also at greater risk for perioperative acute myocardial infarction,[36] or readmission,[37,42,43] or for developing peripheral arterial disease,[34] or persistent pain in the operated joint,[35] or for any one of a number of complications.[44] Additionally, patients with DM have been shown to stay longer in the hospital after THA[68] and to incur higher resource utilization and costs following total joint arthroplasty.[61] However, these studies have generally categorized patients as either diabetic or not diabetic and have not distinguished between identifiable subpopulations of patients with DM.

Due to their large sample sizes, national databases and registries are particularly effective for the analysis of rare adverse events and particular subpopulations. Among

available databases The American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database is particularly useful for comparing adverse event rates because it includes high-quality, chart-abstracted data that is collected for 30 days postoperatively regardless of hospital discharge.[31,69] For example, a recent study of perioperative adverse events after lumbar fusion found that patients with insulin dependent diabetes mellitus (IDDM) were at increased risk for many more perioperative adverse events than patients with non-insulin dependent diabetes mellitus (NIDDM).[66]

There is one prior study that used the ACS NSQIP database to investigate the association of IDDM and NIDDM on perioperative adverse events in the total joint population. That study used data collected between 2005 and 2011. That study considered total knee arthroplasty patients together with THA patients and found that patients with IDDM were at greater risk for infection relative to patients without DM (7% versus 5%) and they were also at greater risk for any "medical complication"[57] which is a composite of many adverse events. However, that analysis did not find that patients with IDDM were at greater risk for any particular complications other than infection relative to patients without DM. Since that study the number of THA cases available in the ACS NSQIP database has more than quadrupled (16,392 vs. 71,733 patients). The increased statistical power afforded by this large sample size allows this study to analyze the THA population in isolation and to investigate associations that were not initially apparent.

This study will for the first time identify the particular medical complications for which patients with IDDM are at risk.

This study assesses the relative risks of perioperative adverse events after THA in patients with IDDM and NIDDM relative to patients without DM. This information will be useful for patient selection, postoperative surveillance, and refinement of risk stratification.

MATERIALS & METHODS

This study used the ACS NSQIP data collected between the years 2005 and 2014. Current Procedural Terminology code 27447 was used to identify patients who underwent primary THA. Perioperative adverse events are tracked during the entire 30 day postoperative period regardless of hospital discharge. The database also records demographic variables including patient age, sex, height, weight, and smoking status among other comorbidities. Body mass index (BMI) was calculated from patient height and weight. The Human Investigation Committee at our institution approved this study.

For the purpose of controlling for confounding comorbidities, a modified version of the Charlson comorbidity index (CCI)[70] that has been adapted to the ACS NSQIP database[71] was used to categorize patient comorbidity burden. Studies have demonstrated that this modified CCI predicts similar outcomes as the original CCI.[72,73] The comorbidities used to determine the modified CCI include (followed by their CCI point values): myocardial infarction within the six months prior to surgery (1), congestive heart failure (1), peripheral vascular disease or rest pain (1), any history of transient ischemic attack or cerebrovascular accident (1), chronic obstructive pulmonary disease (1), diabetes mellitus (1), hemiplegia (2), end stage renal disease (2), ascites or esophageal varices (3),

and disseminated cancer (6). To calculate the CCI for a given case these point values are summed and an additional point is added for each age decade older than age 40. Although DM is included as a comorbid condition in the original CCI, it was removed from the modified CCI calculation for this study because DM is the comorbidity that this study evaluates.

The ACS NSQIP database records individual adverse events during the first 30 postoperative days. A prior study from our group asked orthopaedic surgeons at multiple institutions to weight each of these complications relative to a single patient's death. In order of severity weight relative to death[74] these adverse events are (weight): death (1), cardiac arrest requiring cardiopulmonary resuscitation (0.151), stroke or cerebrovascular accident (0.010), septic shock (0.087), myocardial infarction (0.042), acute renal failure (0.040), pulmonary embolism (0.030), sepsis (0.018), organ space infection (0.018), ventilator time greater than 48 hours (0.015), deep surgical site infection (0.015), unplanned intubation (0.014), renal insufficiency (0.009), return to the operating room (0.009), superficial surgical site infection (0.007), deep vein thrombosis (0.006), wound dehiscence (0.006), readmission to hospital (0.006), pneumonia (0.006), and urinary tract infection (0.003). In this study, pulmonary embolism and deep vein thrombosis were considered together as "thrombotic events," superficial surgical site infection, deep wound infection, and organ space infection were considered together as a "wound-related infection," and sepsis and septic shock were also considered together.

Postoperative length of stay (LOS) and readmission are also directly reported in the ACS NSQIP database. LOS is defined as the number of days from the operation date until discharge. Readmission is defined as any admission for any reason that occurs after discharge and within 30 days of surgery. While most postoperative variables in the ACS NSQIP database are only reported if they occur within the first 30 days, postoperative LOS is reported beyond 30 days. However, in order to limit the influence of outliers this study considered patients with LOS longer than 30 days to have had LOS equal to 30 days. LOS was considered to be extended if the stay lasted longer than one standard deviation (2.1 days) longer than the mean (3.0 days) of all hospital stays in the cohort. However, ACS NSQIP records LOS in terms of whole numbers. For this reason, any LOS longer than 5 days was considered to be extended.

The occurrence of readmission within 30 days of surgery is reported in the ACS NSQIP database for cases that occurred in 2011 or later, but it is not reported for earlier cases. Hence, the analysis of readmission includes 64,141 of 71,733 cases, representing 89.4% of all cases included in this study.

In the ACS NSQIP database diabetes status can be recorded one of three ways. There are patients who require daily insulin therapy to treat their diabetes (IDDM), those who use non-insulin pharmacologic agents (NIDDM), and patients who do not have DM. Patients without DM either do not have insulin resistance or hyperglycemia or are using dietary modifications alone to control hyperglycemia.

Statistical analyses were performed using STATA version 13 (StataCorp LP, College Station, TX). Statistical significance was set at a 2-sided alpha level of 0.05, but the chance of finding one or more spurious significant differences in 17 tests at that alpha level is 58.2%. For this reason the level of significance for comparisons of adverse event rates for each of 17 adverse events was adjusted to 0.003 according to Bonferroni's correction.[75] Likewise, instead of reporting 95% confidence intervals of these relative risks, 99.7% confidence intervals are reported in this study. Demographics were compared between patients with NIDDM, patients with IDDM, and those without DM using Pearson chi-squared tests.

Adverse event rates were compared between patients with NIDDM, IDDM, and those without DM using Poisson regression with robust error variance. These multivariate analyses were adjusted for the demographics of age (15–54, 55–64, 65–74, ≥75 years old), sex, BMI (18–24, 25–29, 30–34, and ≥ 35 kg/m^2), CCI, and smoking status in order to control for potential confounders. Poisson regression with robust error variance was used as an alternative to logistic regression so that the strengths of association could be reported as relative risks rather than odds ratios.[76,77]

RESULTS

In total, 71,733 patients who underwent THA between the years of 2005 and 2014 were identified in the ACS NSQIP database, and 6,305 of these patients (9%) had NIDDM, 1,920 patients (3%) had IDDM, and 63,508 patients did not have DM (88%).

Table 1 presents the differences in demographics of patients with NIDDM, IDDM, and patients without DM. Patients with DM were older than patients without DM ($p < 0.001$). Patients with DM were more likely to be male ($p < 0.001$). Patients with IDDM were more likely to have a BMI greater than 35 kg/m^2. Patients with NIDDM and IDDM had greater CCIs than those without DM ($p < 0.001$). Patients who were current smokers were not equally distributed between groups ($p = 0.016$), but the real differences in smoking rates were small (See Table 1).

Patients with NIDDM had an increased relative risk for 3 of 17 adverse events relative to patients without DM. These were sepsis or septic shock (relative risk [RR] = 1.90, 99.7% confidence interval [CI] = 1.14 - 3.19, $p < 0.001$), readmission (RR = 1.28, CI = 1.06 - 1.55, $p < 0.001$), and extended LOS (RR = 1.35, CI = 1.16 - 1.58, $p < 0.001$). These results are shown in Table 2 and they are represented graphically in a forest plot in Figure 1.

