**Objectives:** To investigate the proportion of insulin-dependent diabetes mellitus (IDDM) patients among diabetic patients undergoing total joint arthroplasty (TJA) and whether insulin dependence is associated with postoperative complications.

**Methods:** A systematic literature search was performed in EMBASE, PubMed, Ovid, Medline, the Cochrane Library, Web of Science, the China Science and Technology Journal Database, and China National Knowledge Infrastructure from the inception dates to 10 September 2019. Observational studies reporting adverse events with IDDM following TJA were included. Primary outcomes were cardiovascular complications, pulmonary complications, kidney complications, wound complications, infection, and other complications within 30 days of surgery. Secondary outcomes were the proportion of IDDM patients among diabetic patients undergoing TJA and its time trend.

**Results:** A total of 19 studies involving 85,689 participants were included. Among patients undergoing TJA, 26% of diabetic patients had IDDM. Compared with non-insulin-dependent diabetes (NIDDM), the incidences of cardiac arrest (risk ratio [RR], 2.346; 95% confidence interval [CI], 1.553 to 3.546), renal failure (relative risk [RR], 2.758; 95% CI, 1.830 to 4.156), deep incisional surgical site infection (RR, 1.968; 95% CI, 1.107 to 3.533), wound dehiscence (RR, 2.209; 95% CI, 1.830 to 4.156), and death (RR, 2.292; 95% CI, 1.568 to 3.349) were all significantly increased in IDDM. A significant time trend was witnessed for the prevalence of IDDM (P = 0.014). There was no statistical significance for organ/space surgical site infection, thrombotic events (deep venous thrombosis/ pulmonary embolism), and revision rates.

**Conclusion:** Insulin-dependent diabetes is an independent high-risk factor for increased adverse outcomes relative to NIDDM, suggesting that hierarchical and optimal blood glucose management may contribute to reducing the adverse complications after surgery for these patients. In addition, because the risk of sepsis, deep wound infection, organ/ space surgical site infection, urinary tract infection, renal insufficiency, and renal failure significantly increase after TJA in IDDM patients, more active postoperative antimicrobial prophylaxis may be needed on the premise of protecting renal function.

**Key words:** Complications; Diabetes Mellitus; Insulin; Prevalence; Total joint arthroplasty

**Address for correspondence** Bin Shen, Department of Orthopaedics, Orthopedic Research Institute, West China hospital, Sichuan University, Chengdu, Sichuan Province, China 610041 Tel: +86-13881878767; Fax: +86-028-85423438; Email: shenbin_1971@163.com

**Grant Sources:** This study was supported through grants from the National Natural Science Foundation of China (81802210 and 81672219), the Key Project of Sichuan Science and Technology Department (2018SZ0223 and 2018SZ0250), and the National Clinical Research Center for Geriatrics, West China Hospital. Sichuan University (Z20191008 and Z2018B20).

**Disclosure:** All authors declare that they have no conflict of interest with other people or organizations that could inappropriately influence this work.

Received 23 May 2020; accepted 14 January 2021
Introduction

Total joint replacement (TJA) is a common and effective method to relieve the pain from osteoarthritis (OA). Globally, the rate of TJA is projected to increase accordingly with the rising prevalence of OA. Meanwhile, diabetes mellitus (DM) is a pressing public health issue, and its prevalence is expected to increase by 69% and 20%, respectively, in developing and developed countries between 2010 and 2030. There is evidence from clinical and animal models to suggest an underlyingly independent link between DM and severity of OA. Therefore, the number of TJA procedures is likely to increase in diabetic patients. Furthermore, an association between DM and adverse events, hospital readmission, and increased death rates has been witnessed in lower extremity arthroplasty and shoulder arthroplasty.

However, these aforementioned studies generally classify patients as DM and non-DM patients, without further considering whether they are relying on insulin to achieve glycemic control. Studies have found that patients dependent on insulin have a higher risk of perioperative adverse events, especially cardiac complications after elective non-cardiac surgery. Although this concept of stratification has recently been reported in TJA patients, the relationship between insulin dependence and risk of adverse events has not been well recognized. This information will help in managing patients’ expectations, in preoperative risk stratification, in implementing appropriate prevention, and with monitoring measures.

This meta-analysis aims to answer the following questions. First, what is the current proportion of insulin-dependent DM (IDDM) in diabetic patients undergoing TJA? Second, has there been an increase in the proportion of IDDM in TJA over the past decade? Finally, is IDDM associated with an increased risk of adverse events after TJA?

Method

This meta-analysis was performed in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and the PRISMA Checklist guidelines (Appendix 2).

Search Strategy

The electronic databases of EMBASE, PubMed, Ovid, Medline, the Cochrane Library, Web of Science, China Science and Technology Journal Database, and China National Knowledge Infrastructure were searched from the inception dates to 10 September 2019. The search terms were as follows: (Human Isophane Insulin OR Protaphane OR Protaph OR Insulin OR Humulin OR Novolin OR Insulare) AND (arthroplasty OR knee replacement OR shoulder replacement OR hip replacement). We also identify other possible original studies by searching the Google search engine.

Inclusion Criteria

Studies were included based on the following criteria: (i) cohort or case-control studies focused on the influence of IDDM on the postoperative complication rate of total joint arthroplasty (TJA); (ii) sufficient sample size in each study; (iii) availability of reported outcomes, including proportion of IDDM patients, cardiac arrest, stroke, sepsis, myocardial infarction, extended length of stay (>5 days), on ventilator >48 h, renal failure, superficial incisional surgical site infection (SSI), deep incisional SSI, organ/space SSI, thrombotic event (vein thrombosis embolism/pulmonary embolism), reoperation, readmission, wound dehiscence, urinary tract infection, renal insufficiency, revision, unplanned intubation, pneumonia, and death. The exclusion criteria were: (i) studies that used treatments involving glucose control or combining other drugs; (ii) studies enrolling patients undergoing unicompartmental joint replacement or acute joint arthroplasty due to fracture; and (iii) review articles, expert opinions, and trials that do not consider complications.

