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Perioperative hyperglycaemia and incidence of post-operative complications in patients undergoing total knee arthroplasty

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Abstract
Purpose The aim of this study was to assess whether hyperglycaemia in the post-operative period of total knee arthroplasty (TKA) affects post-operative complications regardless of diabetes mellitus (DM) diagnosis.
Methods All patients who had undergone primary TKA were included in the study. The following data were recorded: DM diagnosis, and pre- (BGL1), intra- (BGL2) and post-operative blood glucose levels (BGL3). After 1-year follow-up, medical, infectious and mechanical or surgery-related complications were recorded.
Results Of the 833 patients included, 130 (15.6 %) were diabetic. Median BGL1, BGL2 and BGL3 were 106.13, 93.49 and 134.16 mg/dl, respectively. After follow-up, 173 (20.8 %) patients presented complications, including 48 (5.76 %) medical complications and 94 (11.28 %) infections. Surgery-related complications presented in 31 (3.72 %) patients. A statistically significant association was found between BGL3 $\geq$ 126 mg/dl and complications (OR 1.95, $p < 0.001$), medical complications (OR 3.98, $p < 0.001$), and infections (OR 1.76, $p < 0.006$).
Conclusions Hyperglycaemia during the post-operative period in diabetic and non-diabetic patients undergoing TKA increases post-operative medical and infectious complications. Glycemic control during this period must be performed in order to reduce these complications.
Level of evidence Retrospective case series, Level IV.

Keywords Total knee arthroplasty · Diabetes mellitus · Hyperglycaemia · Complications

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Introduction

Several studies have investigated risk factors for poor outcome after joint replacement. Lately great deal of attention has been paid to diabetes mellitus (DM) due to the rising prevalence of this pathology in patients undergoing major joint replacements [2, 10, 12, 15, 18, 20]. It has been estimated that more than 8 % of diabetic patients undergo primary or revision total hip or knee arthroplasty in the US [5]. Several studies have shown that DM is associated with a high risk of complications in patients undergoing major joint arthroplasty: post-operative infection, deep vein thrombosis, brain stroke, cerebrovascular disease and medical complications [13, 16–18, 21, 25]. Other post-operative outcomes such as length of hospital stay (LHS), in-hospital mortality and hospital charges are higher in patients with DM [18].

Many possible explanations for the poorer outcomes in DM patients have been proposed. One of them is glycemic dysregulation. A relation between hyperglycaemia and adverse outcomes in orthopaedic surgery has been described [28]. Most studies have been performed in diabetic patients and report that, regardless of diabetes type, uncontrolled patients have increased rates of surgical and systemic complications, higher mortality and increased LHS [17]. One study found that a large number of non-diabetic patients developed hyperglycaemia during the first 2 days after major limb surgery [26]. Hyperglycaemia in non-diabetic patients has been associated with increased rate of infection and worse outcomes in cardiac surgery [7], general surgery [4], colorectal surgery [19], spinal surgery [23] and mastectomy [30]. In patients undergoing lower limb arthroplasty, one study found that DM and post-operative morning hyperglycaemia were predictors of post-operative infection. Even patients without DM who developed post-operative hyperglycaemia (blood glucose levels >140 mg/dl, 24 h after surgery) had significantly increased risk for infection [22].

To our knowledge, no previous studies have simultaneously correlated pre-operative, intra-operative and post-operative blood glucose levels with post-operative complications after total knee arthroplasty (TKA) in diabetic and non-diabetic patients. The goal of our study was to assess the association between perioperative hyperglycaemia and post-operative complications and LHS after 1-year follow-up in patients who undergo primary TKA. Our hypothesis was that hyperglycaemia in the post-operative period is associated with post-operative complications regardless DM diagnosis. If the hypothesis is correct, a proper action in glucose control during this period must be performed in order to reduce post-operative complications.

Materials and methods

After obtaining the institutional review board's approval, we consulted the records on all patients who had undergone primary TKA from November 2009 to July 2011. We retrospectively reviewed our hospital's computerized database (Hospital Clinic, Barcelona), a third level university hospital with a specialized surgical team that performs only TKA procedures.

All patients who had undergone a primary TKA were included in the study. Exclusion criteria were: revision knee arthroplasties, patients lost before 1-year follow-up and patients with incomplete data.

All patients were operated upon consecutively and by the same specialized surgical team following a standard surgical protocol. Regional anaesthesia (epidural) with peripheral nerve blockade (sciatic and crural nerves) for pain control was used unless contraindicated. All interventions were performed with a tourniquet placed on the upper thigh. A medial parapatellar surgical approach with patellar eversion was used. Various knee prosthesis models were used. All femoral components were cemented; the tibial component might be cemented or not depending on the surgeon's preferences and the patient's characteristics. Patelloplasty without patellar prostheses was generally performed. After cementation and before closing the wound, the tourniquet was released in order to check for any bleeding; two drains were placed and maintained for 48 h after surgery.