Patients with IDDM were at increased relative risk for 11 of 17 adverse events relative to patients without DM. These were death (RR = 5.92, CI = 2.07 - 16.93, $p < 0.001$), sepsis or septic shock (RR = 3.53, CI = 1.86 - 6.70, $p < 0.001$), myocardial infarction (RR = 4.65, CI = 2.31 - 9.34, $p < 0.001$), wound-related infection (RR = 1.95, CI = 1.29 - 2.96, $p < 0.001$), unplanned intubation (RR = 3.03, CI = 1.29 - 7.11, $p < 0.001$), renal insufficiency (RR = 6.26, CI = 2.23 - 17.52, $p < 0.001$), return to the operating room (RR = 1.53, CI = 1.05 - 2.22, $p < 0.001$), readmission (RR = 2.11, CI = 1.64 - 2.73, $p < 0.001$), pneumonia (RR = 4.17, CI = 2.18 - 7.98, $p < 0.001$), urinary tract infection (RR = 1.73, CI = 1.06 - 2.81, $p < 0.001$), and extended length of stay (RR = 2.26, CI = 1.85 - 2.76, $p < 0.001$). These results are shown in Table 2 and they are represented graphically in a forest plot in Figure 2.

Many more adverse events were associated with IDDM than with NIDDM. Furthermore, the relative risks of adverse events were greater for patients with IDDM than for patients with NIDDM (sepsis or septic shock: RR = 3.53 versus 1.90, respectively, readmission: RR = 2.11 vs. 1.28, and LOS: RR = 2.26 vs. 1.35).

DISCUSSION

Multiple studies have shown that DM is associated with an increased rate of adverse events after THA.[34-44,55,57] Many of the prior studies, however, did not distinguish between identifiable subpopulations of patients with DM. Many factors could be used to identify subpopulations that are at increased risk for adverse events after THA, and this information could be useful for patients and providers.

This study of a large cohort of patients with DM who underwent THA found that patients who use insulin in the management of diabetes are at great risk for perioperative adverse events independent of demographic and comorbid factors. The results of this study are consistent with recent research that shows that patients with IDDM are at a greater risk for medical complications when undergoing TJA, [57] but this study shows that insulin dependence is also an independent risk factor for many specific adverse events including death, sepsis or septic shock, myocardial infarction, wound-related infection, unplanned intubation, renal insufficiency, return to the operating room, readmission, pneumonia, urinary tract infection, and extended length of stay (greater than 5 days).

There are limitations to this analysis. The reliability of findings that are based on database studies is controversial. Specific to THA, a recent study found differences between populations and outcomes between the National Hospital Discharge Survey (NHDS) database and the Nationwide Inpatient Sample (NIS) database and that study concluded that large databases can have limited reliability and should be interpreted with caution.[78] While that study used the administratively-coded NHDS and NIS, this study used the professionally chart-abstracted ACS NSQIP database which differs significantly from NHDS and NIS in methods of data collection and follow-up. In contrast to the data in administrative databases that are based on reimbursement claims and have been shown to be limited,[62] inconsistent,[63] and fraught with errors,[64] ACS NSQIP data are chart-abstracted and prospectively collected, and high-quality data is ensured by routine auditing. This is demonstrated by an agreement rate between clinical reviewers of greater than 98%.[65] Reliability and internal validity are particularly important when cohorts are defined by clinical criteria and for these reasons cohorts identified in the ACS NSQIP database may be considered to more accurately reflect the real characteristics of the study population and the rates of adverse events than studies that use the administratively-coded NHDS and NIS databases.

However, in this study patients with IDDM, NIDDM, and without DM are defined by their use of insulin or other medications. For this reason, it is possible that some patients who actually have DM are included in the group without DM if those patients

are not using any medications to control hyperglycemia. Furthermore, the ACS NSQIP database does not record perioperative glucose levels or indicators of glycemic control. Recent studies have shown that lowering average blood glucose in the three months prior to surgery may be important to prevent postoperative morbidity and mortality[61] and that the relationship between average blood glucose level and complication risk is linear.[79] Average blood glucose is often monitored by glycated hemoglobin (HbA1c) level, but because the ACS NSQIP database does not record HbA1c levels the average blood glucose level of patients before surgery or in the postoperative period could not be evaluated, and this is a limitation of this study. Because the multivariate analyses could not be adjusted for HbA1c level, it is not possible to determine whether or not insulin dependence is a risk factor independent of average blood glucose level. Studies have also shown that perioperative glycemic control is an important risk factor for adverse events,[80] but perioperative blood glucose levels are not recorded in the ACS NSQIP database either, and for this reason this study is unable to determine if insulin dependence is a risk factor independent of perioperative blood glucose levels.

It should be mentioned that the mechanism of the association between IDDM and the risk of adverse events is not known. For example, the results of this study should not be interpreted to imply that insulin use itself is directly associated with adverse events, and perioperative insulin regimens should not be modified based on the results of this study. It is possible that patients with IDDM more often have advanced DM relative to patients with NIDDM, and this may account for some of the differences in the relative risks of

adverse events, but advanced DM may not account for all of the differences, and this should be an area of future research.

Despite these limitations, this study of postoperative adverse events in 71,733 patients with DM who underwent THA in a prospectively-collected national database has shown for the first time that IDDM is an independent risk factor for 11 distinct perioperative adverse events while patients with NIDDM are at increased risk for only 3 of these adverse events relative to patients without DM. Absolute risks of these adverse events given patient demographics and comorbidities can be found using the ACS NSQIP surgical risk calculator at (http://riskcalculator.facs.org).[59] This study controlled for those demographics and comorbidities to show that patients with IDDM had increased relative risk of many more adverse events than patients with NIDDM relative to patients without DM independent of demographics and comorbidities.

CONCLUSION

The results of this study show that insulin dependence is an independent risk factor for adverse events after THA. Orthopaedic surgeons should be aware of the utility of insulin dependence as a predictor of adverse events. Although the relationship between average blood glucose level as measured by HbA1c and perioperative glycemic control as measured by perioperative blood glucose level are well recognized risk factors for adverse events,[60] the association between insulin dependence and the risks for adverse events has not been well appreciated. This information will be useful for patient selection, preoperative risk stratification, and postoperative expectations.

TABLE 1. Demographics of 71,733 patients who underwent total hip arthroplasty.

	Without DM		NIDDM		IDDM		
	Number	Percentage	Number	Percentage	Number	Percentage	p-value
Overall	63,508	100.0%	6,305	100.0%	1,920	100.0%	
Age							**<0.001**
15-54	12,108	19.1%	630	10.0%	248	12.9%	
55-64	18,722	29.5%	1,754	27.8%	550	28.7%	
65-74	18,860	29.7%	2,303	36.5%	653	34.0%	
75+	13,818	21.8%	1,618	25.7%	469	24.4%	
Sex							**<0.001**
Female	35,552	56.0%	3,196	50.7%	934	48.7%	
Male	27,956	44.0%	3,109	49.3%	986	51.4%	
BMI							**<0.001**
18-25	14,391	22.7%	539	8.6%	179	9.3%	
25-30	22,639	35.7%	1,613	25.6%	467	24.3%	
30-35	15,426	24.3%	1,905	30.2%	509	26.5%	
> 35	11,052	17.4%	2,248	35.7%	765	39.8%	
CCI							**<0.001**
0-2	20,157	31.7%	1,248	19.8%	435	22.7%	
3	19,999	31.5%	2,188	34.7%	633	33.0%	
≥ 4	23,352	36.8%	2,869	45.5%	852	44.4%	
Smoker							**0.016**
No	55,049	86.7%	5,545	88.0%	1,673	87.1%	
Yes	8,459	13.3%	760	12.1%	247	12.9%	

DM - Diabetes mellitus, NIDDM - Non-insulin dependent diabetes mellitus
IDDM - Insulin dependent diabetes mellitus, CCI - Charlson comorbidity index, modified
Bolding indicates statistical significance at $p < 0.05$, Underlining indicates median.

