Preoperative blood glucose concentrations and postoperative outcomes after elective non-cardiac surgery: an observational study†

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Editor’s key points
- Perioperative treatment of hyperglycaemia can reduce the risk of infection and possibly other adverse outcomes.
- Undiagnosed or undertreated diabetes is common in the perioperative setting.
- This study found that surgical patients with preoperative hyperglycaemia, but without a diagnosis of diabetes, had higher mortality 1 yr after surgery.
- It is likely that routine preoperative measurement of haemoglobin A1c in known or suspected diabetics will improve their ongoing care.

**Background.** The association between preoperative blood glucose (BG) concentration and outcomes after non-cardiac surgery and the impact of the diabetes diagnosis status remain unclear. We tested two hypotheses: that preoperative BG is related to surgical outcomes; and that this relationship depends on the diabetes diagnosis status of the patient.

**Methods.** We retrospectively analysed data on 61536 consecutive elective non-cardiac surgery patients treated at our tertiary care facility. Logistic regression models were used to test the hypotheses before and after adjustment for baseline patient characteristics. Our primary outcome was a composite of in-hospital serious complications and mortality. A second primary outcome was 1 yr mortality.

**Results.** The crude incidence of the composite in-hospital outcome was significantly related to preoperative BG (P < 0.001), but not after covariable adjustment (P = 0.40). This relationship did not significantly differ between patients with and without diagnosed diabetes (P = 0.09). One year mortality was significantly related to preoperative BG, both univariably (P < 0.001) and after covariable-adjustment (P < 0.001). Patients with diagnosed diabetes and preoperative euglycaemia generally had worse 1 yr mortality than those without diabetes at the same BG (e.g. odds ratio (OR) [95% confidence interval (CI)] of 1.27 (1.06, 1.53) at 6 mmol litre\(^{-1}\) (108 mg dl\(^{-1}\)), P = 0.003). Conversely, hyperglycaemic patients with diagnosed diabetes displayed a significantly lower 1 yr mortality than hyperglycaemic patients without diabetes [OR (95% CI) of 0.58 (0.44, 0.77) at 12 mmol litre\(^{-1}\) (216 mg dl\(^{-1}\)), P < 0.001].

**Conclusions.** For elective non-cardiac surgery, preoperative hyperglycaemia should be given greater consideration in patients without diabetes than in those with diagnosed diabetes.

**Keywords:** anaesthesia, general; diabetes mellitus; general surgery; hyperglycaemia; mortality

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Current data offer no guidance on whether an elective procedure should be cancelled in the light of a given level of hyperglycaemia. The lack of guidance stems in part from the fact that the association between preoperative blood glucose (BG) concentration and postoperative complications after non-cardiac surgery is not very clear. In non-cardiac surgery patients, preoperative BG levels above 11.1 mmol litre\(^{-1}\) (200 mg dl\(^{-1}\)) have been shown to be associated with a 2.1-fold higher risk in overall 30 day mortality and a four-fold higher risk of 30 day cardiovascular mortality. Hyperglycaemia was associated with a four-fold increased risk of pulmonary embolism (PE) in a small study of patients undergoing total joint replacement. Preliminary results were presented at the American Society of Anesthesiologists Annual Meeting, October 18, 2010, in San Diego, CA, USA.

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However, these studies were limited; for they evaluated only particular outcomes (PEU and 30 day mortality) in specific non-cardiac surgery subpopulations. Moreover, no data are available on the association between preoperative hyperglycaemia and serious postoperative complications and 1 yr mortality in a large cohort of patients undergoing different non-cardiac surgical procedures.

In the intensive care unit (ICU) setting, the effect of BG concentrations on outcomes appears to be dependent on diabetic status. Hyperglycaemia upon admission to the ICU has been shown to be an independent risk factor for in-hospital mortality only in patients without diabetes. Hyperglycaemia during the ICU stay was associated with significantly increased ICU mortality in patients without, compared with those with, diabetes mellitus, suggesting that hyperglycaemia may bear different clinical and biological implications in patients depending on their chronic metabolic status. Furthermore, a meta-analysis of two randomized trials showed reduced mortality with intensive insulin therapy in ICU patients was evident only in patients without a history of diabetes mellitus. However, in elective non-cardiac surgery, the impact of a patient’s diabetes diagnosis status on the association between preoperative glucose concentrations and postoperative outcomes and mortality has not been investigated.