Quality Assessment

Two authors (WLM and LMY) independently assessed the methodological quality of observational studies based on the nine-star system of the Newcastle–Ottawa scale (NOS). The NOS evaluates study population representativeness, comparability of IDDM and non-insulin dependent DM (NIDDM), assessment of outcomes, follow-up length, and adequacy of follow up (Table 1).

The evidence quality of outcomes was systematically assessed by the two reviewers (WLM and YP) based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (https://gdt.gradepro.org/app/) (Appendix 1). Although the GRADE approach considers the results of observational studies as evidence of low quality, there are a series of criteria to improve the assessment of quality levels, including a substantial effect (risk increased or decreased at least twofold), a dose-response gradient, no confounding factors, and no bias. The evidence quality of each outcome is shown in Table 4.

Definition of Outcomes

The primary outcomes were cardiovascular complications, pulmonary complications, kidney complications, wound complications, infection, and other complications within 30 days of surgery (unless specifically mentioned).
Understanding these outcomes can help in managing postoperative care and monitoring, improving the quality and safety of TJA. Secondary outcomes were the proportion of IDDM patients among diabetic patients undergoing TJA and its time trend.

Cardiovascular Complications
Cardiac arrest (requiring external or open cardiopulmonary resuscitation), stroke (resulting in residual neurologic deficit), and myocardial infarction (defined on the presence of the ICD-9-CM code 410.xx) were considered cardiovascular complications.

Pulmonary Complications
On ventilator >48 h, unplanned intubation, and pneumonia (hospitalized or radiologically confirmed) were considered pulmonary complications.

Kidney Complications
Renal insufficiency (an increase in serum creatinine level ≥0.3 mg/dL within 48 h) and renal failure (deterioration in renal function sufficient to require dialysis) were considered kidney complications.

Wound Complications
Wound dehiscence, superficial incisional SSI (infections with purulent drainage that occurred at the incision sites), and deep incisional SSI (clinically diagnosed infections below the fascia or joint capsule with persistent wound discharge or joint pain) were considered wound complications.

Infection
Urinary tract infections (an infection in the kidneys, ureters, bladder, or urethra), organ/space SS (infection involves organs or spaces), and sepsis (severe infection resulting in multiple organ affection) were considered postoperative infections.

Other Complications
Extended length of stay (>5 days), reoperation (unplanned return to the operating room or procedure requiring a second anesthetic event), thrombotic events (VTE and PE within 90 days), readmission (≥1 night in hospital and potentially surgically related), prosthetics revision (removal or replacement of at least one prosthetic component), and death were considered other complications.

Data Analysis
The relative risk (RR) and 95% confidence interval (CI) were calculated in Stata/SE (15.1 for Mac 64-bit Intel) for discontinuous data; \( P < 0.05 \) was considered statistical significance. The \( F \) statistic was used for calculating the heterogeneity of eligible studies and its results were interpreted as follows: 25%, low heterogeneity; 50%, moderate heterogeneity; and 75%, high heterogeneity. To address heterogeneity and publication bias, multiple sensitivity analyses, including outlier removal, subgroup analysis according to type of surgery and areas, Duval and Tweedie's trim, and fill methods, were...
performed. If $I^2$ still existed (>50%), we used the random-effect model. Egger and Harbord's test based on outcomes was used to assess publication bias for continuous and discontinuous data, respectively.

Moment mixed-effect meta-regression was applied to assess time trends, and due to the varied duration of study enrollment, the beginning, middle, and end year of patient enrollment were used for regression.

Results

Search Results

There were 1772 initial studies obtained after systematic searching. A total of 949 duplicates and 780 articles were excluded by screening abstracts. We ended up with 43 eligible studies: 19 met the inclusion criteria, 10 studies were not on TJA, 8 studies did not contain available data, 4 articles did not contain a control group, and 2 studies were non-clinical trials and were excluded. The flow chart in Fig. 1 shows the selection process of eligible studies.

Study Characteristics

The included 19 studies were published between June 1993 and July 2019, involving 85,689 patients undergoing TJA. The included articles’ demographics are listed in Table 1. The specific complications developed are further listed in Tables 2 and 3. All but 14 studies were conducted in the United States. 10–14, 17–22, 25, 28–30; 2 were from Denmark, 16, 23, and the remaining 3 articles were from France, 27, Finland, 26, and Korea, respectively. The mean age of patients among the groups ranged from 63 to 70.1 years. In this meta-analysis, 3 articles included participants undergoing total shoulder arthroplasty (TSA), 10, 15, 21, 6 included total knee arthroplasty (TKA), 15, 20, 24, 27–29, 2 included revision total knee arthroplasty (rTKA), 14, 15, 1 included total hip arthroplasty (THA), 16, and the rest of the studies included both TKA and THA, 16, 18, 19, 22, 23, 25, 26. The mean NOS score was 6.18 (maximum 9), suggesting that this meta-analysis included high-quality studies.

Proportion

All 19 studies that were included reported the specific numbers of NIDDM and IDDM patients. Two articles 27, 29 were excluded because there were too few participants and there was high heterogeneity in the sensitivity analysis. Two studies reported the proportion of IDDM patients in among TSA patients10, 13, 21, whereas 2 articles reported the proportion of IDDM patients among revision knee arthroplasty patients14, 15, 4 reported the proportion of IDDM patients among THA patients16, 17, 26, 30, 6 studies reported the proportion of IDDM patients among TKA patients16, 18, 20, 24, 26, 28 and 1 study separately reported the proportion of IDDM patients among THA and TKA patients16. In addition, 4 studies separately reported the proportion of IDDM patients among THA and TKA patients16, 22, 23, 25. The pooled analysis showed that the proportion of IDDM patients in total joint replacement group accounted for 26% (95% CI, 24% to 28%) of DM patients (Egger’s test, $P = 0.518$) (Fig. 2). Because of the high heterogeneity of TKA, THA, and TKA and THA groups, we conducted the subgroup analysis according to the research areas. The results showed that the proportion of IDDM patients in the Denmark group was obviously lower than that in the United States (Fig. 3), which potentially explains the high heterogeneity.

