Elevated Postoperative Blood Glucose and Preoperative Hemoglobin A1C Are Associated with Increased Wound Complications Following Total Joint Arthroplasty

Louis S. Stryker, MD, Matthew P. Abdel, MD, Mark E. Morrey, MD, Melissa M. Morrow, PhD, Daryl J. Kor, MD, and Bernard F. Morrey, MD

Investigation performed at the Department of Orthopedic Surgery, Mayo Clinic, Rochester, Minnesota

Background: Diabetes is an established risk factor for complications following total joint arthroplasty. However, the correlation between postoperative blood glucose and preoperative hemoglobin A1C levels with complications following total joint arthroplasty is not well described.

Methods: All patients undergoing elective primary total joint arthroplasty at our institution from 2004 through 2011 with both postoperative blood glucose and preoperative hemoglobin A1C levels were identified in a retrospective review. From among 1702 patients, those with wound complications within thirty days after the index arthroplasty were identified. A control group matched for exact age, sex, procedure, tourniquet use, surgical approach, and use of antibiotic cement was also created. Thirty patients met the study group inclusion criteria. The mean patient age was seventy-two years (range, fifty-three to eighty-nine years); the majority (53%) of patients were female.

Results: The odds ratio for developing a wound complication was 3.75 (95% confidence interval, 1.25 to 11.22; p = 0.02) in patients with a mean postoperative glucose of >200 mg/dL, 3.0 (95% confidence interval, 0.97 to 9.30; p = 0.08) in patients with a maximum postoperative blood glucose of >260 mg/dL, and 9.0 (95% confidence interval, 1.14 to 71.20; p = 0.03) in patients with a preoperative hemoglobin A1C value of >6.7%.

Conclusions: Patients with a mean postoperative blood glucose of >200 mg/dL or a preoperative hemoglobin A1C level of >6.7% are at increased risk for wound complications following elective primary total joint arthroplasty. These results show that poor preoperative and postoperative glucose control is independently associated with wound complications.

Level of Evidence: Prognostic Level III. See Instructions for Authors for a complete description of levels of evidence.

Epidemiologic projections indicate an increasing demand for total joint arthroplasty in both the lower and upper extremities1,2. Furthermore, there has been a concomitant increase in the incidence and prevalence of diabetes mellitus among the general population and in patients undergoing total joint arthroplasty3. An estimated 26.9% of the population at the age of sixty-five years and older in the United States carry the diagnosis of diabetes4. In addition to its numerous associated medical complications, diabetes is an independent risk factor for complications following total joint arthroplasty5-15.

Blood glucose levels are the standard in establishing the diagnosis of diabetes. The current diagnostic blood glucose levels from the American Diabetes Association are a fasting plasma glucose level of ≥ 126 mg/dL or a two-hour, post-challenge blood glucose level of ≥ 200 mg/dL16. The role of hemoglobin A1C, a serologic marker for average glucose over a two to three-month period, has expanded in the diagnosis and treatment of diabetes.

Disclosure: None of the authors received payments or services, either directly or indirectly (i.e., via his or her institution), from a third party in support of any aspect of this work. One or more of the authors, or his or her institution, has had a financial relationship, in the thirty-six months prior to submission of this work, with an entity in the biomedical arena that could be perceived to influence or have the potential to influence what is written in this work. No author has had any other relationships, or has engaged in any other activities, that could be perceived to influence or have the potential to influence what is written in this work. The complete Disclosures of Potential Conflicts of Interest submitted by authors are always provided with the online version of the article.
The current recommendation for a diagnosis of diabetes is a hemoglobin A1C level of \( \geq 6.5\% \). In addition to the enhanced risk of complications associated with the diagnosis of diabetes mellitus, multiple studies have linked hyperglycemia with increased rates of adverse outcomes in a variety of conditions, often irrespective of a diagnosis of diabetes mellitus. Similarly, elevated hemoglobin A1C has also been shown to be a risk factor in other non-orthopaedic surgical patients.

Although the link between adverse outcomes and the diagnosis of diabetes in patients undergoing total joint arthroplasty has been established, the association between postoperative blood glucose and preoperative hemoglobin A1C levels and wound complications has not been thoroughly studied. This study aimed to elucidate the relationships between postoperative blood glucose levels (both mean and maximum) and preoperative hemoglobin A1C levels with thirty-day wound complications in patients who had undergone elective primary total joint arthroplasty.

**Materials and Methods**

**Patient Selection**

A multidisciplinary retrospective review of our institution’s total joint registry identified 1702 patients undergoing elective primary total hip, total knee, or total shoulder arthroplasty who had hemoglobin A1C levels drawn within three months before surgery. The study interval of January 1, 2004, through April 20, 2011, was chosen because the methodology for testing glycosylated hemoglobin changed at our institution on January 1, 2004. Institutional review board approval was obtained prior to study initiation.

