Clinical Nutrition 38 (2019) 1765–1772

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Determinants, time trends and dynamic consequences of postoperative hyperglycemia in nondiabetic patients undergoing major elective abdominal surgery
A prospective, longitudinal, observational evaluation

Luca Gianotti [a, *], Marta Sandini [a], Roberto Biffi [b], Daniele Marrelli [c], Andrea Vignali [d], Sebastian K.S. Begg [e], Davide P. Bernasconi [f]

[a] School of Medicine and Surgery, Milano-Bicocca University, Department of Surgery, San Gerardo Hospital, Monza, Italy
[b] Department of Gastrointestinal Surgery, European Institute of Oncology, Milan, Italy
[c] Department of Medicine, Surgery and Neurosciences, Unit of Surgical Oncology, University of Siena, Siena, Italy
[d] Department of Gastrointestinal Surgery, San Raffaele Scientific Institute, Vita e Salute University, Milan, Italy
[e] Pancreatic Biology Laboratory, Department of Surgery, Massachusetts General Hospital, Boston, MA, United States
[f] Centre of Biostatistics for Clinical Epidemiology, School of Medicine and Surgery, Milano-Bicocca University, Monza, Italy

ARTICLE INFO

Article history:
Received 16 May 2018
Accepted 24 July 2018

Keywords:
Hypergycemia
Surgery
Infection
Trend
Joint regression model
Outcomes

SUMMARY

Background & aims: In retrospective studies an indisputable causal relationship between hyperglycemia and postoperative infections cannot be entirely disclaimed. We aimed investigate whether the time trends of blood glucose levels in the perioperative period could be a determinant of surgery-related infections.

Methods: Adult patients without diabetes who were candidates for elective major abdominal operation were prospectively enrolled in a longitudinal, observational multicenter study. The blood glucose level was measured every 6 h for 3 days. We calculated the association between blood glucose (BG) levels and the risk of occurrence of surgery-related infections using a joint regression modeling for longitudinal and time-to-event outcomes which accounts for the effect of other risk factors.

Results: Between January 2016 and November 2017, we obtained 6078 BG measures distributed on different time-points in 452 patients. There was a nearly 3-fold increased risk of having hyperglycemia, defined as BG $\geq$ 125 mg/dL, if the BG level at admission was >100 mg/dL (OR = 2.986, P < 0.001).The hazard of infection for each 10 mg/dL increase of BG levels over time was marginal (HR = 1.065, P = 0.045). The calculated risk of having an infection was 9.6% for BG going from 110 mg/dL during surgery to 84 mg/dL at the end of day 3, 10.5% for BG decreasing from 140 to 114, 11.8% for BG decreasing from 180 to 154 and 24.5% for BG increasing from 80 to 145, 24.7% for BG increasing from 110 to 175, and 25.4% for BG increasing from 140 to 205.

Conclusions: The time trends of BG – as opposed to the absolute concentration –are major determinants of the risk of postoperative infections.

1. Introduction

Several large cohort studies [1–6] propose perioperative hyperglycemia as a significant determinant of surgery-related infections. However, an indisputable causal relationship between these two events cannot be entirely established for several reasons. First, for the retrospective nature of the above studies. Second, in most of these studies only a single assessment of blood glucose (BG) level (often the highest) at different time points (preoperative, day of operation, postoperative days) was gathered in an indeterminate period of the day despite the well-defined intra-day fluctuation of glycemia [7,8]. Third, none of these studies considered the potential interference between BG and confounders, such as corticosteroids administration, intravenous dextrose infusion, and intake of oral carbohydrates

* Corresponding author. Department of Surgery, San Gerardo Hospital, Via Pergolesi 33, 20900, Monza, Italy. Fax: +39 039 2333652.
E-mail address: luca.gianotti@unimib.it (L. Gianotti).

https://doi.org/10.1016/j.clnu.2018.07.028
0261-5614/

[9,10]. Therefore, the determinants of perioperative hyperglycemia and the effect of BG variation over time and the impact of persistent hyperglycemia or spontaneous normalization of BG levels during and after surgery on outcomes are largely unexplored.

As patients receiving treatment for hyperglycemia have a lower risk of infection to those with high BG levels [5,6,11], a tight and rigid monitoring of BG levels is recommended to identify potentially dangerous hyperglycemia episodes and to promptly treat patients with and without history of diabetes [12–16]. This vigilant glycemic monitoring requires repeated BG measurements which are time-consuming for care providers and uncomfortable for patients. These limitations reduce the applicability and postoperative hyperglycemia, with its potentially harmful consequences, may be largely underestimated in patient without diabetes or low-risk patients [15–17].