Time Trend in the Proportion of Patients with Insulin Dependence

Significant time trends in the proportion of patients with insulin dependence were not observed in the first and middle enrollment year for studies published after 2000 in the meta-regression ($P = 0.509$ and 0.149, respectively). However, the meta-regression showed a significant trend in the end enrollment year for studies published after 2000, with an outlier removed ($P = 0.014$) (Fig. 4).

Postoperative Complications

The results of the meta-analyses are listed in Table 4.

Cardiovascular Complications

The occurrence of cardiac arrest was reported in 5 studies including 61,817 patients; no heterogeneity was found among these studies ($I^2 = 0$), and cardiac arrest occurred more often in IDDM patients with an RR of 2.346 (95% CI 1.553 to 3.546). Stroke after TJA was documented in 6 studies, including 62,803 patients with $I^2 = 0$. Stroke occurred more often in IDDM patients with an RR of 2.182 (95% CI 1.432 to 3.325). A total of 7 studies examined the risk of myocardial infarction. After pooled analysis, the result showed that an increased risk of myocardial infarction was associated with IDDM (RR, 1.874; 95% CI 1.461 to 2.402; $I^2 = 0$).

Pulmonary Complications

Four studies were able to be pooled for the occurrence of being on a ventilator >48 h with no heterogeneity ($I^2 = 0$), and the results indicated an almost threefold greater rate in IDDM patients (RR, 2.868; 95% CI, 1.829 to 4.496). Although there were 4 and 5 articles reporting on the occurrence of unplanned intubation and pneumonia, respectively, they could not be pooled in the fixed-effect model because of high heterogeneity ($I^2 = 58%$ and 65%, respectively). Outlier removal was performed in these indicators; however, the heterogeneity remained at a high level ($I^2 > 50$%). In an effort to elucidate the unexplainable high heterogeneity, a predefined subgroup analysis according to type of TJA was performed on unplanned intubation and pneumonia (Table 5), and the association was found to be significant in both subgroups: TKA (RR, 1.885; 95% CI, 1.099 to 3.235) and TKA and THA (RR, 2.279; 95% CI, 1.519 to 3.421), respectively) and rTKA (RR, 2.833; 95% CI, 1.081 to 7.424) and TKA (RR, 3.284; 95% CI, 1.866 to 5.781), respectively). Duval and Tweedie’s trim and fill methods were used to test the stability of the model and there was significant increased
risk of pneumonia (RR, 1.759; 95% CI, 1.074 to 2.879; \( P = 0.025 \)). No significant increased risk was witnessed with unplanned intubation (RR, 1.312; 95% CI, 0.837 to 2.058, \( P = 0.237 \)). After pooling the results in the random-effect model, the meta-analysis both showed increased risks of unplanned intubation (RR, 1.043; 95% CI, 0.715 to 1.521) and pneumonia (RR, 1.759; 95% CI, 1.073 to 2.882) in IDDM patients.

**Kidney Complications**

Adverse events that occurred in kidneys were separately reported as renal failure and renal insufficiency in 5 studies with \( I^2 \) of 0% and 52.5%, respectively. After pooling the results in the fixed and random-effect model, respectively, the results both indicated a twofold greater rate of adverse events in IDDM patients ([RR, 2.758; 95% CI, 1.830 to 4.156] and [RR, 1.976; 95% CI, 1.142 to 3.418] respectively). Due to high heterogeneity, the predefined subgroup analysis (stratified by the type of TJA) was performed for renal insufficiency (Table 5), and the association was significant in two subgroups: TKA and TKA/THA ([RR, 2.888; 95% CI, 1.641 to 5.082] and [RR, 2.925; 95% CI, 1.850 to 4.626], respectively). Duval and Tweedie’s trim and fill methods were further performed to test the model stability and the results still showed positive significance (RR = 1.981, 95% CI: 1.150 to 3.413, \( P = 0.014 \), with two studies estimated on the left side).

**Wound Complications**

Five studies involving 55,092 patients reported on the rate of wound dehiscence, and the meta-analysis showed that IDDM