All patients received standardized perioperative management for infection prophylaxis. Intravenous antibiotic (cefuroxime 1 g.) was administered before surgery and another dose after surgery. Oral antithrombotic prophylaxis was administered and maintained for 6 weeks after surgery. Regular post-operative protocol physiotherapy was performed. 48 h after the intervention, the patients started walking and were discharged from the hospital 6 days after surgery if no complications were recorded.

The following data were taken from the anaesthesiologist's review performed 2 months before surgery: demographic information (age, sex), body mass index (BMI kg/m^2), the American Society of Anesthesiologists physical status classification system (ASA I, II, III, IV), diagnosis and type of DM. From pre-operative laboratory data, glycated haemoglobin levels (HbA1c %) (as an indicator of glycemic control status in patients with diagnosis of DM) and pre-operative blood glucose level (BGL1 mg/dl) (2 months before surgery) were recorded. The intra-operative blood glucose level (BGL2 mg/dl) (BM test during surgery) was recorded from the anaesthesiologist's control sheet during surgery. The post-operative blood glucose level (BGL3 mg/dl) (next morning after surgery) was taken from laboratory data during patient hospitalization. All blood glucose levels were obtained while patients were fasting. Patients with DM were treated with a glucose solution 5 % before surgery and a mobile insulin control depending on blood glucose test every 6 h. Patients without DM were treated with sodium chloride solution 0.9 %. LHS (days) was collected from the discharge report.

After 1-year follow-up, we recorded all complications that occurred. We categorized these post-operative complications as medical, infectious and mechanical or surgery-related with the need for revision surgery. No test–retest reliability measurement was considered to be necessary.

The study was approved by the Hospital's Ethics Committee (Hospital Clinic, University of Barcelona; ID: 2012/8037).

Statistical analysis

A descriptive analysis was performed using univariate frequency tables for categorical variables or mean values and standard deviation (SD) for continuous variables. We used independent *t* tests for continuous variables and χ^2 tests for categorical variables for comparisons between groups. Blood glucose values were analysed as continuous and categorical variables. For this study, hyperglycaemia was defined as BG level ≥126 mg/dl in any perioperative period. Uncontrolled DM was defined as HbA1c level ≥6.5 %. We decided to use these parameters according to the definition of DM by the American Diabetes Association (ADA) [3]. The confidence interval was established at 95 % and statistical significance at $p = 0.05$.

Results

Nineteen hundred and twenty-two patients underwent TKA from November 2009 to July 2011. Of these patients, 833 met the inclusion criteria. Median age was 71.3 years, the majority were female 624 (74.9 %) versus male 209 (25.1 %). One hundred and thirty (15.6 %) were diabetic. Most patients (667, 80 %) had a pre-operative ASA score of I or II. Mean BMI was 31.1 kg/m^2. (SD 4.8). Mean BGL1 was 106.1 mg/dl (SD 29), mean BGL2 was 93.5 mg/dl (SD 24.4), and mean BGL3 was 134.2 mg/dl (SD 45.95). Mean LHS was 6.7 days (SD 2.5) (Table 1).

After 1-year follow-up, 173 (20.8 %) patients presented some kind of complication. Of these, 48 (27.7 % of complicated patients; 5.8 % overall) had a medical complication: acute myocardial infarction, deep venous thrombosis, pulmonary thromboembolism, cardiac arrhythmias, hepatic encephalopathy or stroke. Infection was present in 94 (54.3 % of complicated patients; 11.3 % overall): urinary tract infection, wound infection (superficial), prosthetic infection (deep), phlebitis or sepsis. Other complications were recorded in 31 (18 % of complicated patients; 3.7 % overall): aseptic loosening of the implants, knee stiffness, femoropatellar pain, instability, periprosthetic, fracture, neuroma and extensor mechanism rupture. New surgery was performed in 78 (45.1 % of complicated patients; 9.4 % overall) due to one of the previously mentioned complications.

Regarding glycemic control, 110 patients (13.2 %) had a BGL1 ≥ 126 mg/dl. BGL2 ≥ 126 mg/dl was found in 67 (8 %) and BGL3 ≥ 126 mg/dl in 391 (46.9 %) patients.

No statistically significant association was found between pre-operative and intra-operative hyperglycaemia and post-operative complications. We also did not find association between diagnosis of DM and complications. Uncontrolled DM was not associated with any complications or LHS.