TABLE 2. Relative risks of adverse events within 30 days of THA in patients without DM versus those with NIDDM and IDDM

	Non-DM	NIDDM				IDDM			
	Percent	Percent	RR	(CI)	p-value	Percent	RR	(CI)	p-value
Death	0.09	0.08	0.79	(0.19 - 3.29)	0.626	0.57	5.92	(2.07 - 16.93)	**<0.001**
Cardiac arrest	0.08	0.06	0.67	(0.13 - 3.40)	0.455	0.21	2.17	(0.42 - 11.23)	0.157
Stroke/cerebrovascular accident	0.11	0.10	0.78	(0.22 - 2.83)	0.564	0.31	2.69	(0.73 - 9.92)	0.022
Sepsis/septic shock	0.31	0.73	1.90	(1.14 - 3.19)	**<0.001**	1.41	3.53	(1.86 - 6.70)	**<0.001**
Myocardial infarction	0.22	0.33	1.34	(0.66 - 2.72)	0.216	1.09	4.65	(2.31 - 9.34)	**<0.001**
Renal failure	0.04	0.11	1.94	(0.50 - 7.49)	0.141	0.21	3.38	(0.64 - 17.84)	0.027
Thrombotic event (PE/DVT)	0.64	0.75	1.04	(0.65 - 1.67)	0.793	0.83	1.17	(0.54 - 2.57)	0.537
Wound-related infection	1.09	1.74	1.21	(0.86 - 1.66)	0.065	2.92	1.95	(1.29 - 2.96)	**<0.001**
On ventilator > 48 hours	0.09	0.13	1.10	(0.34 - 3.55)	0.802	0.36	3.12	(0.84 - 11.60)	0.009
Unplanned intubation	0.19	0.30	1.19	(0.55 - 2.54)	0.502	0.78	3.03	(1.29 - 7.11)	**<0.001**
Renal insufficiency	0.07	0.22	2.42	(0.93 - 6.33)	0.006	0.62	6.26	(2.23 - 17.52)	**<0.001**
Return to the operating room	1.89	2.47	1.09	(0.84 - 1.42)	0.301	3.54	1.53	(1.05 - 2.22)	**0.001**
Wound dehiscence	0.09	0.10	0.75	(0.21 - 2.69)	0.490	0.36	2.79	(0.80 - 9.74)	0.013
Readmission	3.02	4.55	1.28	(1.06 - 1.55)	**<0.001**	7.60	2.11	(1.64 - 2.73)	**<0.001**
Pneumonia	0.33	0.48	1.40	(0.77 - 2.57)	0.093	1.41	4.17	(2.18 - 7.98)	**<0.001**
Urinary tract infection	1.13	1.62	1.27	(0.92 - 1.77)	0.025	2.14	1.73	(1.06 - 2.81)	**0.001**
Extended length of stay (> 5 days)	4.64	6.95	1.35	(1.16 - 1.58)	**<0.001**	11.61	2.26	(1.85 - 2.76)	**<0.001**

These multivariate analyses use Poisson regression and control for the patient characteristics presented in Table 1.
All variables were entered into the model as they are listed in Table 1. Readmission data only available for years 2011-2014.
DM - Diabetes mellitus, NIDDM - Non-insulin dependent diabetes mellitus, IDDM - Insulin dependent diabetes mellitus
Bolding and gray shading indicate statisitcal significance at $p < 0.003$, adjusted according to Bonferroni's correction.
RR - Relative risk, CI - Confidence interval, note: 99.7% confidence interval according to Bonferroni's correction.
THA - Total hip arthroplasty

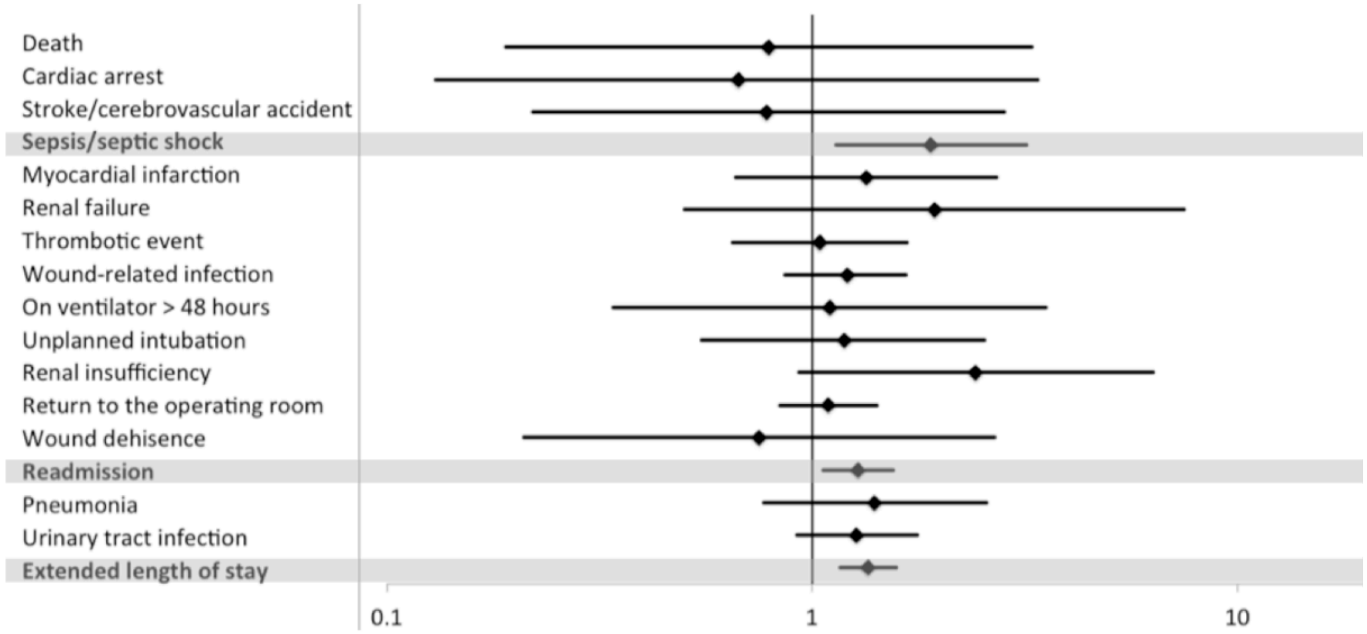

FIGURE 1. Relative risks of perioperative adverse events after total hip arthroplasty in patients with non-insulin dependent diabetes mellitus (NIDDM). Forest plot on logarithmic scale in horizontal axis. Adverse events listed at left. Diamonds central to the horizontal lines indicate relative risks. Horizontal lines denote the 99.7% confidence intervals of those relative risks, per Bonferroni's correction. The vertical line indicates a relative risk of 1. Therefore, horizontal lines that cross the vertical line indicate relative risks that are not statistically significant. **Bolding** and gray shading indicate relative risks that are statistically significant.