Of the 1702 patients, 237 had a complication within thirty days after surgery. Patients were then stratified on the basis of complication type, with the inclusion of patients with complications most associated with diabetes mellitus or poor glycemic control. This group included seventy-two patients with complications not commonly associated with diabetes mellitus or glycemic control. Patients with complications not commonly associated with diabetes mellitus or glycemic control were excluded from the analysis. This group included 165 patients with complications of fracture, ligament injury, vascular injury, limited joint motion, soft-tissue contracture, instability, nerve palsy, pulmonary embolism, deep-vein thrombosis, and component failure. Medical charts were then reviewed and in-hospital glucose levels were recorded. Patients without at least two consecutive days of in-hospital postoperative glucose levels were excluded, leaving forty-one patients (Fig. 1).

A 1:1 matched control group was then created from the 1465 patients who did not have complications within thirty days after surgery and also had at least two consecutive days of in-hospital postoperative glucose levels. The control group was matched for exact age, sex, procedure, surgical approach, tourniquet use, and use of bone cement, as well as whether antibiotics were placed in the cement.

Eleven patients from the study group were subsequently excluded from analysis as a suitable control group match based on the above criteria was not available. This exclusion left thirty patients in the study group for analysis with their matched controls.

The total joint database employed for this study includes all patients who have undergone a total joint arthroplasty at our institution since 1969. The database includes patient demographic characteristics, date of last evaluation, implant used, whether the implant was removed, reoperations, and complications. Patients are scheduled for regular clinic evaluations at one, two, and five years following arthroplasty and every five years thereafter. If patients are unable to attend their clinic visits, our total joint database staff routinely sends a comprehensive questionnaire to them and radiographs are requested.

Within the study group, there were sixteen women (53%) and fourteen men (47%). There were twenty-two total knee arthroplasties (73%), seven total hip arthroplasties (23%), and one total shoulder arthroplasty (3%). The average patient age at time of surgery was seventy-two years (range, fifty-three to eighty-nine years). All total knee arthroplasties included the use of tourniquets during the procedure. Of the patients undergoing total hip arthroplasties, five underwent procedures with anterolateral approaches and two underwent procedures with posterior approaches. Antibiotic-impregnated bone cement was used in nine patients (30%), cement without antibiotics in fifteen patients (50%), and no cement in six patients (20%). The six patients in whom no cement was used all underwent cementless total hip arthroplasties (see Appendix).

Twenty-eight patients (93%) in the case study group and twenty-nine patients (97%) in the control group had been diagnosed with diabetes at the time of surgery.
time of surgery. One patient from each group (3%) was diagnosed with impaired fasting glucose or glucose intolerance. One patient from the case group (3%) did not have the diagnosis of diabetes at the time of surgery. Additionally, five patients in the case group (17%) and four patients in the control group (13%) had been diagnosed with chronic renal insufficiency at the time of the arthroplasty. Two patients (7%) from each group had been diagnosed with congestive heart failure prior to surgery and one patient in the case group (3%) had been diagnosed with cirrhosis. None of the patients in either group had been diagnosed with an inflammatory arthropathy at the time of the surgery.

The overall operative time (and standard deviation) was 129 ± 39 minutes for the study group compared with 120 ± 45 minutes for the control group (p = 0.42). The mean body mass index (BMI) (and standard deviation) was 37.2 ± 8.5 kg/m² for the study group compared with 34.9 ± 8.3 kg/m² for the control group (p = 0.19) (Table I).

Variables of Interest
Both groups of patients underwent chart review for the confirmation of thirty-day complications, postoperative blood glucose levels (both mean and maximum), and preoperative hemoglobin A1C values. Baseline characteristics of age, sex, procedure, surgical approach, tourniquet use, and use of antibiotic-impregnated bone cement were also included.

Statistical Methods
Dichotomous variables are presented as counts with percentages. Continuous data variables underwent testing for normality with use of the Shapiro-Wilk test using an alpha threshold of 5%. Normally distributed continuous data variables are reported as the mean and the standard deviation. Non-normally distributed continuous data variables are reported as the median and the interquartile range (IQR) (25th to 75th percentiles). For the univariate analyses of categorical variables, taking into account the matched study design, comparisons between the two groups were tested with use of the McNemar test. In a McNemar test (2 × 2 Bowker test), the odds ratio is calculated from discordant pairs. Similarly, paired t tests were utilized for comparisons of the matched continuous variables. A significant difference was defined as p < 0.05.