On the other hand, we found a statistically significant association between BGL3 ≥ 126 mg/dl and complications (OR 1.95, $p < 0.001$) (Fig. 1); medical complication

Table 1 Demographic and perioperative patient data

N	833
Age: mean (SD)	71.3 years (8.6)
Gender: *n* (%)	
Male	209 (25.1)
Female	624 (74.9)
DM: *n* (%)	130 (15.6)
ASA: *n* (%)	
I	71 (8.5)
II	596 (71.5)
III	161 (19.3)
IV	5 (0.6)
BMI: mean (SD)	31.1 kg/m^2 (4.8)
BGL1: mean (SD)	106.1 mg/dl (29)
BGL2: mean (SD)	93.5 mg/dl (24.4)
BGL3: mean (SD)	134.2 mg/dl (45.9)
LHS: mean (SD)	6.7 days (2.5)

DM diabetes mellitus, *ASA* American Society of Anesthesiologists physical status classification system, *BMI* body mass index, *BGL1* pre-operative blood glucose level, *BGL2* intraoperative blood glucose level, *BGL3* post-operative blood glucose level, *LHS* length of hospital stay, *SD* standard deviation

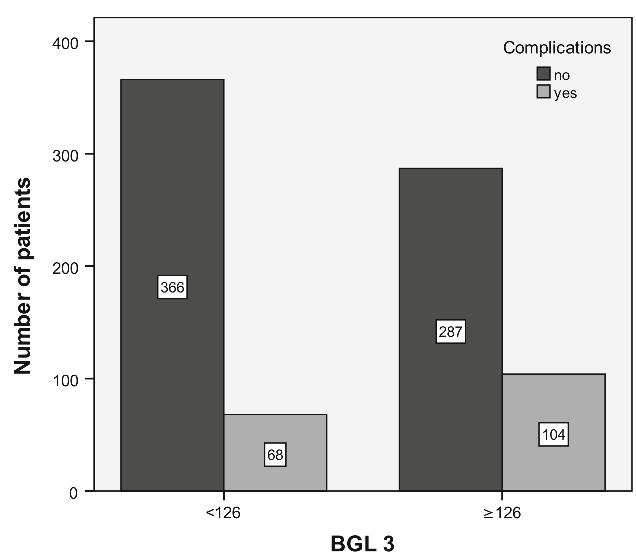

Fig. 1 Post-operative blood glucose level and complications

(OR 3.98, $p < 0.001$) (Fig. 2); and infection (OR 1.76, $p < 0.006$) (Fig. 3).

Patients' demographic data such as BMI, age and gender were not significantly and independently associated with post-operative complications.

Patients with DM had a higher LHS (7.1 days, SD 2.9) than non-diabetic patients (6.6 days SD 2.4) ($p = 0.026$).

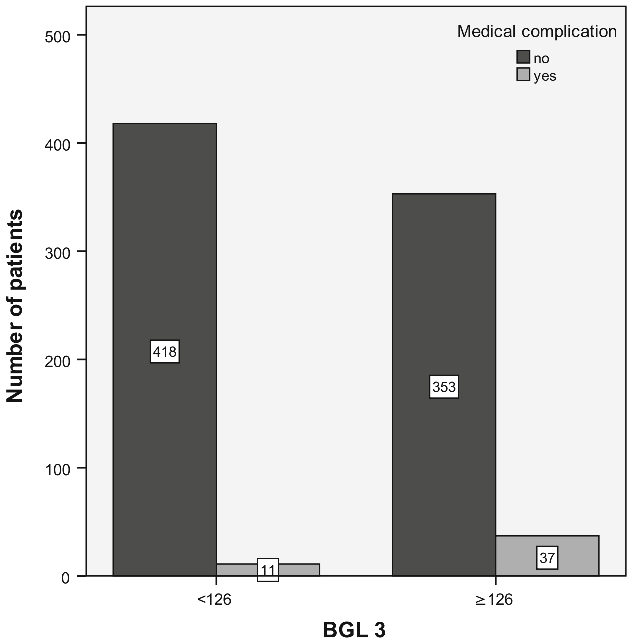

Fig. 2 Post-operative blood glucose level and medical complications

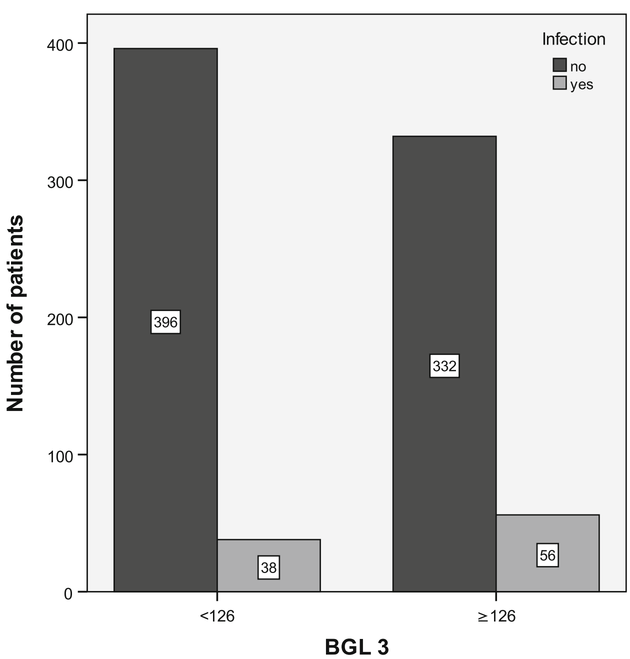

Fig. 3 Post-operative blood glucose level and infection

Discussion

The most important finding of this study was that hyperglycaemia in the immediate post-operative period (BGL3) affects post-operative medical and infectious complications.