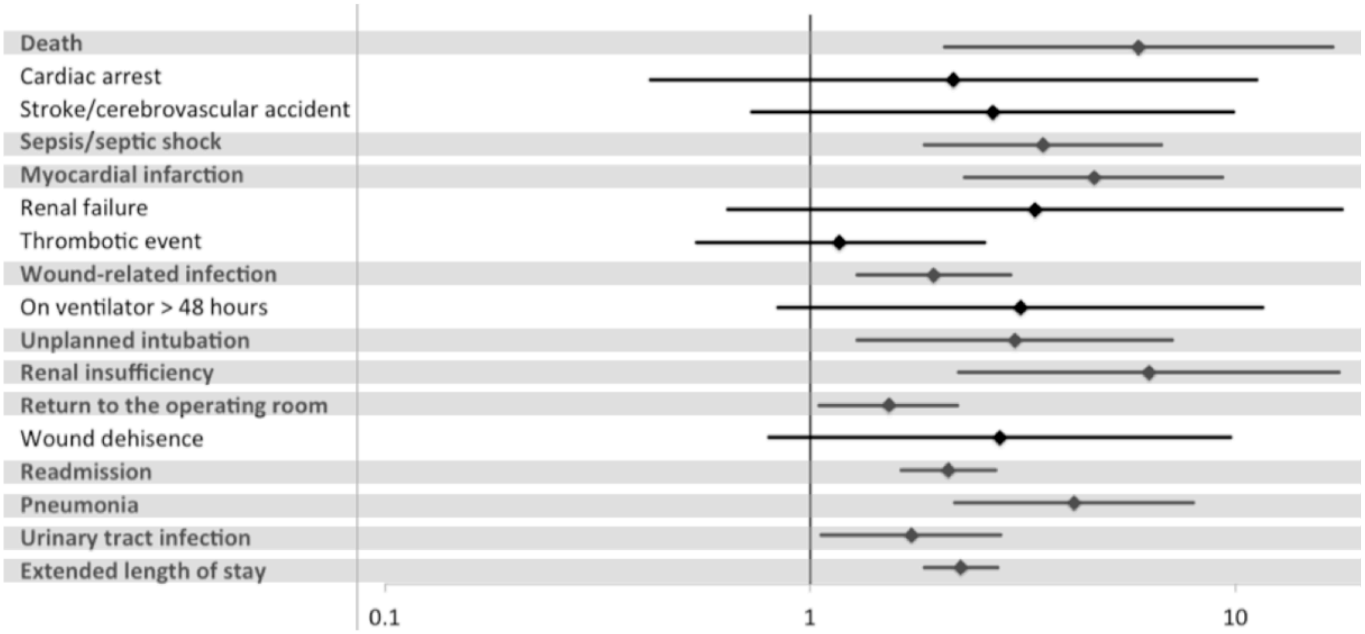

FIGURE 2. Relative risks of perioperative adverse events after total hip arthroplasty in patients with insulin dependent diabetes mellitus (IDDM). Forest plot on logarithmic scale in horizontal axis. Adverse events listed at left. Diamonds central to the horizontal lines indicate relative risks. Horizontal lines denote the 99.7% confidence intervals of those relative risks, per Bonferroni's correction. The vertical line indicates a relative risk of 1. Therefore, horizontal lines that cross the vertical line indicate relative risks that are not statistically significant. **Bolding** and gray shading indicate relative risks that are statistically significant.

COMPARISON OF PERIOPERATIVE ADVERSE EVENT RATES FOLLOWING TOTAL KNEE ARTHROPLASTY IN PATIENTS WITH DIABETES: INSULIN DEPENDENCE MAKES A DIFFERENCE.

Webb ML, Golinvaux NS, Ibe I, Lukasiewicz AM, O'Connor MI, Grauer JN.

ABSTRACT

Background – Total knee arthroplasty (TKA) is an effective treatment option for patients with advanced osteoarthritis and has become one of the most frequently performed orthopaedic procedures. With the increasing prevalence of diabetes mellitus (DM) the burden of its sequelae and associated surgical complications has also increased, and 1 in 5 patients in the US who will undergo total joint arthroplasty has DM. For these reasons, it is important to understand the association between DM and the rates of perioperative adverse events following TKA.

Methods – A retrospective cohort study was conducted using the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database. Patients who underwent TKA between the years 2005 and 2014 were identified and characterized as having insulin dependent diabetes mellitus (IDDM), non-insulin dependent diabetes mellitus (NIDDM), or neither. Multivariate Poisson regression was used to control for demographic and comorbid factors and to assess the relative risks of multiple adverse events in the initial 30 postoperative days.

Result – A total of 114,102 patients who underwent TKA were selected (4,881 (4.3%) with IDDM, 15,367 (13.5%) with NIDDM, and 93,854 (82.2%) without DM). Compared to patients with out DM, patients with NIDDM were found to be at an increased relative risk for 2 of 17 adverse events studied. These were myocardial infarction (MI) and extended postoperative length of stay (LOS) (greater than 5 days). Compared to patients with out DM, patients with IDDM were found to be at an increased relative risk for 12 of 17 adverse events studied. These were sepsis or septic shock, MI, renal failure, ventilator time great than 48 hours, unplanned intubation, renal insufficiency, return to the operating room, wound dehiscence, readmission to hospital within 30 postoperative days, pneumonia, urinary tract infection, and extended LOS. Patients with IDDM and NIDDM were both at greater risk for MI and extended LOS. Patients with IDDM were at greater risk for MI (relative risk [RR] = 2.71 versus 1.67) and extended LOS (RR = 1.99 versus 1.42).

Conclusions – Compared to patients with NIDDM, patients with IDDM are at greater risk for many more perioperative adverse relative to patients without DM. These findings have important implications for patient selection, preoperative risk stratification, and postoperative expectations.

INTRODUCTION

Total knee arthroplasty (TKA) is one of the most commonly performed orthopaedic procedures in the United States (US) and the number of TKAs performed in the US per annum continues to increase.[2,46,56,69] Concurrently, the prevalence of diabetes mellitus (DM) in the US is also increasing,[9-11] and the effects of DM on surgical outcomes has become a greater focus as surgeons explore all avenues to optimize patient outcomes. In 2009, 20% of the patients in the Nationwide Inpatient Sample had DM[7] and 19% of patients in the Kaiser Permanente Total Joint Replacement Registry had DM.[6]

Patients with DM have been found to have a greater risk of complications than patients without DM following many orthopaedic procedures.[55,61,66,67] In particular, previous retrospective studies have found that relative to patients without DM those patients with DM who underwent TKA had greater rates of mortality,[47] surgical site infections,[41,48,49,56,57,81] and periprosthetic joint infections.[39,40] Patients with DM were also more likely to be discharged to a location other than home[50] and to be readmitted to hospital.[42] Patients with DM were also more likely to experience periprosthetic fracture and aseptic loosening,[4] persistent pain in the operated joint,[35] and revision arthroplasty within 5 years.[52] Additionally, patients with DM also had poorer functional

outcomes[51] and higher resource utilization following total joint arthroplasty.[61] These studies, however, have generally categorized patients as either those with DM or those without DM and in doing so prior studies have not recognized important differences among patients with DM that may be useful as predictors of adverse events.

Due to the large number of patients therein, national databases and registries enable the analysis of rare adverse events and particular subpopulations. The American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) is one such database that has received specific attention due to high-quality, chart-abstracted data that is collected for 30 days postoperatively regardless of hospital discharge.[31,69] To that end, a recent ACS NSQIP study evaluating the effect of diabetes on outcomes after lumbar fusion found that those with insulin dependent diabetes mellitus (IDDM) were at greater risk for many more perioperative adverse events than patients with non-insulin dependent diabetes mellitus (NIDDM).[66]

There is also a single institution study from the Mayo Clinic in Rochester, MN in which all morbidly obese patients (BMI $\geq$ 40 kg/m^2) who underwent primary TKA between 1995 and 2011 with a minimum of two years of follow-up were retrospectively reviewed. This study found that patients with DM type 2 had similar outcomes as patients without DM, but patients with DM type 2 and insulin dependence had increased risks of reoperation, revision, periprosthetic joint infection, and decreased 10-year implant survivorship when compared to patients without DM.[53] However, other than

periprosthetic joint infection that study did not investigate the rates of any of the other adverse events that this study investigates.

A study of the ACS NSQIP database from 2006 to 2010 found that patient age and diabetes were both independent predictors of 30 day mortality after TKA.[47] That study included 15,321 patients and did not stratify patients by insulin dependence. This study of ACS NSQIP from 2005-2014 includes 114,102 patients and does stratify by insulin dependence.

One prior study of the ACS NSQIP database has evaluated the effect of IDDM and NIDDM in the total joint population based on data through 2011. Overall, a greater risk of postoperative infection was identified in the IDDM cohort (7% versus 5%). Patients with IDDM were also at greater risk for a "medical complication"[57] which is a composite of many complications. However, that analysis considered total hip arthroplasty patients together with TKA patients, and did not find that IDDM patients were at greater risk for any particular complications other than infection relative to patients without DM. In addition, since the time of that study the number of TKA cases available in the ACS NSQIP database has more than quadrupled, allowing our study to be powered to investigate associations that were not initially apparent. This study identifies particular medical complications for which patients with IDDM are at risk.

A goal of the current study is to assess the relative risk of adverse events after TKA in patients with IDDM and NIDDM in comparison to patients without DM. This information will be useful for patient counseling and risk stratification, preoperative planning, and postoperative surveillance. Adequate assessment of risks will facilitate appropriate patient education and surgeon preparedness in regard to the risks of adverse events.