We tested the hypotheses that in elective non-cardiac surgery patients, preoperative BG concentration is related to postoperative in-hospital outcomes and to 1 yr mortality, and that this relationship is more pronounced in patients without a diagnosis of diabetes mellitus.

**Methods**

Data were extracted with the Cleveland Clinic Institutional Review Board’s approval of the Anaesthesiology Institute’s Perioperative Health Documentation System for quality improvement purposes and for research on patients who present for non-cardiac surgery. The need for informed consent was waived. Data were aggregated from the electronic anaesthesia information system and hospital electronic medical records (EMR). Supplemental patient characteristics and clinical data in other institutional databases were imported into the registry either manually or through computer interfaces. Data validations were built into the registry to ensure the quality of data.

**Selection and description of participants**

The studied population was defined as patients undergoing elective non-cardiac surgery at our institution between January 2005 and November 2009, and included only the most recent operation per patient (Table 1). Patients were excluded if data were unavailable for the specified type of surgery or preoperative glucose concentration measurement. Patients with American Society of Anesthesiologists Physical Status (ASA PS) of > IV were also excluded.

**Technical information**

Glucose concentrations were measured by the central laboratory at the time of the preoperative evaluation (as a part of a basic or complete metabolic panel) in patients who had significant past medical history, including diabetes, undergoing surgery of more than low risk, or both. Moreover, in patients with a diabetes diagnosis, glucose concentrations were measured immediately before operation by the point-of-care testing using the Accu-Chek Inform system (Roche Diagnostics, Indianapolis, IN, USA). Each Accu-Check device was checked in three dimensions (linearity, inter-method (lab vs meter), and meter–meter) and used only when acceptable results on all three metrics were found. Additionally, calibrations with low and high controls were performed daily to ensure continued high performance. Glucose measurement included in the analysis was the last value available before surgery documented in the EMR for a given patient. No glucose concentration measurements performed after the induction of anaesthesia for surgery was included. The history of diabetes mellitus was screened for as follows: a Health Quest system which is an online system of patients’ self-reporting is required to be completed by all surgical candidates and validated by a surgical team member. Also a history and physical examination is mandated to be completed within 30 days of surgery. Patients were considered diagnosed with diabetes if they had a history of either type 1 or type 2 diabetes, and/or receiving insulin or oral hypoglycaemic medications.

During the time of the study, the target ranges for BG control in the hospital were as follows: in the recovery room, < 11.1 mmol litre
superscript(1) (200 mg dl
superscript(1)), whereas in the ICU, it was 3.9–7.2 mmol litre
superscript(1) (70–130 mg dl
superscript(1)) for the first 2 yr, and 4.4–6.7 mmol litre
superscript(1) (80–120 mg dl
superscript(1)) for the last 3 yr; whereas on the regular nursing wards, it was 3.9–8.3 mmol litre
superscript(1) (70–150 mg dl
superscript(1)).

In-hospital morbidity outcomes were identified by ICD-9 codes for postoperative complications. In addition, using laboratory measurements, we identified patients with postoperative myocardial infarctions (for details, see Table 2, second column). One year mortality was determined through searching hospital EMR and the Social Security Death Index through mid-2011.

**Statistical analysis**

First, a preliminary analysis was undertaken to study the relationship between preoperative BG concentrations and haemoglobin A1c (HbA1c) values, among those who had HbA1c measured within 90 days before the date of surgery. For this preliminary analysis, we used quantile regression. Restricted cubic splines were used to model potential nonlinear relationships.