Median BGL1 and BGL2 were both below the diagnostic levels of diabetes according to the ADA definition in fasting patients [3]. Median BGL3 was well above the diagnostic levels of diabetes in both diabetic and non-diabetic patients. These findings corroborate those of other studies in which non-diabetic patients also had very high post-operative blood glucose levels, probably due to a physiological response to injury which increased serum cortisol production and insulin resistance and led to subsequent hyperglycaemia [29].

As we included medical complications, infections and mechanical or surgery-related post-operative complications after 1-year follow-up, our post-operative complication rate was high. In other studies, only infection or medical complications have been recorded [5, 13, 16, 21]. Our design also explains why a large number of the complicated patients required revision surgery. Another reason might be the median BMI, which suggests a higher risk of metabolic syndrome, glycemic dysregulations and complications [8, 27, 31].

In contrast to other studies, we found no relation between diagnosis of DM and complications. Also patients with uncontrolled DM did not have more complication or increased LHS. These findings are controversial; some authors have found significantly high odds of surgical and systemic complications, higher mortality rate and increased LHS in patients with uncontrolled DM [17], while others have shown no relation between HbA1c levels and post-operative complications such as infection [11].

Only patients with DM had prolonged LHS. This result is in agreement with those of other studies that show significantly high odds of surgical and systemic complications, higher mortality and increased LHS after low extremity total joint replacement in patients with uncontrolled DM [17]. Probably, patients with long-term DM had more associated medical comorbidities and required longer hospitalization time.

Unlike other authors, we found no association between BGL1 or BGL2 and post-operative complications [1, 6, 7, 9, 14, 22, 23, 30]. One reason might be that the duration of surgery is shorter in knee arthroplasty than in cardiac or neurological interventions, and so the stress created in the organism is insufficient to induce hyperglycaemia. Tight glycemic control with insulin therapy has been proposed in order to reduce complication rates in neurosurgery, cardiac and paediatric cardiac surgery though the results obtained varied: some authors report better clinical outcomes and lower infection rates while others noted no change in infection rate, mortality or LHS compared with standard care [1, 14, 24].

The statistical analysis showed that a BGL3 ≥ 126 mg/dl best predicted post-operative complications (medical and infectious) in this group of patients regardless of diabetic diagnosis. Other studies have taken a BGL3 cut-off point of 140 mg/dl to predict prosthetic infection after lower limb arthroplasty [22].

Few patients had pre-operative or intra-operative hyperglycaemia but almost half of the sample developed hyperglycaemia in the post-operative period. This finding corroborates the theory of stress-induced hyperglycaemia already described [29]. Another reason for this might be that some of these patients had an unknown diagnosis of DM. Patients with post-operative hyperglycaemia developed more complications regardless of DM diagnosis; they developed more medical complications, some of them severe and life threatening. Most of the studies conducted in orthopaedics surgery analyse only post-operative infection. Three of these studies analyse infection requiring surgical intervention as an end-point, and one of them also includes pneumonia, urinary tract infection and sepsis [6, 9, 22, 27]; we wanted to analyse also medical complications that could have negative impact on patients' outcome.

Like other studies, a strong association between post-operative hyperglycaemia and infections was found [6, 22, 27]. However, we included not only deep infection requiring surgical intervention, but also wound infection, urinary tract infection, phlebitis and sepsis. These outcomes can be attributed to de fact that hyperglycaemia affects all major components of innate immunity and impairs the host's ability to combat infection [29].

A limitation of the study is its retrospective design, which restricts the amount of data available and means that some patients may have been lost to follow-up. Its main strength is the high volume of patients because it was conducted at a highly specialized orthopaedic centre, and all patients were applied a similar pre-operative, intra-operative and post-operative protocol.

Clinical relevance of this study is that detection of post-operative hyperglycaemia or unknown diabetes in these patients and early treatment could reduce the incidence of medical and infectious complications after TKA surgery.

Conclusion

During the immediate post-operative period of patients that undergo TKA, proper glucose level control must conducted in order to reduce medical and infectious post-operative complications. This glycemic control must be performed in both diabetic and non-diabetic patients.

Patients with post-operative hyperglycaemia should also be followed by primary care physicians in order to control glucose levels or establish a correct diagnosis of DM.

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