Results
Complications in the thirty patients constituting the study population occurred at an average of fourteen days (range, one to twenty-nine days) after the index arthroplasty. Specific complications included delayed healing or drainage in eleven patients (37%), contained hematoma in nine patients (30%), draining hematoma in three patients (10%), superficial infection in three patients (10%), superficial necrosis or skin slough in three patients (10%), and dehiscence in one patient (3%) (see Appendix). No deep infections were identified within thirty days after the index arthroplasty in the study group. No complications occurred in the matched group within thirty days after the index arthroplasty.

In examining markers for glycemic control, there were some significant differences between the study group and the matched control group. The mean postoperative mean glucose level (and standard deviation) was 217 ± 42 mg/dL (range, 134 to 292 mg/dL) in the study group compared with 185 ± 33 mg/dL (range, 116 to 236 mg/dL) (p < 0.01) in the control group (Fig. 2). The median maximum postoperative glucose level was 272 mg/dL (25th to 75th percentile IQR, 225 to 336 mg/dL) in the study group compared with 230 mg/dL (25th to 75th percentile IQR, 199 to 273 mg/dL) in the control group.

The values for the maximum postoperative glucose level in the control group were determined to be a non-normal distribution. As such, median values with 25th to 75th percentile IQR are reported for both the control group and the study group.

Source of Funding
No external sources of funding were received for this study.

The Journal of Bone & Joint Surgery - jbjs.org
Volume 95-A • Number 9 • May 1, 2013
Elevated glucose and hemoglobin A1C associated with wound complications following arthroplasty

Fig. 3
Box plot of the maximum glucose levels. The margins of the box represent the 25th to 75th percentile. The horizontal line represents the median sample value. Lines extending from the box represent the outermost data points that fall within 1.5*IQR of the 1st and 3rd quartiles or, if no data points reach the computed range, represent the upper and lower data point values, excluding outliers. The outlier appears in the control group.

Fig. 4
Box plot of the hemoglobin A1C levels. The margins of the box represent the 25th to 75th percentile. The horizontal line represents the median sample value. Lines extending from the box represent the outermost data points that fall within 1.5*IQR of the 1st and 3rd quartiles or, if no data points reach the computed range, represent the upper and lower data point values, excluding outliers. The outlier appears in the control group.
study group compared with 227 mg/dL (25th to 75th percentile IQR, 184 to 268 mg/dL) in the control group (p = 0.02) (Fig. 3). The mean preoperative hemoglobin A1C level (and standard deviation) was 6.8% ± 0.8% (range, 5.2% to 7.9%) in the study group compared with 6.4% ± 0.8% (range, 5.0% to 8.6%) in the matched control group (p = 0.11) (Table I) (Fig. 4).

Some further significant differences were identified when calculating odds ratios for thirty-day wound complications in association with these laboratory values (Table II). The odds ratio for the increased risk of wound complication following primary total joint arthroplasty was 3.75 (95% confidence interval [95% CI], 1.25 to 11.22; p = 0.02) for a mean postoperative blood glucose level with a threshold of 200 mg/dL, 3.0 (95% CI, 0.97 to 9.30; p = 0.08) for a maximum postoperative blood glucose level with a threshold of 260 mg/dL, and 9.0 (95% CI, 1.14 to 71.20; p = 0.03) for a preoperative hemoglobin A1C level of >6.7% (see Table II and Appendix).

**Discussion**

A clear relationship between the diagnosis of diabetes mellitus and adverse outcomes has been established for a multitude of orthopaedic procedures. Diabetic patients undergoing total joint arthroplasty, spine surgery, and operative treatment of ankle fractures have higher rates of perioperative complications, including mortality, infection, transfusion, pneumonia, non-routine discharge, increased length of stay, and total hospital charges. Few studies in the orthopaedic literature have attempted to delineate the association between perioperative glycemic control and postoperative complication rates, as opposed to the diagnosis of diabetes mellitus alone. In an analysis of patients undergoing total joint arthroplasty recorded in the Nationwide Inpatient Sample, Marchant et al. showed that patients who had undergone arthroplasty and were diagnosed with uncontrolled diabetes mellitus had an increased risk of stroke, urinary tract infection, ileus, postoperative hemorrhage, transfusion, infection, and death when compared with patients with controlled diabetes. Not surprisingly, there was also an associated increased length of stay and postoperative charges in the patients with uncontrolled diabetes.