To evaluate if preoperative BG concentration was related to the incidence of each endpoint, we used logistic regression models. Using a model without covariates, we first estimated for a given outcome its crude (unadjusted) incidence as a function of preoperative glucose concentration. Natural cubic splines with five degrees of freedom were used to model
potential non-linearities in the incidence function (and for any continuous predictors used in the logistic regression models described henceforth). After estimation of the crude incidence function, we developed a multivariable model which estimated the incidence function after adjusting for potential confounding variables. These potential confounding variables are listed in Table 1.

Before multivariable modelling, a single approximate Bayesian bootstrap imputation was used to impute missing potential confounder values (because only three patients had a history of cerebrovascular or transient ischaemic attack, we combined this variable with the history of carotid disease for modelling purposes). The null hypothesis of no relationship between pre-operative glucose and the outcome was evaluated within both the unadjusted and potential confounder-adjusted models using the Wald $\chi^2$ tests.

Since certain surgeries were represented by too few patients to accommodate direct adjustment (i.e. small cell sizes), we adjusted for the type of surgery as follows: first, we aggregated patients’ primary procedure into one of 244 categories of the US Agency for Healthcare Research and Quality Clinical Classifications Software. Next, three senior anaesthesiologists (B.A., J.F., and M.A.) independently rated each of these 244 categories from 0 to 10 on a scale of surgical risk. The mean of the three raters’ estimates of surgical risk was then used for adjustment in our multivariable models.

For the second hypothesis, regarding the differences between patients with and without a history of diabetes mellitus,

<table>
<thead>
<tr>
<th>% Missing</th>
<th>Factor</th>
<th>All patients $(n = 61,536)$</th>
<th>Patients without diabetes diagnosis $(n = 51,809)$</th>
<th>Patients with diabetes diagnosis $(n = 9,727)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.6</td>
<td>BG (mmol litre$^{-1}$)</td>
<td>5.2 (4.7, 6.1)</td>
<td>5.1 (4.6, 5.7)</td>
<td>7.0 (5.6, 9.5)</td>
</tr>
<tr>
<td></td>
<td>BG (mg dl$^{-1}$)</td>
<td>94 (84, 110)</td>
<td>92 (83, 103)</td>
<td>126 (100, 171)</td>
</tr>
<tr>
<td></td>
<td>Age (yr)</td>
<td>57.3 (15.5)</td>
<td>56.3 (15.8)</td>
<td>63.0 (12.9)</td>
</tr>
<tr>
<td></td>
<td>Male gender</td>
<td>47.3%</td>
<td>46.5</td>
<td>51.7</td>
</tr>
<tr>
<td></td>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Caucasian</td>
<td>84.4%</td>
<td>85.6</td>
<td>77.9</td>
</tr>
<tr>
<td></td>
<td>African American</td>
<td>11.9%</td>
<td>10.7</td>
<td>18.0</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>3.7%</td>
<td>3.7</td>
<td>4.1</td>
</tr>
<tr>
<td></td>
<td>Year of surgery</td>
<td>2007.1 (1.3)</td>
<td>2007.1 (1.3)</td>
<td>2007.1 (1.3)</td>
</tr>
<tr>
<td></td>
<td>Body mass index (kg m$^{-2}$)</td>
<td>28 (24, 33)</td>
<td>27 (24, 32)</td>
<td>31 (27, 37)</td>
</tr>
<tr>
<td>7.9</td>
<td>ASA Physical Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>4.2%</td>
<td>5.0</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>43.5%</td>
<td>48.3</td>
<td>18.0</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>46.8%</td>
<td>42.5</td>
<td>69.9</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>5.4%</td>
<td>4.2</td>
<td>11.9</td>
</tr>
<tr>
<td></td>
<td>Cancer</td>
<td>29.3%</td>
<td>29.1</td>
<td>30.3</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>49.0%</td>
<td>43.3</td>
<td>79.6</td>
</tr>
<tr>
<td></td>
<td>Coronary artery disease</td>
<td>13.2%</td>
<td>10.6</td>
<td>27.2</td>
</tr>
<tr>
<td></td>
<td>History of CABG</td>
<td>4.9%</td>
<td>3.8</td>
<td>10.8</td>
</tr>
<tr>
<td></td>
<td>History of PCI</td>
<td>5.2%</td>
<td>4.3</td>
<td>10.0</td>
</tr>
<tr>
<td></td>
<td>Myocardial infarction</td>
<td>5.5%</td>
<td>4.4</td>
<td>11.0</td>
</tr>
<tr>
<td></td>
<td>Congestive heart failure</td>
<td>4.3%</td>
<td>3.1</td>
<td>10.7</td>
</tr>
<tr>
<td></td>
<td>Ventricular arrhythmia</td>
<td>1.3%</td>
<td>1.1</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td>Cerebrovascular attack/TIA</td>
<td>0.0%</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Carotid disease</td>
<td>0.1%</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>Liver disease</td>
<td>2.4%</td>
<td>1.7</td>
<td>5.9</td>
</tr>
<tr>
<td></td>
<td>COPD</td>
<td>10.1%</td>
<td>9.5</td>
<td>13.3</td>
</tr>
<tr>
<td>56.7</td>
<td>Smoker</td>
<td>28.3%</td>
<td>29.6</td>
<td>21.1</td>
</tr>
<tr>
<td>1.5</td>
<td>Deep vein thrombosis</td>
<td>1.4%</td>
<td>1.2</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>Serum haematocrit (%)</td>
<td>40.8 (4.8)</td>
<td>41.1 (4.6)</td>
<td>39.3 (5.3)</td>
</tr>
<tr>
<td></td>
<td>Serum creatinine $&gt;176.8;\mu$mol litre$^{-1}$ ($&gt;2;mg;dl^{-1}$)</td>
<td>3.7%</td>
<td>2.9</td>
<td>7.9</td>
</tr>
<tr>
<td></td>
<td>Surgical risk score#</td>
<td>4.1 (1.6)</td>
<td>4.1 (1.7)</td>
<td>4.2 (1.6)</td>
</tr>
</tbody>
</table>
Table 2  Summary of complications comprising the in-hospital composite outcome. CKMB, creatine kinase myocardial band; TnT, cardiac troponin T