MATERIALS & METHODS

The ACS NSQIP database gathers patient data from 517 participating hospitals in the US. Data is collected during the entire 30 day postoperative period regardless of hospital discharge, and data is de-identified before being shared with participating institutions. The current study was approved by the Human Investigation Committee at our institution.

Patients who underwent TKA were identified using Current Procedural Terminology code 27447. Demographic variables available from the ACS NSQIP database include patient age, sex, height, weight, and smoking status (current smoker within 1 year). Body mass index (BMI) was calculated using patient height and weight.

For each case, a comorbidity score was calculated using a modified version of the Charlson comorbidity index (CCI)[70] that has been adapted to the ACS NSQIP database.[71] Studies have demonstrated that such modified CCIs predict similar outcomes as the original CCI.[72,73] The comorbidities used to determine the modified CCI include (followed by their CCI point values): myocardial infarction within the six months prior to surgery (1), congestive heart failure (1), peripheral vascular disease or rest pain (1), any

history of transient ischemic attack or cerebrovascular accident (1), chronic obstructive pulmonary disease (1), diabetes mellitus (1), hemiplegia (2), end stage renal disease (2), ascites or esophageal varices (3), and disseminated cancer (6). To calculate the CCI for a given case these point values are summed and an additional point is added for each age decade older than age 40. Although DM is included as a comorbid condition in the original CCI, it was removed from the modified CCI calculation for this study because DM is the comorbidity that this study investigates.

The ACS NSQIP database tracks patients for the occurrence of individual adverse events during the first 30 postoperative days. A prior study in our group asked orthopaedic surgeons at multiple institutions to weight each of these complications relative to a single patient's death. In order of severity weight relative to death[74] these adverse events are (weight): death (1), cardiac arrest requiring cardiopulmonary resuscitation (0.151), stroke or cerebrovascular accident (0.010), septic shock (0.087), myocardial infarction (0.042), acute renal failure (0.040), pulmonary embolism (0.030), sepsis (0.018), organ space infection (0.018), ventilator time greater than 48 hours (0.015), deep surgical site infection (0.015), unplanned intubation (0.014), renal insufficiency (0.009), return to the operating room (0.009), superficial surgical site infection (0.007), deep vein thrombosis (0.006), wound dehiscence (0.006), readmission to hospital (0.006), pneumonia (0.006), and urinary tract infection (0.003). In this study, pulmonary embolism and deep vein thrombosis were considered together as "thrombotic events," superficial surgical site infection, deep wound infection, and organ space infection were

considered together as a “wound-related infections,” and sepsis and septic shock were also considered together.

Postoperative length of stay (LOS) and readmission are also directly reported in the ACS NSQIP database. LOS is defined as the number of days from the operation date until discharge. Readmission is defined as any admission for any reason that occurs after discharge and within 30 days of surgery. While most postoperative variables in the ACS NSQIP database are only reported if they occur within the first 30 days, postoperative LOS is reported beyond 30 days. However, in order to limit the influence of outliers on the analysis this study considered patients with postoperative LOS longer than 30 days to have had postoperative LOS equal to 30 days. Length of stay was considered to be extended if the stay lasted longer than one standard deviation (1.8 days) longer than the mean (3.2 days) of all hospital stays in the cohort. For this reason, any LOS longer than 5 days was considered to be extended.

The occurrence of readmission within 30 days of surgery is reported in the ACS NSQIP database for cases that occurred in 2011 or later, but not for earlier cases. Hence, the analysis of readmission includes only 99,508 of 114,102 cases, but this represents 87.2% of all cases included in this study.

The ACS NSQIP database records one of three possible DM statuses for each case. Patients are either those who use daily insulin therapy to treat their diabetes (IDDM),

those who use non-insulin pharmacologic agents (NIDDM), or patients who do not have DM. Patients who do not have DM either do not have insulin resistance or hyperglycemia or are using dietary modifications alone to control hyperglycemia.

Ellman, Matthew 4/27/2016 12:36 AM

Comment [1]: Might say patients who are classified as not having DM include patients without DM or those with DM who are not using medication for DM. We don't really know whether diet /lifestyle is being used to control hyperglycemia, just that they are not on medication.

Also: was analysis done based on DM or no DM (I see this was removed from CCI) or determined among those on no DM medicines what percentage have DM listed in their history? If so, that would be useful to report.

Matthew Webb 4/27/2016 12:36 AM

Comment [2]: This is the NSQIP definition of diabetes. NSQIP data are collected by clinical reviewers who actually call patients to verify the information that is ambiguous, so yes we do actually know that they are using dietary modifications. The language that I use here is specific to the definitions provided in the NSQIP User Guide (see variable number 21). This is the only way that DM is defined in NSQIP. When we use it in the CCI (as in other studies) we group IDDM and NIDDM as "Yes, diabetes" and the rest as "No DM." See attached user guide.

Statistical analyses were performed using STATA version 13 (StataCorp LP, College Station, TX). Statistical significance was set at a 2-sided alpha level of 0.05, but because the chance of finding one or more spurious significant differences in 17 tests is 58.2% the level of significance for comparisons of adverse event rate for each of these 17 adverse events was adjusted to 0.003 according to Bonferroni's correction.[75] Likewise, instead of reporting 95% confidence intervals of these relative risks, 99.7% confidence intervals are reported in this study. Demographics were compared between patients with NIDDM, patients with IDDM, and those without DM using Pearson chi-squared tests.

Adverse event rates were compared between patients with NIDDM, IDDM, and those without DM using Poisson regression with robust error variance. These multivariate analyses were adjusted for the demographics of age (15–54, 55–64, 65–74, ≥75 years old), sex, BMI (18–24, 25–29, 30–34, and ≥ 35 kg/m^2), CCI, and smoking status in order to control for potential confounders. Poisson regression with robust error variance was used as an alternative to logistic regression so that the strengths of association could be reported as relative risks rather than odds ratios.[76,77]

RESULTS

In total, 114,102 patients who underwent TKA between the years of 2005 and 2014 were identified in the ACS NSQIP database. Of these, 15,367 patients (14%) had NIDDM, 4,881 patients (4%) had IDDM, and 93,854 patients did not have DM (82%).

Table 1 presents the differences in demographics of patients with NIDDM, patients with IDDM, and patients without DM. Patients with DM were older than patients without DM ($p < 0.001$). Patients with DM were more likely to be male ($p < 0.001$). Patients with IDDM were more likely to have a BMI greater than 35 kg/m^2. Patients with NIDDM of IDDM had a greater CCI than those without DM ($p < 0.001$). There was no difference in smoking status between patients with NIDDM, patients with IDDM, and those without DM ($p = 0.050$).

Compared to patients without DM, patients with NIDDM had an increased relative risk for 2 of 17 adverse events studied. These were myocardial infarction (MI) (relative risk [RR] = 1.67, 99.7% confidence interval [CI] = 1.01 - 2.77, $p = 0.002$) and extended LOS (RR = 1.42, CI = 1.28 - 1.57, $p < 0.001$). These results are shown in Table 2 and they are represented graphically in a forest plot in Figure 1.

Compared to patients without DM, patients with IDDM were at increased relative risk for 12 of 17 adverse events investigated. These were sepsis or septic shock (RR = 2.42, CI = 1.38 - 4.23, $p < 0.001$), MI (RR = 2.71, CI = 1.38 - 5.33, $p < 0.001$), renal failure (RR = 4.66, CI = 1.78 - 12.22, $p < 0.001$), ventilator time greater than 48 hours (RR = 2.88, CI = 1.07 - 7.74, $p = 0.001$), unplanned intubation (RR = 2.45, CI = 1.21 - 5.01, $p < 0.001$), renal insufficiency (RR = 3.03, CI = 1.48 - 6.19, $p < 0.001$), return to the operating room (RR = 1.51, CI = 1.09 - 2.09, $p < 0.001$), wound dehiscence (RR = 2.04, CI = 1.04 - 3.98, $p = 0.001$), readmission (RR = 1.65, CI = 1.35 - 2.01, $p < 0.001$), pneumonia (RR = 2.47, CI = 1.48 - 4.12, $p < 0.001$), urinary tract infection (RR = 1.53, CI = 1.05 - 2.20, $p < 0.001$), and extended length of stay (RR = 1.99, CI = 1.72 - 2.31, $p < 0.001$). These results are shown in Table 2 and they are represented graphically in a forest plot in Figure 2.