![Study selection diagram](image-url)
| Study       | Design       | Period       | Outcome assessment                                                                 | Outcomes determined                                      | Adjusted factors       |
|------------|--------------|--------------|------------------------------------------------------------------------------------|-----------------------------------------------------------|------------------------|
| Lung¹³     | Case-control | 2015–2016    | Readmission                                                                        | None                                                      | Baseline characteristics|
|            |              |              | Non-routine discharge                                                             |                                                            |                        |
|            |              |              | Postoperative SSI                                                                  |                                                            |                        |
|            |              |              | Postoperative renal failure                                                        |                                                            |                        |
|            |              |              | Postoperative myocardial infarction                                                |                                                            |                        |
|            |              |              | Postoperative pneumonia                                                            |                                                            |                        |
|            |              |              | Postoperative PE                                                                  |                                                            |                        |
|            |              |              | Postoperative transfusion due to bleeding                                           |                                                            |                        |
| Lee¹⁴      | Retrospective| 2005–2016    | Superficial incisional SSI                                                         | Pneumonia                                                 | Unadjusted             |
|            |              |              | Deep incisional SSI                                                                | Blood transfusions                                        |                        |
|            |              |              | Organ/space SSI                                                                   | Septic shock                                              |                        |
|            |              |              | Wound disruption                                                                    | Extended LOS (>5 days)                                    |                        |
|            |              |              | Pneumonia                                                                          |                                                            |                        |
|            |              |              | Deep incisional SSI                                                                |                                                            |                        |
|            |              |              | Superficial SSI                                                                    |                                                            |                        |
|            |              |              | Wound dehiscence                                                                   |                                                            |                        |
|            |              |              | Urinary tract infection                                                            |                                                            |                        |
|            |              |              | Cardiac arrest                                                                     |                                                            |                        |
|            |              |              | Stroke                                                                             |                                                            |                        |
|            |              |              | Pulmonary Embolism (DVT)                                                           |                                                            |                        |
|            |              |              | Renal insufficiency                                                                |                                                            |                        |
|            |              |              | Acute renal failure                                                                 |                                                            |                        |
|            |              |              | Urinary tract infection                                                            |                                                            |                        |
|            |              |              | Stroke                                                                             |                                                            |                        |
|            |              |              | Cardiac arrest                                                                     |                                                            |                        |
|            |              |              | Sepsis                                                                             |                                                            |                        |
|            |              |              | Deep SSI                                                                           |                                                            |                        |
|            |              |              | Superficial SSI                                                                    |                                                            |                        |
|            |              |              | Wound dehiscence                                                                   |                                                            |                        |
|            |              |              | Urinary tract infection                                                            |                                                            |                        |
|            |              |              | Return to operating room                                                           |                                                            |                        |
|            |              |              | extended Length of stay                                                           |                                                            |                        |
|            |              |              | (>5 days)                                                                          |                                                            |                        |
| Gu¹⁵       | Retrospective | 2007–2016    | Death                                                                              | Pneumonia                                                 | Unadjusted             |
|            |              |              | Cardiac complications                                                               | Re-intubate                                               |                        |
|            |              |              | Acute renal failure                                                                 | Fail to wean >48 h                                        |                        |
|            |              |              | Renal insufficiency                                                                | Renal fail                                                |                        |
|            |              |              | Pulmonary complications                                                             | Cardiac arrest                                            |                        |
|            |              |              | VTE/PE                                                                             | Death                                                     |                        |
|            |              |              | Stroke                                                                             | Return to operating room                                  |                        |
|            |              |              | Sepsis                                                                             | Extended LOS                                              |                        |
|            |              |              | Deep SSI                                                                           | Superficial SSI                                           |                        |
|            |              |              | Superficial SSI                                                                    | Postoperative blood transfusion                           |                        |
|            |              |              | Return to operating room                                                           |                                                            |                        |
|            |              |              | extended Length of stay                                                           |                                                            |                        |
|            |              |              | (>5 days)                                                                          |                                                            |                        |
| Pele¹⁶     | Prospective  | 2010–2015    | Myocardial infarction                                                              | Myocardial infarction                                     | Unadjusted             |
|            | Retrospective| 2005–2014    | Death                                                                              | Sepsis                                                    | Age                    |
|            |              |              | Cardiac arrest                                                                     | Myocardial infarction                                     | Gender                 |
| Study | Design | Period | Outcome assessment | Outcomes determined | Adjusted factors |
|-------|--------|--------|--------------------|---------------------|-----------------|
| Fu10  | Retrospective | 2011-2014 | Any complications | Sepsis, Myocardial infarction, Renal failure, Heart failure, Thrombotic event (PE/DVT), wound-related infection | Renal failure, On ventilator >48 h, Unplanned intubation, Renal insufficiency, Return to the operating room, Wound dehiscence | Age, CCI, Smoking status |
| Webb18 | Retrospective | 2005-2014 | Death | Sepsis, Myocardial infarction, Renal failure, Thrombotic event (PE/DVT), wound-related infection | Sepsis, Myocardial infarction, Renal failure, Unplanned intubation, Renal insufficiency, Return to the operating room, Wound dehiscence, Pneumonia, Urinary tract infection, Extended length of stay (>5 days) | Age, Gender, CCI, Smoking status |
| Bohl19 | Prospective | 2005-2013 | Sepsis | Sepsis | Baseline demographic, Comorbidty, Unadjusted |
| Watts20 | Retrospective | 1995-2011 | Reoperation | Reoperation | Unadjusted |
### TABLE 2 Continued

| Study       | Design      | Period      | Outcome assessment   | Outcomes determined           | Adjusted factors                     |
|-------------|-------------|-------------|----------------------|------------------------------|--------------------------------------|
| Gregory21   | Prospective | 2005–2012   | Revision             | Revision                     | Unadjusted                           |
|             |             |             | Periprosthetic Joint Infection | Periprosthetic Joint Infection | Age                                   |
| Lovecchio22 | Retrospective | 2005–2011  | TSA Complication     | TSA Complication             | Unadjusted                           |
|             |             |             | Overall complication | Overall complication         | Age, Sex                              |
|             |             |             | Surgical complications | Medical complications       | Race                                 |
|             |             |             | Superficial wound    | Pneumonia                    | BMI                                   |
|             |             |             | Deep incision/organ space | Unplanned intubation         | Smoking                               |
|             |             |             | Medical complications | Renal insufficiency          | Steroid use                           |
|             |             |             | Pneumonia             | Urinary tract infection      | Hypertension, COPD                    |
|             |             |             | Unplanned intubation  | Sepsis                       | Anesthesia type                       |
|             |             |             | On ventilation >48 hours | Readmission                 |                                       |
|             |             |             | Renal insufficiency   | 30-day mortality rate        |                                       |
|             |             |             | Urinary tract infection | Stroke                      |                                       |
|             |             |             | Stroke                | Cardiac arrest               |                                       |
|             |             |             | Myocardial infarction | Sepsis                       |                                       |
| Christoffer23 | Prospective | 2010–2012  | Extended LOS (>4 days) | Diabetes-related morbidity   | Demographics, Comorbidity            |
|             |             |             | 30-day readmissions   |                               | Department of surgery                |
|             |             |             | 90-day readmissions   |                               |                                       |
|             |             |             | Diabetes-related morbidity |                            |                                       |
| Iorio29     | Retrospective | 2004–2009  | Infection             | Infection                    | Unadjusted                           |
| Meding27    | Prospective | 1980–1989   | Revision              | Deep infection               | Unadjusted                           |
|             |             |             | Deep infection        | Neuropathy                   |                                       |
|             |             |             | Wound                 | Manipulation                 |                                       |
|             |             |             | Neuropathy            | Urinary tract infection      |                                       |
|             |             |             | Manipulation          |                               |                                       |
| Serna29     | Retrospective | 1987–1999  | Revision              | None                         | Unadjusted                           |
|             |             |             |                       |                              |                                       |