<table>
<thead>
<tr>
<th>Complication</th>
<th>Description</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality</td>
<td></td>
<td>298 (0.48)</td>
</tr>
<tr>
<td>Neurological complications</td>
<td>Nervous system complications, anoxic brain damage, cerebral hypoxia, stroke</td>
<td>387 (0.63)</td>
</tr>
<tr>
<td>Cardiac complications</td>
<td>Cardiac arrest, cardiac insufficiency, cardiorespiratory failure, heart failure, myocardial infarction (postoperative CKMB $\geq 4.0%$ and CK $&gt; 220$ unit litre$^{-1}$ or postoperative cardiac TnT $&gt; 0.1$ ng ml$^{-1}$)</td>
<td>1492 (2.42)</td>
</tr>
<tr>
<td>Pulmonary and respiratory complications</td>
<td>Pneumothorax, PE/infarction, adult respiratory distress syndrome, pulmonary oedema, acute respiratory insufficiency, shock lung, tracheostomy complications, transfusion-related acute lung injury</td>
<td>1737 (2.82)</td>
</tr>
<tr>
<td>Infectious complications</td>
<td>Ventilator-associated pneumonia, Mendelson’s syndrome, pneumonia/aspiration, sepsis, septicemia, other postoperative infections</td>
<td>1362 (2.21)</td>
</tr>
<tr>
<td>Urinary complications</td>
<td>Urinary tract stoma, internal anastomosis and bypass of urinary tract, oliguria/anuria, acute renal failure/insufficiency, acute tubular necrosis</td>
<td>748 (1.22)</td>
</tr>
<tr>
<td>Haemorrhagic complications</td>
<td>Haemorrhage, haematoma, seroma</td>
<td>1626 (2.64)</td>
</tr>
<tr>
<td>Wound disruption</td>
<td>Dehiscence of operation wound, disruption of suture materials or other closure method, rupture of operation wound</td>
<td>325 (0.53)</td>
</tr>
<tr>
<td>Composite outcome</td>
<td>One or more of the above complications</td>
<td>6100 (9.91)</td>
</tr>
</tbody>
</table>