Of note, not only were many more adverse events associated with IDDM than with NIDDM, the relative risks of MI and extended LOS were greater for patients with IDDM than for patients with NIDDM (MI: RR = 2.71 versus 1.67, respectively, and extended LOS: RR = 1.99 versus 1.42).

DISCUSSION

It is generally accepted that DM is a risk factor for increased rates of complications following TKA.[4,6,7,35,39-42,46-53,55-57,69] Despite the prevalence of DM and the heterogeneity among patients with DM, many of these prior studies did not distinguish between identifiable subpopulations of patients with DM. Careful classification of patients with DM could identify groups that are at particular risk for adverse events in the perioperative period, and this information could be useful for postoperative expectations and refinement of risk stratification.

This study identified a large population that underwent TKA and found that patients who use insulin in the management of DM are at greater risk for perioperative adverse events independent of demographics and comorbid factors. The results of this study are consistent with recent research that shows that patients with IDDM are at a greater risk for medical complications when undergoing TJA,[57] but this study shows that insulin dependence is also an independent risk factor for many other adverse events including sepsis or septic shock, MI, renal failure, ventilator time greater than 48 hours, unplanned intubation, renal insufficiency, return to the operating room, wound

dehiscence, readmission, pneumonia, urinary tract infection, and extended length of stay.

This study has several limitations. In our analysis patients with IDDM, NIDDM, and without DM are defined by their use of insulin or other medications. For this reason, it is possible that some patients who actually have DM are included in the group without DM if those patients are not using any medications to control hyperglycemia. Furthermore, there is an increasing awareness that lowering average blood glucose in the 3 months prior to surgery may be important to prevent postoperative morbidity and mortality.[61] Average blood glucose is often monitored by glycated hemoglobin (HbA1c) level, but because the ACS NSQIP database does not record HbA1c level the average blood glucose level of individuals in this cohort before surgery or in the postoperative period could not be evaluated, and this is a limitation of this study. Because the multivariate analyses could not be adjusted for HbA1c level, it is not possible to determine whether insulin dependence is a risk factor independent of average blood glucose level. Likewise, studies have also shown that perioperative glycemic control is an important risk factor for adverse events,[80] but perioperative blood glucose levels are not recorded in the ACS NSQIP database either, and for this reason it is also not possible for this study to determine if insulin dependence is a risk factor independent of perioperative blood glucose levels.

It should be mentioned that the mechanism of the association between IDDM and the risk of adverse events is not known. The results of this study should not be interpreted to imply that insulin use itself is directly associated with adverse events. For example, perioperative insulin regimens should not be modified based on the results of this study. It is possible that patients with IDDM more often have advanced DM relative to patients with NIDDM, and this may account for some of the differences in the relative risks of adverse events, but advanced DM may not account for all of the differences, and this should be an area of future research.

Despite the above limitations, this study of postoperative adverse events in 114,102 patients in a prospectively-collected national database who underwent TKA is unique in its size and scope. For the first time this study shows that insulin dependence is an independent risk factor for 12 adverse events while patients with NIDDM are at increased risk for only 2 of these adverse events (MI and extended LOS) relative to patients without DM. Absolute risks of these adverse events given patient demographics and comorbidities can be found using the ACS NSQIP surgical risk calculator at (http://riskcalculator.facs.org).[59] This study controlled for those demographics and comorbidities to show that patients with IDDM had increased relative risks of many more adverse events than patients with NIDDM relative to patients without DM independent of demographics and comorbidities.

CONCLUSION

This study found that insulin dependence is an independent risk factor for adverse events after TKA. Already 1 in 5 patients who will undergo total joint arthroplasty in the US has DM. As the prevalence of DM and the frequency of TKA both increase, the population of patients who will be candidates for TKA is also likely to increase. For these reasons, orthopaedic surgeons should be aware of the utility of insulin dependence as a predictor of adverse events. Although average glucose level as measured by HbA1c and perioperative blood glucose level are well recognized risk factors for adverse events,[60] the association between insulin dependence and the risk for adverse events has not been well appreciated. This information will be useful for patient selection, preoperative risk stratification, and postoperative management.

TABLE 1. Demographics of 114,102 patients who underwent total knee arthroplasty.

	Without DM		NIDDM		IDDM		
	Number	Percentage	Number	Percentage	Number	Percentage	p-value
Overall	93,854	100.0%	15,367	100.0%	4,881	100.0%	
Age							**<0.001**
15-54	10,758	11.5%	1,133	7.4%	430	8.8%	
55-64	28,095	29.9%	4,503	29.3%	1462	30.0%	
65-74	33,143	35.3%	6,307	41.0%	2,035	41.7%	
75+	21,858	23.3%	3,424	22.3%	954	19.6%	
Sex							**<0.001**
Female	59,527	63.4%	9,210	59.9%	2,775	56.9%	
Male	34,327	36.6%	6,157	40.1%	2,106	43.2%	
BMI							**<0.001**
18-25	10,857	11.6%	752	4.9%	162	3.3%	
25-30	27,894	29.7%	3,026	19.7%	719	14.7%	
30-35	26,632	28.4%	4,462	29.0%	1303	26.7%	
> 35	28,471	30.3%	7,127	46.4%	2,697	55.3%	
CCI							**<0.001**
0-2	22,000	23.5%	2,742	17.8%	928	19.0%	
3	33,580	35.8%	5,925	38.6%	1,866	38.2%	
≥ 4	38,266	40.8%	6,700	43.6%	2,087	42.8%	
Smoker							0.050
No	85,773	91.4%	14,133	92.0%	4,454	91.3%	
Yes	8,081	8.6%	1,234	8.0%	427	8.8%	

DM - Diabetes mellitus, NIDDM - Non-insulin dependent diabetes mellitus
IDDM - Insulindependent diabetes mellitus, CCI - Charlson comorbidity index, modified
Bolding indicates statistical significance at $p < 0.05$, Underlining indicates median.

TABLE 2. Relative risks of adverse events within 30 days of TKA in patients without DM versus those with NIDDM and IDDM

	Non-DM	NIDDM				IDDM			
	Percent	Percent	RR	(CI)	p-value	Percent	RR	(CI)	p-value
Death	0.06	0.11	1.81	(0.78 - 4.22)	0.034	0.14	2.40	(0.74 - 7.75)	0.024
Cardiac arrest	0.08	0.12	1.33	(0.60 - 2.92)	0.280	0.23	2.23	(0.85 - 5.86)	0.012
Stroke/cerebrovascular accident	0.07	0.11	1.52	(0.67 - 3.44)	0.126	0.18	2.67	(0.94 - 7.62)	0.005
Sepsis/septic shock	0.27	0.35	1.22	(0.77 - 1.92)	0.197	0.72	2.42	(1.38 - 4.23)	**<0.001**
Myocardial infarction	0.18	0.31	1.67	(1.01 - 2.77)	**0.002**	0.49	2.71	(1.38 - 5.33)	**<0.001**
Renal failure	0.05	0.12	2.03	(0.85 - 4.88)	0.015	0.29	4.66	(1.78 - 12.22)	**<0.001**
Thrombotic event (PE/DVT)	1.54	1.57	0.98	(0.80 - 1.21)	0.786	1.52	0.94	(0.66 - 1.35)	0.616
Wound-related infection	0.79	0.94	1.10	(0.83 - 1.45)	0.304	1.25	1.37	(0.92 - 2.05)	0.018
On ventilator > 48 hours	0.07	0.10	1.40	(0.59 - 3.34)	0.239	0.23	2.88	(1.07 - 7.74)	**0.001**
Unplanned intubation	0.15	0.23	1.38	(0.78 - 2.44)	0.087	0.43	2.45	(1.21 - 5.01)	**<0.001**
Renal insufficiency	0.10	0.16	1.15	(0.58 - 2.28)	0.553	0.47	3.03	(1.48 - 6.19)	**<0.001**
Return to the operating room	1.15	1.32	1.10	(0.87 - 1.39)	0.220	1.88	1.51	(1.09 - 2.09)	**<0.001**
Wound dehiscence	0.19	0.18	0.81	(0.44 - 1.52)	0.321	0.47	2.04	(1.04 - 3.98)	**0.001**
Readmission	2.86	3.34	1.12	(0.97 - 1.29)	0.022	5.02	1.65	(1.35 - 2.01)	**<0.001**
Pneumonia	0.32	0.36	1.09	(0.70 - 1.71)	0.542	0.82	2.47	(1.48 - 4.12)	**<0.001**
Urinary tract infection	0.98	1.09	1.08	(0.83 - 1.39)	0.392	1.54	1.53	(1.05 - 2.20)	**<0.001**
Extended length of stay (> 5 days)	4.37	6.38	1.42	(1.28 - 1.57)	**<0.001**	9.01	1.99	(1.72 - 2.31)	**<0.001**