BMI, body mass index; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; LOS, length of stay; PE, pulmonary embolism; SSI, surgical site infection; TSA, total shoulder arthroplasty; VTE, venous thromboembolism.
| Author   | Status   | Any | CR | Stroke | Sepsis | MI   | LOS(>5d) | Ventilator >48 h | RF/RI  | SupSSI | Deep SSI | O/S SSI | VTE/PE | Re-op | Read | Wound dehiscence | Urinary tract infection | Revision | Pneumonia | Death |
|---------|----------|-----|----|--------|--------|------|---------|-------------------|--------|--------|-----------|---------|--------|-------|------|-------------------|------------------------|----------|-----------|-------|
| Lung    | IDDM     | NA  | NA | NA     | NA     | 0.5% | NA     | NA                | NA     | NA     | NA       | NA      | NA     | 5.5% | NA  | NA                | 0.5%                   | NA       | 0.8%      | NA    |
| Lee     | IDDM     | NA  | 0.5%| 0.2%   | 2.6%   | 0.6% | 23%    | 0.3%              | 0.9%   | 0.4%   | 1.0%      | 1.6%    | 1.1%   | 4.5% | 6.6%| 1%                | 1.3%                   | NA       | 2%        | 0.6%  |
| Gu      | IDDM     | NA  | 0.0%| 0.2%   | 1.6%   | 0.4% | 17%    | 0.0%              | 0.6%   | 1.0%   | 0.4%      | 1.8%    | 1.3%   | 3.5% | 6.1%| 1%                | 1.5%                   | NA       | 0%        | 0.3%  |
| Pelle   | IDDM     | NA  | NA  | NA     | NA     | NA   | NA     | NA                | NA     | NA     | NA       | NA      | NA     | NA   | NA  | NA                | NA                    | NA       | NA        | NA    |
| Webb    | IDDM     | NA  | 0.2%| 0.2%   | 0.7%   | 0.5% | 9.0%   | 0.2%              | 0.8%   | NA     | NA       | 1.5%    | 1.9%   | 5.0% | 0.5%| 1.5%               | NA                    | 0.8%      | 0.1%      |
| Fu      | IDDM     | NA  | 0.1%| 0.1%   | 0.4%   | 0.3% | 6.4%   | 0.1%              | 0.3%   | NA     | NA       | 1.6%    | 1.3%   | 3.2% | 0.2%| 1.1%               | NA                    | 0.4%      | 0.1%      |
| Webb    | IDDM     | NA  | 0.0%| 0.0%   | 0.0%   | NA   | NA     | NA                | NA     | NA     | NA       | NA      | 0.7%   | 0.9% | 2.9%| NA                | 0.4%                   | NA        | NA        | 0.1%  |
| Watts   | IDDM     | NA  | NA  | NA     | NA     | NA   | NA     | NA                | NA     | NA     | NA       | NA      | NA     | NA   | NA  | NA                | NA                    | NA        | NA        | NA    |
| Lovecchio | IDDM | NA  | 0.1%| 0.1%   | 0.5%   | 0.3% | 6.5%   | 0.1%              | 0.3%   | NA     | NA       | 1.3%    | 1.7%   | 3.7% | 0.2%| 1.1%               | NA                    | 0.4%      | 0.1%      |
| Christoffer | IDDM | NA  | NA  | NA     | NA     | NA   | NA     | NA                | NA     | NA     | NA       | NA      | NA     | NA   | NA  | NA                | NA                    | NA        | NA        | NA    |
| Meding  | IDDM     | NA  | NA  | NA     | NA     | NA   | NA     | NA                | NA     | NA     | NA       | NA      | NA     | 8.5% | NA  | NA                | 1.6%                   | NA        | NA        | NA    |
| Serna   | IDDM     | NA  | NA  | NA     | NA     | NA   | NA     | NA                | NA     | NA     | NA       | NA      | NA     | 2.1% | NA  | 2.4%               | 0.9%                   | 0.6%      | NA        | NA    |
| NIDDM   | NA       | NA  | NA  | NA     | NA     | NA   | NA     | NA                | NA     | NA     | NA       | NA      | NA     | NA   | NA  | NA                | NA                    | NA        | NA        | NA    |
| Watts   | NIDDM    | NA  | NA  | NA     | NA     | NA   | NA     | NA                | NA     | NA     | NA       | NA      | NA     | NA   | NA  | NA                | NA                    | NA        | NA        | NA    |