Results

Data from 75 654 ASA PS I–IV patients undergoing elective non-cardiac surgery at our institution between January 2005 and November 2009 were available. Excluded were patients with missing preoperative BG concentration ($n=12 060$) and also patients with missing data on type of surgery ($n=1306$) and patients with missing preoperative medications data ($n=752$) (see flow chart, Fig. 1). The resulting sample comprised 61 536 patients. Patient and pre-surgical characteristics are summarized in Table 1. The overall median (first quartile, third quartile) serum glucose concentration for the sample was 5.2 (4.7, 6.1) mmol litre$^{-1}$ [94 (84, 110) mg dl$^{-1}$]; the median glucose for the patient with diabetes diagnosis was 7.0 (5.5, 9.5) mmol litre$^{-1}$ [126 (100, 171) mg dl$^{-1}$] and 5.1 (4.6, 5.7) mmol litre$^{-1}$ [92 (83, 103) mg dl$^{-1}$] for patients without diabetes diagnosis. Of the 51 809 patients without diagnosed diabetes, 1616 (3.1%) had a BG value $> 8$ mmol litre$^{-1}$ (144 mg dl$^{-1}$) and 390 (0.8%) had a BG $> 11$ mmol litre$^{-1}$ (198 mg dl$^{-1}$).

There were 3929 patients who had available HbA1c values measured within 90 days before their operation. Quantile regression curves estimating from these cases the 10th percentile, first quartile, median, third quartile, and 90th percentile of serum glucose as a function of HbA1c are shown in Supplementary material, Appendix S1.

Individual outcomes comprising the composite in-hospital outcome were uniformly represented (incidences of 1–3%) except for mortality (0.5%) and wound disruption (0.5%) (Table 2). Overall, the crude incidence (Bonferroni-adjusted 95% confidence interval (CI)) was 9.91% (9.65%, 10.19%). The crude incidence was significantly related to preoperative BG concentration ($P<0.001$, Fig. 2a), ranging from $\sim 8$–11% for patients with glucose concentration of 4–6 mmol litre$^{-1}$ (72–108 mg dl$^{-1}$) to $\sim 12$–16% for those with glucose concentration above 7 mmol litre$^{-1}$ (126 mg dl$^{-1}$). However, the incidence was not significantly related to preoperative BG concentration after adjustment for covariables ($P=0.40$, Fig. 2b).

The crude incidence (Bonferroni-adjusted 95% CI) of 1 yr mortality was 5.41% (5.24%, 5.60%). This crude incidence was significantly related to preoperative BG concentration, reaching a minimum of 3.5% at a concentration of 4.7 mmol litre$^{-1}$ (85 mg dl$^{-1}$) and increasing to $> 9$% for preoperative BG levels above 10 mmol litre$^{-1}$ (180 mg dl$^{-1}$) (Fig. 2c). After covariable adjustment, a statistically significant relationship remained ($P<0.001$, Fig. 2c).

There were 9727 patients (15.8%) who were previously diagnosed as having diabetes mellitus. The crude incidence of the composite in-hospital outcome for patients with diabetes was $\sim 15$% regardless of preoperative BG level, whereas for
patients without diabetes, the incidence ranged from 7–9% for patients with glucose concentration of 3.3–5.5 mmol litre\(^{-1}\) (60–100 mg dl\(^{-1}\)) to 13–15% for patients whose preoperative BG concentration was above 8 mmol litre\(^{-1}\) (144 mg dl\(^{-1}\)) (Fig. 3A). However, after adjustment for covariates, we found that the relationship between preoperative BG and the probability of postoperative complication did not significantly differ between patients with and without diabetes mellitus (\(P=0.09\); Fig. 3B).