These multivariate analyses use Poisson regression and control for the patient characteristics presented in Table 1.
All variables were entered into the model as they are listed in Table 1. Readmission data only available for years 2011-2014.
DM - Diabetes mellitus, NIDDM - Non-insulin dependent diabetes mellitus, IDDM - Insulin dependent diabetes mellitus
Bolding and gray shading indicate statisitcal significance at $p < 0.003$, adjusted according to Bonferroni's correction.
RR - Relative risk, CI - Confidence interval, note: 99.7% confidence interval according to Bonferroni's correction.
TKA - Total knee arthroplasty

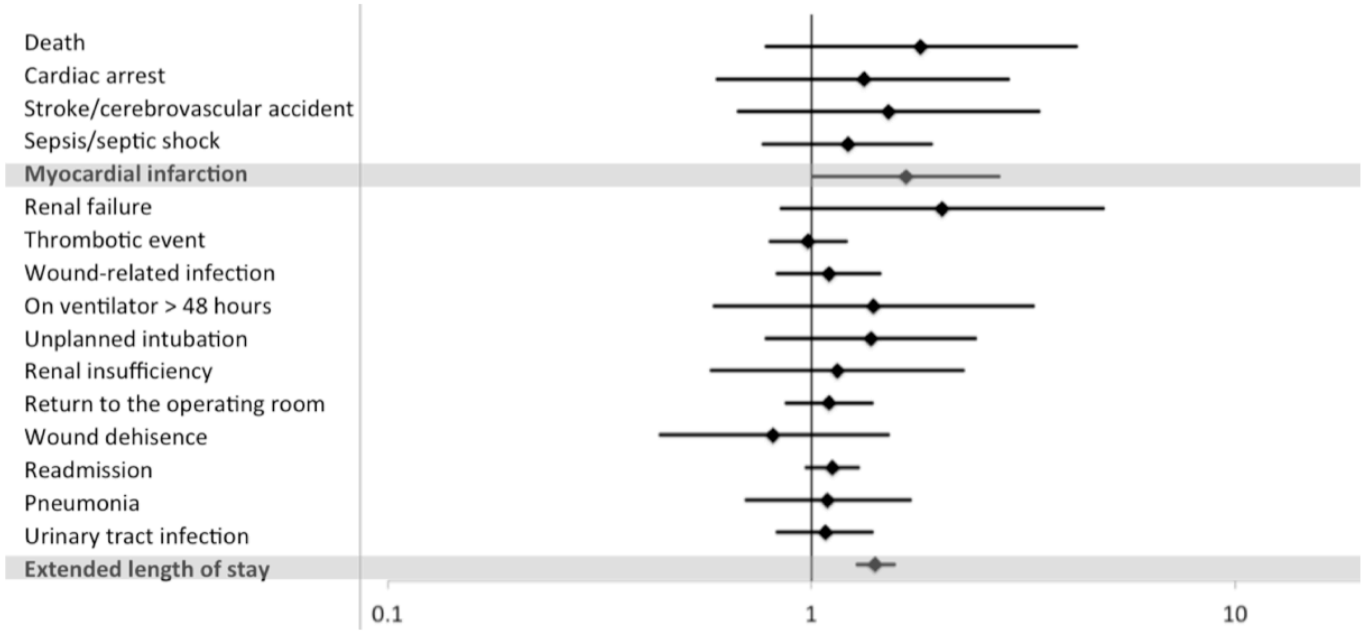

FIGURE 1. Relative risks of perioperative adverse events after total knee arthroplasty in patients with non-insulin dependent diabetes mellitus (NIDDM). Forest plot on logarithmic scale in horizontal axis. Adverse events listed at left. Diamonds central to the horizontal lines indicate relative risks. Horizontal lines denote the 99.7% confidence intervals of those relative risks, per Bonferroni's correction. The vertical line indicates a relative risk of 1. Therefore, horizontal lines that cross the vertical line indicate relative risks that are not statistically significant. **Bolding** and gray shading indicate relative risks that are statistically significant.

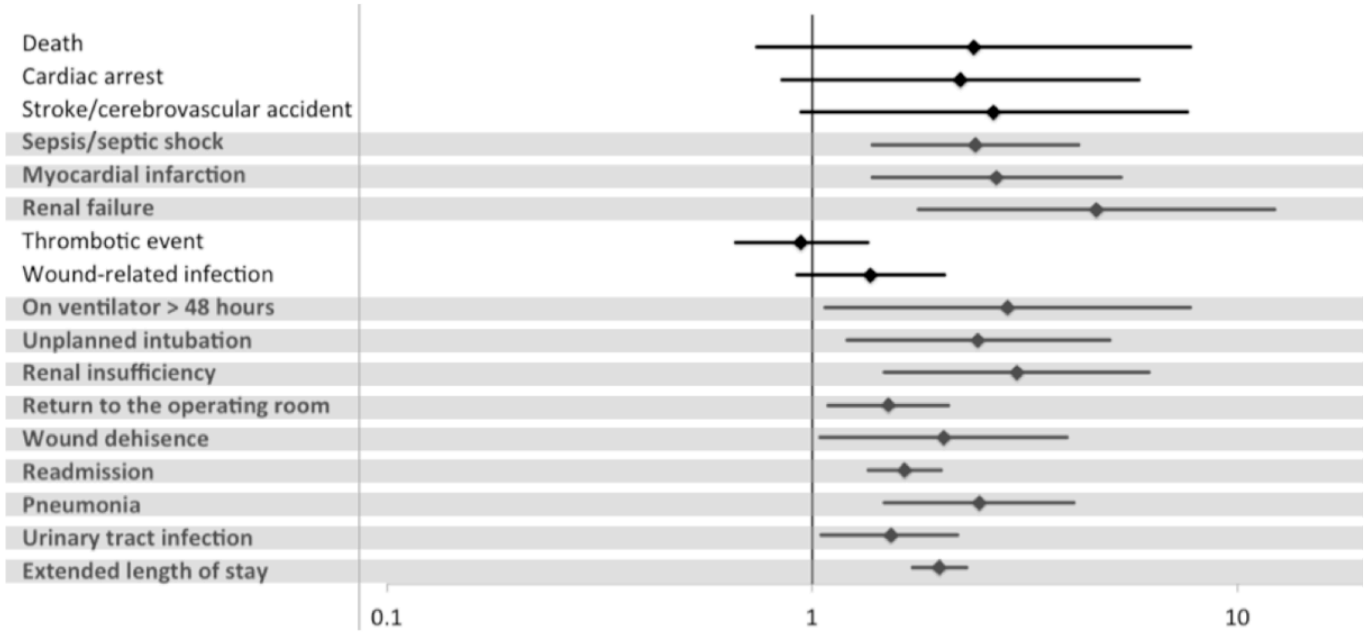

FIGURE 2. Relative risks of perioperative adverse events after total knee arthroplasty in patients with insulin dependent diabetes mellitus (IDDM). Forest plot on logarithmic scale in horizontal axis. Adverse events listed at left. Diamonds central to the horizontal lines indicate relative risks. Horizontal lines denote the 99.7% confidence intervals of those relative risks, per Bonferroni's correction. The vertical line indicates a relative risk of 1. Therefore, horizontal lines that cross the vertical line indicate relative risks that are not statistically significant. **Bolding** and gray shading indicate relative risks that are statistically significant.