Any, any complications; CR, cardiac arrest; Deep SSI, deep incisional surgical site infection; IDDM, insulin dependent diabetes mellitus; LOS(>=5 days), extended length of stay >=5 days; MI, myocardial infarction; NA, not available; NIDDM, non-insulin dependent diabetes mellitus; O/S SSI, organ/space surgical site infection; Read, readmission; Re-op, reoperation; RF/RI, renal failure/renal insufficiency; Sup SSI, superficial surgical site infection; VTE/PE, venous thromboembolism/pulmonary embolism.
| Outcomes                          | Number of studies | Number of patients | IDDM | NIDDM | RR (95% CI)                          | P     | Heterogeneity | Model | Harbord’s test | GRADE evidence |
|----------------------------------|-------------------|--------------------|------|-------|--------------------------------------|-------|---------------|-------|----------------|----------------|
| Cardiac arrest                   | 5(7, 14, 20, 24, 31) | 15,380             | 46,437| 2.343 | (1.546 to 3.550)                    | **P < 0.001** | $I^2 = 0\%$, $P = 0.529$ | Fixed | $P = 0.160$ | ⚤ ⚤ ⚤ |
| Stroke                           | 6(7, 9, 14, 20, 24, 31) | 15,675             | 47,128| 2.180 | (1.434 to 3.313)                    | **P < 0.001** | $I^2 = 6.6\%$, $P = 0.374$ | Fixed | $P = 0.649$ | ⚤ ⚤ ⚤ |
| Sepsis                           | 7(7, 9, 14, 17, 20, 24, 31) | 19,973             | 58,425| 1.952 | (1.643 to 2.319)                    | **P < 0.001** | $I^2 = 0\%$, $P = 0.684$ | Fixed | $P = 0.330$ | ⚤ ⚤ ⚤ |
| Myocardial infarction            | 7(7, 14, 17, 20, 23, 24, 31) | 16,262             | 48,460| 1.854 | (1.442 to 2.382)                    | **P < 0.001** | $I^2 = 0\%$, $P = 0.807$ | Fixed | $P = 0.699$ | ⚤ ⚤ ⚤ |
| Extended length of stay (>5 days) | 3(7, 14, 20)         | 12,853             | 39,374| 1.448 | (1.362 to 1.539)                    | **P < 0.001** | $I^2 = 0\%$, $P = 0.744$ | Fixed | $P = 0.693$ | ⚤ ⚤ ⚤ |
| On ventilator >48 h              | 5(13, 14, 20, 24, 31) | 15,380             | 46,437| 2.918 | (1.912 to 4.453)                    | **P < 0.001** | $I^2 = 0\%$, $P = 0.617$ | Fixed | $P = 0.027$ | ⚤ ⚤ ⚤ |
| Renal failure                    | 5(13, 14, 20, 24, 29) | 14,208             | 42,186| 2.753 | (1.822 to 4.158)                    | **P < 0.001** | $I^2 = 0\%$, $P = 0.522$ | Fixed | $P = 0.990$ | ⚤ ⚤ ⚤ |
| Superficial incisional SSI       | 2(13, 24)           | 2,146              | 4,225 | 0.354 | (0.159 to 0.790)                    | **P = 0.111** | $I^2 = 0\%$, $P = 0.515$ | Fixed | -              | ⚤ ⚤ ⚤ |
| Deep incisional SSI              | 2(13, 24)           | 2,146              | 4,225 | 1.967 | (1.106 to 3.498)                    | **P = 0.021** | $I^2 = 0\%$, $P = 0.962$ | Fixed | -              | ⚤ ⚤ ⚤ |
| Organ/Space SSI                  | 2(13, 24)           | 2,146              | 4,225 | 0.916 | (0.608 to 1.380)                    | **P = 0.676** | $I^2 = 0\%$, $P = 0.822$ | Fixed | -              | ⚤ ⚤ ⚤ |
| Thrombotic event (VTE/PE)        | 5(9, 13, 14, 20, 24) | 14,123             | 41,955| 0.975 | (0.829 to 1.148)                    | **P = 0.764** | $I^2 = 0\%$, $P = 0.970$ | Fixed | $P = 0.177$ | ⚤ ⚤ ⚤ |
| Reoperation                      | 7(9, 13, 14, 18, 20, 24, 31) | 15,839             | 47,494| 1.444 | (1.381 to 1.728)                    | **P < 0.001** | $I^2 = 0\%$, $P = 0.309$ | Fixed | $P = 0.246$ | ⚤ ⚤ ⚤ |
| Readmission                      | 7(9, 13, 14, 20, 21, 29, 31) | 15,122             | 47,050| 1.494 | (1.381 to 1.728)                    | **P < 0.001** | $I^2 = 0\%$, $P = 0.277$ | Fixed | $P = 0.374$ | ⚤ ⚤ ⚤ |
| Wound dehiscence                 | 4(13, 14, 20, 24)   | 13,828             | 41,264| 2.203 | (1.596 to 3.040)                    | **P < 0.001** | $I^2 = 0\%$, $P = 0.190$ | Fixed | $P = 0.048$ | ⚤ ⚤ ⚤ |
| Urinary tract infection          | 7(9, 13, 14, 16, 20, 24, 31) | 15,793             | 47,339| 1.400 | (1.211 to 1.619)                    | **P < 0.009** | $I^2 = 0\%$, $P = 0.123$ | Fixed | $P = 0.617$ | ⚤ ⚤ ⚤ |
| Renal insufficiency              | 5(9, 13, 14, 20, 24) | 14,123             | 41,955| 1.971 | (1.141 to 3.403)                    | **P = 0.015** | $I^2 = 0\%$, $P = 0.078$ | Random | $P = 0.049$ | ⚤ ⚤ ⚤ |
| Revision                         | 3(16, 22)          | 291                | 621   | 2.330 | (0.681 to 7.974)                    | **P = 0.178** | $I^2 = 57.4\%$, $P = 0.096$ | Random | $P = 0.300$ | ⚤ ⚤ ⚤ |
| Unplanned intubation             | 4(13, 14, 20, 31)   | 14,405             | 44,547| 1.043 | (0.715 to 1.521)                    | **P = 0.028** | $I^2 = 58.0\%$, $P = 0.067$ | Random | $P = 0.035$ | ⚤ ⚤ ⚤ |
| Pneumonia                        | 6(13, 14, 20, 24, 29, 31) | 15,760             | 47,359| 1.965 | (1.238 to 3.120)                    | **P = 0.004** | $I^2 = 0\%$, $P = 0.13$ | Random | $P = 0.631$ | ⚤ ⚤ ⚤ |
| Death                            | 6(9, 13, 14, 20, 24, 31) | 15,675             | 47,128| 2.292 | (1.568 to 3.349)                    | **P < 0.001** | $I^2 = 0\%$, $P = 0.464$ | Fixed | $P = 0.354$ | ⚤ ⚤ ⚤ |

CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; IDDM, insulin dependent diabetes mellitus; NIDDM, non-insulin dependent diabetes mellitus; No. of studies; No. of patients, number of patients; PE, pulmonary embolism; RR, relative risk; SSI, surgical site infection; VTE, venous thromboembolism. $p < 0.05$ values have been bold.
was associated with wound dehiscence (RR, 2.209; 95% CI, 1.596 to 3.040; $I^2 = 38.7\%$). Surgical site infection (SSI) was reported separately in superficial SSI and deep incisional SSI with no heterogeneity ($I^2 = 0\%$), with RR of 0.352 (95% CI 0.157 to 0.788) and 1.978 (95% CI 1.107 to 3.533), respectively.