The crude incidence of 1 yr mortality was estimated to be \(\sim 8–11\%\) across the range of preoperative BG concentrations for patients with diabetes, except for those with concentrations 3.3–5.0 mmol litre\(^{-1}\) (60–90 mg dl\(^{-1}\)), where the incidence was \(\sim 10–14\%\) (Fig. 3c). The crude incidence for patients without diabetes was strongly related to preoperative BG, ranging from 3–5% for patients with glucose concentrations of 3.3–5.5 mmol litre\(^{-1}\) (60–100 mg dl\(^{-1}\)) to \(>12\%\) for patients with preoperative BG above 12 mmol litre\(^{-1}\) (216 mg dl\(^{-1}\)). After adjusting for covariates, significantly different relationships between patients with and without diabetes mellitus remained (\(P<0.001\); Fig. 3b). The generalized Wald test \(P\)-values were equal to 0.33 for the patients with diagnosed diabetes and \(<0.001\) for the patients without, indicating no significant relationship between glucose concentration and 1 yr mortality for patients with diagnosed diabetes, but a strong relationship among patients without that diagnosis.

Adjusted OR curves comparing patients with and without diabetes mellitus on both primary endpoints are shown in Figure 4 and summarized numerically in the Supplementary material, Appendix S2. The adjusted OR for the composite outcome was generally not significantly different from 1.0 over the range of preoperative BG concentrations. On the other hand, the adjusted OR for 1 yr mortality was significantly and non-linearly related to preoperative BG. Based on the pointwise confidence bounds in Figure 4, patients with diagnosed diabetes and with preoperative BG of 3.6–4.9 mmol litre\(^{-1}\) (65–88 mg dl\(^{-1}\)) had significantly increased odds of mortality compared with those without diabetes diagnosis. This OR declined as preoperative BG increased. Patients with diabetes and preoperative BG \(>8.5\) mmol litre\(^{-1}\) (153 mg dl\(^{-1}\)) had significantly lower odds of mortality than those without diabetes.

**Discussion**

We evaluated the statistical relationship between preoperative BG concentration and postoperative in-hospital outcomes and also 1 yr mortality, and the impact of a diagnosis of diabetes
mellitus on these relationships, in a very large cohort of patients undergoing elective non-cardiac surgery. In our cohort, preoperative hyperglycaemia was directly related to poor postoperative in-hospital outcomes and 1 yr mortality in the univariable model for all patients. In the multivariable model, the independent association between hyperglycaemia and 1 yr mortality, but not in-hospital composite outcome, remained significant. A preoperative diagnosis of diabetes mellitus significantly altered these associations. For a given level of hyperglycaemia, patients with diabetes mellitus had a lower risk of 1 yr mortality, whereas for low to normal pre-operative BG concentrations, patients with diabetes mellitus diagnosis had a higher risk of death compared with those without diabetes.

In other words, the relationship between glucose and 1 yr mortality was weak (a flat curve), if patients were already diagnosed with diabetes. Conversely, if patients did not have diabetes diagnosis, there was a clear increasing rate of 1 yr mortality once glucose concentration increased. That is not to say that diabetic status is not important. If one compared patients without diabetes and normal glucose concentrations (i.e. true negatives) against those with diagnosed diabetes with normal glucose concentrations—so a situation where missed diabetes diagnosis would not be an issue—mortality is higher among patients with diagnosed diabetes.

Our results on in-hospital outcomes appear at variance with results from prior studies performed on non-cardiac surgery patients. Preoperative hyperglycaemia (>11.1 mmol litre⁻¹ (200 mg dl⁻¹)) was associated with a four-fold increased risk of PE in a small study of patients undergoing total major joint replacement.² In non-cardiac, non-vascular surgery patients, preoperative BG levels >11.1 mmol litre⁻¹ (200 mg dl⁻¹) have been associated with a 2.1-fold increased risk in overall 30 day mortality.¹