CONCLUSION TO CHAPTERS

Although insulin dependence has been a known predictor of cardiac risk during major noncardiac surgery since 1999,[58] many of the positive findings reported in the chapters above have never before been reported in the orthopaedic literature. For this reason it is important to note that our negative findings are supported by similar findings in the orthopaedic literature. Of note, this study found no association between IDDM or NIDDM and thrombotic events in the THA population of 71,733 or the TKA population of 114,102. Similarly, a prior systematic search of PubMed, Cochrane, MEDLINE, and the American Academy of Orthopaedic Surgeons indexes found 18,075 cases of venous thromboembolism (VTE) among 1,723,350 patients who underwent either THA or TKA and found that although known varicose veins, comorbid congestive heart failure, and a known positive history of VTE were associated with perioperative VTE, previously diagnosed DM had no significant association with VTE after THA or TKA.[82] Another study using the TJA population in the Nationwide Inpatient Sample from 2003 to 2009 found no increased odds of VTE in patients with DM who underwent THA or TKA after controlling for coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, and cerebrovascular disease.[83] In fact, one study of 23,326 patients at Veterans Affairs hospitals who underwent TJA between 2002 and 2009 found that

patients with DM had a lesser risk of VTE than patients without DM.[84] The negative findings of this study are supported by similar negative findings in the literature, and this suggests that the positive findings of this study may be externally valid.

It is also important to note that this study is not the first to investigate the relationship between IDDM and adverse events after TJA. Briefly, DM is defined by a fasting glucose greater than or equal to 126mg/dl, or a 2 hour glucose tolerance test greater than 200mg/dl, or a random glucose greater than 200mg/dl, or a HbA1c level greater than 6.5%.[31] The pathogenesis of DM type 1 is related to autoimmune destruction of the insulin secreting beta cells of the pancreas,[32] and the pathogenesis of DM type 2 is related to acquired insulin resistance. Patients with DM type 1 are always insulin dependent while patients with DM type 2 can be managed with diet and lifestyle modifications or oral hypoglycemic agents initially, but patients with recalcitrant DM type 2 may become insulin dependent.[32,33] Although DM is in this way recognized to be a heterogeneous group of metabolic disorders, very few prior studies of adverse events after TJA distinguished between these identifiable subpopulations of patients with DM.

One prior study from the Mayo Clinic in Rochester, MN found an association between insulin use and periprosthetic joint infection in TJA patients when controlling for age and gender, but this association did not remain when also controlling for BMI and comorbidity burden.[56] A follow-up study of all morbidly obese patients (BMI $\geq$ 40 kg/m^2) who underwent primary TKA between 1995 and 2011 with a minimum of two

years of follow-up found that patients with DM type 2 had similar outcomes when compared to patients without DM, but this study also found that those patients with DM type 2 and insulin dependence had increased risks of reoperation, revision, periprosthetic joint infection, and decreased 10-year implant survivorship when compared to patients without DM.[53] These findings suggests that insulin dependence may be a stronger predictor of adverse events than DM alone. Other than periprosthetic joint infection, however, that study did not investigate the rates of the 16 other adverse events that this study investigated.

A secondary analysis of an observational study of 8,055 patients in Denmark also found that patients treated with insulin were at an increased risk for a composite measure of "diabetes-related morbidity" after TJA, but the authors of that study cautioned against drawing conclusions from that secondary analysis.[55] In that observational study, 890 patients with DM type 2 who underwent TJA were matched with 7,165 patients without DM. That study used the Danish National Database of Reimbursed Prescriptions to stratify patients with DM by treatment regimen (insulin, oral antihyperglycemic agents only, and diet only). The Danish National Health Registry was used to track adverse events including readmission and extended LOS. The study found that only the patients with DM type 2 treated with insulin were at an increased risk of postoperative morbidity. These patients were at an increased risk for the composite outcome of "diabetes-related morbidity" which was defined as any one of cardiac arrhythmia, acute congestive heart failure, myocardial infarction, periprosthetic or wound infections, renal

insufficiency, stroke or transient ischemic attack, pneumonia, sepsis, LOS greater than 4 days caused by urinary tract infection or dysregulated blood glucose, or any other infection that led to readmission.[55] In contrast to this composite outcome, our analysis investigates each of these adverse events individually.

In a similar manner, a previous study using an ACS NSQIP sample less than one quarter the size of this study found an association between IDDM and a composite of "medical complications,"[57] but that study did not isolate the THA or TKA populations and did not find an association between IDDM and any particular adverse events.

This study is not without limitations. The reliability of findings that are based on database studies is controversial. A recent study compared the patient characteristics of the populations that underwent total hip arthroplasty for hip osteoarthritis in two commonly used databases and also compared the adverse event rates that these databases reported. That study found differences between demographic characteristics and outcomes between databases and concluded that large databases can have limited reliability and should be interpreted with caution.[78] That study compared the National Hospital Discharge Survey (NHDS) database to the Nationwide Inpatient Sample (NIS) database. This study, however, uses the ACS NSQIP database. The ACS NSQIP database differs significantly from NHDS and NIS in methods of data collection and follow-up. In contrast to administrative databases that are based on reimbursement claims and have been shown to be limited,[62] inconsistent,[63] and fraught with errors,[64] ACS NSQIP data

are chart-abstracted and prospectively collected, and high-quality data is ensured by routine auditing. This is demonstrated by an agreement rate between clinical reviewers of greater than 98%.[65] Reliability and internal validity are particularly important when cohort subpopulations are defined by clinical criteria, and for these reasons studies of ACS NSQIP may more accurately reflect the real demographic characteristics of the population under study and may more accurately reflect the real rate of postoperative adverse events than studies that use the administratively-coded NHDS and NIS databases.

Although the ACS NSQIP database distinguishes between IDDM and NIDDM, the database lacks data concerning DM type. A prior study of NIS from 1988 to 2003 studied the effect of DM type on the risk of adverse events. That study identified 65,769 patients with DM who underwent TJA and compared the adverse event rates of those with DM type 1 (8,728 patients) to those with DM type 2 (57,041 patients). That study found that patients with DM type 1 were at greater risk for death, myocardial infarction, pneumonia, postoperative hemorrhage, wound infection, and urinary tract infection.[54] And patients with DM type 1 were also found to have longer LOS and greater inflation-adjusted costs of surgery.[54]

Noting that insulin is essential for the pharmacological management of DM type 1 and considering the findings of the previously discussed study from the Mayo Clinic,[53] it is certain that the effects of DM type and insulin dependence are confounding. The ACS

NSQIP database, however, does not record DM type. For that reason, although DM type is clearly related to perioperative adverse event rates, this study could not control for DM type and this study could not determine if the increased relatives risk of insulin dependence were independent of DM type.

Similarly, although ACS NSQIP does record some pre-operative lab values, it does not record preoperative HbA1c level. Whether or not HbA1c level should be considered during patient optimization for elective surgery is controversial. While some authors suggest that HbA1c levels are not reliable for predicting the risk of infection after TJA,[41] other authors suggest that perioperative glycemic control[80] or correction of elevated HbA1c over several preoperative months[61,79] could decrease perioperative complication rates, and still other authors note that the linear relationship observed between adverse event rates and HbA1c suggests that efforts to optimize preoperative HbA1c should be revised.[79,85] Regardless of the controversy, this study could not control for preoperative HbA1c level and this study could not determine if the increased relatives risk of insulin dependence were independent of HbA1c level.

These limitations suggest further areas of research and they pose questions that future investigations may answer. This study found that patients with IDDM had increased risks for many perioperative adverse events relative the patients without DM. This study also found that patients with NIDDM did not share many of these risks. These findings should be interpreted with caution. Identifying populations that are at greater

risk for particular adverse events in the perioperative period is important, and although this study has shown that simply noting insulin dependence can herald vastly different outcomes for patients, the rates of the adverse events studied are relatively low for both patients with IDDM and patients with NIDDM. This information will be useful for patient counseling and expectations, preoperative risk stratification, and postoperative management. Identifying particular adverse events will encourage the implementation of appropriate preventative and monitoring measures for at-risk patients, and substantiating these greater risks and costs of providing care to particular subpopulations will contribute to efforts to ameliorate potential disparities in the provision of TJA.

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