**Infection**

The most commonly reported complications in articles were sepsis, reoperation, and urinary tract infection. Seven studies including 79,398 patients reported the occurrence of sepsis for IDDM and NIDDM patients. After analysis of the results, which had an $I^2$ of 0%, the occurrence of sepsis was determined to be significantly higher in IDDM patients (RR, 1.965; 95% CI 1.651 to 2.340). The pooled analysis also revealed that IDDM was associated with a high risk of urinary tract infection (RR, 1.407; 95% CI 1.214 to 1.631; $I^2 = 40.3\%$). No significant differences were found in the occurrence of organ/space SSI.

**Other Complications**

The extended length of stay (>5 days) that occurred during hospitalization was documented in only 3 studies. The absence of heterogeneity among these articles allowed pooling of results and a higher risk of extended length of stay (RR, 1.509; 95% CI 1.4109 to 1.616) was found in IDDM patients compared with NIDDM patients. Seven studies including 63,132 patients reported on the risk of reoperation. The pooled analysis showed that IDDM was associated with a higher risk of reoperation (RR, 1.460; 95% CI 1.295 to 1.646) with no heterogeneity ($I^2 = 0\%$). Seven studies involving 62,172 patients examined the effect of IDDM on readmission, and a
### Fig. 3
Proportion of insulin-dependent in patients with diabetes mellitus (stratified by areas).

| Study ID | Proportion (95% CI) | Weight |
|----------|---------------------|--------|
| America  |                     |        |
| Lung 2019| 0.29 (0.27, 0.32)   | 6.00   |
| Lee 2019 | 0.33 (0.32, 0.35)   | 6.43   |
| Watts 2016| 0.31 (0.27, 0.35)  | 5.11   |
| Fu 2017  | 0.30 (0.27, 0.33)   | 5.78   |
| Webb 2017| 0.24 (0.24, 0.25)   | 6.71   |
| Gu 2018  | 0.34 (0.32, 0.36)   | 6.36   |
| Webb 2016| 0.23 (0.22, 0.24)   | 6.64   |
| Iorio 2012| 0.21 (0.16, 0.25)  | 4.92   |
| Lovecchio 2014 | 0.23 (0.22, 0.24) | 6.82 |
| Bohl 2016 | 0.26 (0.25, 0.27)  | 6.70   |
| Papageioupolos 1996 | 0.23 (0.12, 0.35) | 1.77 |
| Gregory 2015 | 0.26 (0.18, 0.34) | 2.94 |
| Bruce 1993 | 0.28 (0.14, 0.35)  | 2.15   |
| Subtotal (I-squared = 95.8%, p = 0.000) | 0.27 (0.25, 0.29) | 68.15 |

| Denmark      |                     |        |
| Pelle 2018  | 0.20 (0.18, 0.22)   | 6.24   |
| Pelle 2018  | 0.18 (0.16, 0.21)   | 6.10   |
| Christoffe 2014 | 0.20 (0.17, 0.22) | 5.92 |
| Subtotal (I-squared = 0.0%, p = 0.653) | 0.19 (0.18, 0.21) | 18.26 |

| Korea        |                     |        |
| Han 2013    | 0.19 (0.13, 0.25)   | 3.89   |
| Subtotal (I-squared = .%, p = .) | 0.19 (0.13, 0.25) | 3.89 |

| Finland      |                     |        |
| Jamsen 2012 | 0.29 (0.24, 0.34)   | 4.44   |
| Jamsen 2012 | 0.27 (0.24, 0.31)   | 5.27   |
| Subtotal (I-squared = 0.0%, p = 0.564) | 0.26 (0.25, 0.31) | 9.70 |
| Overall (I-squared = 95.2%, p = 0.000) | 0.26 (0.24, 0.27) | 100.00 |

**NOTE:** Weights are from random effects analysis.

### Fig. 4
Meta-regression for the prevalence of insulin-dependent patients among diabetes mellitus patients.
significant increase in the rate of readmission was observed (RR, 1.494; 95% CI, 1.381 to 1.615; I² = 15.8%). It is worth mentioning that there were 6 studies involving 62,803 participants reporting on the risk of death in IDDM patients after TJA with no heterogeneity (I² = 0%) and the pooled analysis showed a greater than twofold risk of death in IDDM patients (RR, 2.292; 95% CI, 1.568 to 3.349). No significant differences were found in the occurrence of thrombotic events (VTE/PE) and revision.

Discussion

The global prevalence of diabetes is expected to rise from 6.4% to 7.7% between 2010 and 2030; therefore, its prevalence in the TJA population might increase accordingly. DM leads to a chronic low-level inflammatory state, accompanied by metabolic disturbance, immune decline, and other negative states. Existing published studies show that diabetic patients are more likely to develop perioperative complications than non-diabetic patients, including wound infection, deep prosthesis infection, and prosthesis revision.

Lovecchio et al.

further stratified 42,339 THA and TKA diabetic patients included in the National Surgical Quality Improvement Program into NIDDM and IDDM groups. The results showed that the risk of 30-day mortality and readmission were significantly increased in IDDM patients, which was consistent with our pooled analysis. A retrospective study by Lee et al.

indicated that insulin dependence was associated with septic shock after rTKA, leading to renal insufficiency and even renal failure. Therefore, the authors recommend strengthening blood sugar control in IDDM patients to reduce the risk of renal failure after rTKA. In addition, IDDM also increases the risk of blood transfusion after rTKA compared with non-diabetes mellitus and NIDDM.