The current study establishes an association between perioperative hyperglycemia and thirty-day wound complications in patients undergoing primary total joint arthroplasty. A mean postoperative blood glucose of >200 mg/dL was a significant risk factor for postoperative wound complications. Likewise, a strong statistical correlation between preoperative hemoglobin A1C levels of >6.7% and thirty-day complications was also noted.
Of note, a hemoglobin A1C level of 6.7% was selected as this level was the upper 95% CI value for the control group mean. Therefore, it may be assumed that patients with hemoglobin A1C levels beyond 6.7% are outside of normal ranges in relation to complication risk. An additional analysis of odds ratios was performed with use of hemoglobin A1C values as cutoffs; a cutoff of 6.5% had an odds ratio of 9 (p = 0.03) and a cutoff of 7.0% had an odds ratio of 5 (p = 0.04). Furthermore, although a significant difference between the case and control group-level means and range for hemoglobin A1C values was not shown, a significant association was shown for a hemoglobin A1C value of >6.7%. These results reflect the individual matching of cases and controls implemented in this study. When considered as a group, rather than individual matching, the identified differences are diluted as expected.

This study had several limitations. First, this study did not show reduction of risk with improved glycemic control, although significant perioperative hyperglycemia thresholds for increased wound complications were identified. Second, the study group comprised a small sample size, which made the calculations of the odd ratios sensitive to small changes in the ratio. The effect of the small sample size was reflected in the wide confidence intervals. Results from this study should be interpreted with caution and are meant to provide preliminary evidence. A larger sample size is needed to better delineate thresholds for increased complication risks. Furthermore, although there was not a substantial discordance between the groups with regard to comorbidities, this factor was not controlled for as part of our analysis. Additionally, our study correlates these laboratory values across total knee, total hip, and total shoulder arthroplasties, which may not be entirely applicable to these procedures independently. Moreover, the case control nature of this study design must be analyzed by calculating an odds ratio rather than a risk ratio. Finally, the thirty-day complication outcome end point may not reflect more long-term complications, such as deep infection, although an association between early postoperative complications and increased deep infection rates has been previously described.

It is important to note that the widespread clinical application of hemoglobin A1C has inherent limitations. Foremost, hemoglobin A1C testing lacked standardization early in its use, making broad interpretation of early studies difficult. In addition, hemoglobin A1C may be inaccurate in patients with certain forms of anemia and hemoglobinopathies due to abnormal red blood cell turnover. In these cases, blood glucose levels must be relied upon. There have also been divergent findings regarding the utility of hemoglobin A1C as a marker for increased complications in patients undergoing penile prostheses surgery. Therefore, in spite of this study’s findings, hyperglycemia may currently be a better marker for complications than hemoglobin A1C. The correlation between preoperative and perioperative hyperglycemia and adverse outcomes logically leads to a search for a protocol to help guide therapy. First, timing of glucose monitoring and control is likely most important within the first two postoperative days. Second, screening postoperative blood glucose levels is important as patients who are newly diagnosed with diabetes have increased adverse outcomes as compared with patients with known diabetes.

Specific goals for perioperative blood glucose levels have not yet been clearly defined. Previously recommended target blood glucose levels have ranged from <110 mg/dL to <180 mg/dL for patients in the intensive care unit and preprandial blood glucose levels of ≤140 mg/dL or random glucose levels of ≤180 mg/dL for inpatients. In a review, Furnary reported that the infection point for increased mortality is likely <150 mg/dL and for surgical site infection it is likely <180 mg/dL. In any case, glucose levels should be maintained as close to normal as safety permits because even mild elevations (≥135 mg/dL) may have clinical importance, particularly for infection in the postoperative patient.

Similarly, the appropriate target for preoperative hemoglobin A1C for patients undergoing elective surgery has yet to be determined. With regard to the current goal of hemoglobin A1C levels, the American Association of Clinical Endocrinologists Diabetic Guidelines recommends <6.5% and the American Diabetes Association recommends <7%. These goals are consistent with the findings of this study as well as those of Jämsen et al., Corpus et al., and Cao et al.

As the demand for total joint arthroplasty increases, the importance of preoperative medical optimization and close perioperative glycemic control are imperative in the prevention of complications and optimization of long-term outcomes. The current study shows significantly increased odds ratios for thirty-day wound complications associated with a mean postoperative blood glucose of >200 mg/dL and a preoperative hemoglobin A1C level of >6.7%.

**Appendix**

Tables showing the demographic characteristics of the study group and the control group, the complications of the study group, and matched pair 2×2 tables for mean blood glucose, maximum blood glucose, and hemoglobin A1C are available with the online version of this article as a data supplement at jbjs.org.

**Note:** The authors would like to acknowledge Kenton R. Kaufman, PhD, for his assistance in this project.

Louis S. Stryker, MD
Matthew P. Abdel, MD
Mark E. Morrey, MD
Melissa M. Morrow, PhD
Daryl J. Kor, MD
Bernard F. Morrey, MD
E-mail address for B.F. Morrey: morrey.bernard@mayo.edu
<table>
<thead>
<tr>
<th>Page Number</th>
<th>Reference</th>
</tr>
</thead>
</table>