An intriguing finding of our current study is that preoperative BG was independently related to long-term outcomes (1 yr mortality) and not to poor short-term in-hospital outcomes. A possible explanation for this finding is that preoperative hyperglycaemia reflects a chronic risk for death independent of the surgery. Another explanation may lie in the pro-inflammatory effect of hyperglycaemia, which could affect 1 yr mortality, especially given that HbA1c percentage generally increased with increasing BG concentrations—indicating a chronic process. BG concentration has been shown to be independently related to C-reactive protein (CRP) levels (a marker of inflammation) in healthy subjects. CRP levels increased continuously across the spectrum of fasting BG concentrations, even within the normal range.¹¹ However, the impact of such a pro-inflammatory response may not be clinically evident immediately. Milazzo and colleagues¹² identified preoperative

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**Fig 2** (A–D) Crude and covariable-adjusted incidence of composite in-hospital morbidity/mortality and 1 yr all-cause mortality for all patients. Estimates given as pointwise 95% confidence bands (confidence bands adjusted for simultaneous comparisons using the Bonferroni method). P-values from the Wald tests assessing the relationship between baseline glucose and each outcome (statistical significance after the Bonferroni correction for simultaneous inference on two outcomes given by asterisks). Covariable-adjusted estimates are adjusted for all factors given in Table 1. To convert to mg dl⁻¹, multiply the mmol litre⁻¹ value by 18.
elevated concentrations of CRP as a predictor of recurrent ischaemia up to 6 yr after operation.

In our study, patients with diagnosed diabetes mellitus and preoperative BG > 8.5 mmol litre\(^{-1}\) (153 mg dl\(^{-1}\)) had significantly lower odds of mortality than those without diabetes diagnosis who had similar preoperative BG concentrations. On the other hand, patients with diagnosed diabetes mellitus and preoperative BG within 3.6–4.9 mmol litre\(^{-1}\) (65–88 mg dl\(^{-1}\)) had a higher 1 yr mortality compared not only with those without diabetes diagnosis with similar levels, but also with those with diagnosed diabetes and higher preoperative BG concentrations.

Patients without diabetes diagnosis who are hyperglycaemic probably have diabetes albeit undiagnosed and thus untreated. Early diagnosis and treatment of diabetes may lessen its burden and delay its associated complications.\(^{13,14}\) In an earlier study, we showed that 21% of non-cardiac surgery patients without a diagnosis of diabetes are hyperglycaemic and more than half of those have undiagnosed diabetes.\(^{15}\) Similar findings have been also reported by Hatzakorzian and colleagues.\(^{16}\) While previously fasting glucose concentrations were used to diagnose diabetes,\(^{16}\) more recently, HbA1c has been advocated to be used as a screening test to diagnose diabetes.\(^{17,18}\)

A confounding factor, however, is that clinicians may have been more inclined to monitor and eventually to treat abnormal perioperative BG levels in patients with a diagnosis of diabetes, but not those without that diagnosis. This differential management is in part explained by clinicians’ belief that sensitivity to i.v. insulin varies depending on prior treatment with insulin.\(^{19}\) In addition, anaesthesiologists are concerned about hypoglycaemia because symptoms are masked by general anaesthesia and sedation.\(^{20}\) Hence, clinicians are more reluctant to treat hyperglycaemia in patients without diabetes diagnosis; because aggressive insulin protocols in cardiac surgery and in critical care patients have been shown to evoke considerably high rates of hypoglycaemia.\(^{21–24}\)

Such a different treatment strategy in patients with and without diabetes diagnosis may have introduced a bias in our observations. Furthermore, patients with preoperative hyperglycaemia who are not diagnosed with diabetes likely had no access to quality general medical care (or poor compliance with maintaining following up with accessible general medical care). One can certainly make the argument that the higher the degree of preoperative glucose concentration, the worse the degree of poor medical care. Needless to say, poor medical care would be expected to be a major determinant of subsequent outcomes.
Likewise, Egli and colleagues observed increased mortality with increasing mean BG concentrations in ICU patients without diabetes mellitus compared with those with diabetes mellitus. Graham and colleagues showed that in the ICU, survivors with diagnosed diabetes had higher maximum glucose concentrations than did non-survivors without a diagnosed diabetes. Also, in their cohort, the unadjusted mortality rates were significantly higher for patients with diabetes than for those without diabetes for a maximum glucose below 7.2 mmol litre\(^{-1}\) (129 mg dl\(^{-1}\)), but the opposite was the case for a maximal BG level of 9.0 mmol litre\(^{-1}\) (162 mg dl\(^{-1}\)).