Therefore, DM is a heterogeneous disease with varying severity in the TJA population. This situation must be taken into consideration when comparing the outcomes of patients with diabetes. Oliva et al.

showed that applying personalized postoperative management based on perioperative risk stratification could reduce the incidence of postoperative complications. With the development of medical economics, further stratification of diabetes based on insulin dependence is critical to take into consideration the rapid growth of the diabetic population.

This analysis involved 81,697 patients undergoing TJA. The results showed that IDDM patients had significantly higher risk of adverse events than NIDDM patients. Although NIDDM patients had higher risk of superficial wound infection, IDDM patients’ risk of stroke, sepsis, myocardial infarction, extended length of stay (>5 days), being on a ventilator >48 h, renal failure, superficial incisional SSI, deep incisional SSI, reoperation, readmission, wound dehiscence, urinary tract infection, renal insufficiency, unplanned intubation, pneumonia, and death increased significantly.

The incidence of deep incisional SSI infection in IDDM patients was almost double that in NIDDM patients. Therefore, the risk of deep incision SSI in patients with more severe or long-term chronic diabetes after TJA might increase. In contrast, the incidence of superficial SSI in IDDM is significantly lower than that in NIDDM, which may be because insulin effectively controls blood sugar levels in peripheral blood.

| TABLE 5 Results of the subgroup analyses |
|------------------------------------------|
| **Outcomes** | **Subgroup** | **Number of studies** | **IDDM** | **NIDDM** | **RR (95% CI)** | **P** | **Heterogeneity** | **Model** |
|----------------|-----------|-----------------|--------|--------|-----------------|------|-----------------|-------|
| Unplanned intubation | TKA | 1<sup>17</sup> | 4,860 | 15,332 | 1.885 (1.099 to 3.235) | <0.001 | - | Random |
| | rTKA | 1<sup>14</sup> | 1,161 | 2,328 | 2.833 (1.081 to 7.424) | <0.004 | - | Random |
| | TKA, THA | 2<sup>18, 22</sup> | 8,306 | 26,719 | 1.433 (0.674 to 3.045) | <0.001 | - | Random |
| | Overall | 4<sup>14, 17, 18, 22</sup> | 14,405 | 44,547 | 1.697 (1.059 to 2.718) | <0.028 | - | Random |
| Pneumonia | TKA | 1<sup>17</sup> | 4,841 | 15,312 | 2.279 (1.519 to 3.421) | <0.001 | - | Random |
| | rTKA | 2<sup>14, 15</sup> | 2,114 | 4,206 | 3.284 (1.866 to 5.781) | <0.001 | - | Random |
| | TSA | 1<sup>13</sup> | 378 | 915 | 0.695 (0.145 to 3.330) | - | - | Random |
| | TKA, THA | 2<sup>18, 22</sup> | 8,312 | 26,739 | 1.431 (0.668 to 3.067) | <0.001 | - | Random |
| | Overall | 6<sup>18-15, 17, 18, 22</sup> | 15,760 | 47,359 | 1.965 (1.238 to 3.120) | <0.004 | - | Random |
| Renal insufficiency | TKA | 1<sup>17</sup> | 4,858 | 15,342 | 2.888 (1.641 to 5.082) | <0.001 | - | Random |
| | rTKA | 2<sup>14, 15</sup> | 6,766 | 21,634 | 1.125 (0.446 to 2.839) | <0.001 | - | Random |
| | TSA | 1<sup>10</sup> | 2,134 | 4,204 | 0.335 (0.017 to 6.574) | <0.001 | - | Random |
| | TKA, THA | 1<sup>18</sup> | 6,766 | 21,634 | 2.925 (1.850 to 4.626) | <0.001 | - | Random |
| | Overall | 5<sup>10, 14, 15, 17, 18</sup> | 14,123 | 41,955 | 1.971 (1.141 to 3.403) | <0.015 | - | Random |

CI, confidence interval; NIDDM, non-insulin dependent diabetes mellitus; No. of studies; No. of patients, number of patients; IDDM, insulin dependent diabetes mellitus; rTKA, revision total knee arthroplasty; RR, relative risk; THA, total hip arthroplasty; TKA, total knee arthroplasty; TSA, total shoulder arthroplasty. P < 0.05 values have been bold.
This is the first review, to our knowledge, to consider the effect of insulin on the complication rate of TJA, and this pooled analysis supports that clinicians should use the diabetic control method as a variable for risks in the preoperative evaluation of total joint replacement in diabetic patients. Our findings can help clinicians to stratify perioperative risks more accurately when questioning patients and provide a theoretical basis for adjusting perioperative management and setting postoperative expectations.

This meta-analysis has several limitations. First, IDDM patients might be in the late stage of DM, during which pancreatic β cells are no longer functioning due to excessive cell damage. NIDDM patients may be in the early and middle stages of DM when pancreatic β cells are still functioning13. Second, we cannot further stratify the patients according to the level of HbA1c; that is, to evaluate insulin’s control of HbA1c. The increased risk of complications in IDDM patients may be the result of an increased level of HbA1c. Finally, although the results of this study suggest that IDDM is a risk factor for increased incidence of complications after surgery, the study was unable to establish a causal link between IDDM and complications after surgery.

Conclusion

Insulin dependence is a high-risk factor for increased postoperative complications of TJA, and hierarchical and optimal blood glucose management may contribute to reducing the adverse complications after surgery. In addition, because the risk of sepsis, deep wound infection, organ/space SSI, urinary tract infection, renal insufficiency, and renal failure increased significantly after TJA in IDDM patients, more active postoperative antimicrobial prophylaxis may be needed on the premise of protecting renal function.

ACKNOWLEDGMENTS

The authors wish to thank Mr Ke Qiu, Mr Dian Fan, and Mr Yuen Teng from West China Hospital for help with the methodology of this study.

Supporting Information

Additional Supporting Information may be found in the online version of this article on the publisher’s web-site:

Appendix S1. Grade evidence level of included studies

Appendix S2. PRISMA 2009 Checklist

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