Cumulatively, the data may suggest that expected benefits, if any, of tight glucose control may be determined by the pre-morbid diabetes diagnosis status. More research is needed to improve our understanding of the complex association between BG and outcome in non-cardiac surgery patients, and randomized controlled studies are required. For such studies, our data may help to define optimal BG target levels for patients with and without diabetes. It should be highlighted as mentioned above that some investigations of tight glucose control in the ICU reported a higher risk of hypoglycaemia. Current recommendations thus favour more moderate targets in the range of 7.8–10.0 mmol litre\(^{-1}\) (140–180 mg dl\(^{-1}\)).

Our study had some limitations. First, this was a retrospective review of a hospital database. As such, there remains the potential of unavailable data confounding the relationships of interest. Specifically, data on intraoperative and postoperative glucose management were unavailable. Accurate study of the relationships of interest while taking into account intraoperative and postoperative glucose management was impossible because this information was available for only a limited number of patients and such information is difficult to obtain in retrospect. Such analysis would require a large prospective clinical study. Secondly, we excluded patients for whom a preoperative BG determination was unavailable, which may have introduced selection bias. Thirdly, the generalizability of our results is limited by the fact that our cohort is from a single institution, and appears to be composed of higher risk patients. Indeed, approximately half of our patients were ASA PS III. Moreover, our hospital had certain targets (as mentioned above) for in-hospital glycaemic management that may have influenced the results. Finally, determination of in-hospital outcomes for our study relied on a search of discharge diagnosis ICD-9-CM codes. Although these codes are susceptible to under-reporting, we nevertheless believe that the discharge diagnosis codes are highly sensitive in determining which patients experience major in-hospital events. Moreover, there is no reason to believe that possible under-reporting could be associated with diabetes diagnosis status or with ascertainable preoperative glucose levels, to the extent that it would introduce bias in our estimates. Finally, the second primary outcome, 1 yr mortality, is a robust endpoint which is not affected by possible bias in the use of the ICD-9-CM codes.

In summary, in elective non-cardiac surgery for a relatively high-risk patient population, 1 yr mortality—but not the studied composite in-hospital morbidity endpoint—was
Independently associated with differences in preoperative BG concentration. Patients without diabetes diagnosis and with preoperative hyperglycaemia showed higher 1 yr mortality than those with diabetes with the same level of preoperative hyperglycaemia. Patients with diagnosed diabetes and pre-operative glucose concentrations in the lower euglycaemic range had a higher 1 yr mortality than those without diabetes with the same levels of preoperative euglycaemia.

Thus, clinicians should consider checking preoperative glucose concentration and screen for hyperglycaemia in patients without the diagnosis of diabetes as it is the case in those with diabetes diagnosis. On making the decision whether to proceed with or delay elective non-cardiac surgery, hyperglycaemia should be considered more so in patients without a diabetes diagnosis compared with those with diabetes. Further research is required to confirm the above findings and determine whether a specific perioperative glucose management strategy can improve outcomes after non-cardiac surgery in patients with and without diabetes mellitus.

**Supplementary material**

Supplementary material is available at *British Journal of Anaesthesia* online.

**Authors’ contributions**

B.A.: design of the study, data retrieval, design and interpretation of the analysis, manuscript drafting, manuscript critical review, and editing; J.K.: design of the study, data retrieval, and manuscript critical review; J.A.: design of the study, critical review, and editing; J.E.D.: design of the study, data processing, statistical analysis, manuscript drafting, critical review, and editing; E.C.: data retrieval, manuscript drafting, critical review, and editing; J.F.: design of the study and manuscript critical review; M.A.: data retrieval, manuscript drafting, critical review, and editing; R.Z.: design of the study, manuscript drafting, critical review, and editing; G.V.B.: design of the study, manuscript drafting, critical review, and editing.

**Declaration of interest**

None declared.

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