Developing a better understanding of the kinetics of perioperative glucose metabolism and identifying determinants of hyperglycemia may help define subgroups of at high-risk. This risk stratification could help allocate resources to patients who would benefit most from strict BG monitoring.

The primary aim of this study was to evaluate whether the time trends and fluctuation of BG levels in the perioperative period could be a determinant of surgical morbidity. Specifically, we assessed the potential association between BG trends over time and the risk of surgery-related infections at each time point by employing a joint regression model for continuous, longitudinal, and time-to-event outcomes adjusted for other perioperative risk factors.

2. Methods

2.1. Study design and participants

We designed as a prospective, longitudinal, observational, multicenter study to be performed at 4 Italian academic tertiary hospitals. Eligible for participation were adult (age >18 years) and candidates for elective major abdominal operation (duration > 2 h) for surgical diseases of the gastrointestinal and genito-urinary tract. The exclusion criteria were as follows: fasting glucose level >125 mg/dL, type 1 and 2 diabetes, any ongoing or history of pancreatic disease, American Society of Anesthesiologists (ASA) physical status classification > 3, preoperative weight loss >10% of the usual body weight in the previous 6 months, ongoing corticosteroid therapy, and any recent history of bacterial infection requiring antibiotic therapy within the previous 3 months.

After the patients were screened according to the inclusion and exclusion criteria, the selected patients or their legal representatives were asked to provide written informed consent. Afterward, the patients were enrolled in the study.

The Ethics Committee of San Gerardo Hospital, Monza, Italy approved the study as an amendment of the PROCY trial [10]. The study was later approved by the Ethics Committees of the other participating hospitals. Patient recruitment started on January 8th, 2016 and ended November 30th, 2017.

This trial was designed, managed, coordinated, and analyzed by the School on Medicine and Surgery of the Milano- Bicocca University at the Department of Surgery of San Gerardo Hospital, Monza, Italy. The coordinating center was responsible for centralized data collection, monitoring, and statistical analysis, and it received support from the Centre of Biostatistics for Clinical Epidemiology of Milano-Bicocca University.

2.2. Interventions

After recruitment, patients were instructed to consume a regular meal the evening before the operation and were allowed to drink water until 2 h prior to surgery. No other clear fluids, sweet beverages or any other type of oral solutions were permitted.

The capillary BG level was measured at the following time-points: at hospital admission (after 6 h of fasting), at arrival in the operating theatre, 1 h after abdominal incision, at the end of the operation, and every day after surgery at 6 and 12 AM, and at 6 and 12 PM for 3 consecutive days. To ensure consistency, all measurements were performed with the same instrument in all centers (Accu-Chek Inform II; Roche Diagnostic SpA, Monza, Italy). The instrument was calibrated with plasma glucose standards obtained from a centralized laboratory. Insulin was a given as *per protocol* when the BG level was >180 mg/dL, as recommended by the American Diabetes Association [18].

Mechanical bowel preparation, wound protectors, wound lavage, and subcutaneous suture were not employed. Hair removal technique and skin preparation were the same in all centres. Antibiotic prophylaxis was given according to the national guidelines. All patients received active warming with a heated blanket and a 38 °C intravenous balanced electrolyte fluid infusion during the surgical procedure. Core body temperature was monitored with a bladder catheter or an esophageal probe, and hypothermia was defined as a body temperature of <35.5 °C for more than 30 min. No corticosteroid administration was allowed during and after the operation.

After the operation patients were permitted to drink regular water at will from postoperative day (POD) 1, but no oral food of any type or other beverages until midnight of POD 2 were allowed. Patients were allowed natural food at will starting from day 3 after the operation.

Intravenous infusions consisted of balanced electrolyte solution according to fluid balance and clinical needs, and i.v. dextrose was not given to any patients for the first 3 days after surgery. Artificial nutrition (enteral and parenteral) was not prescribed unless patients could not resume oral intake within 7 days after the operation or patients experienced complications causing catabolism [19].

Data were collected on paper case report forms and were then transferred to an electronic database with double entry to ensure consistency of records. In case of missing or implausible data, queries were mailed to the participating centers to obtain integrations or corrections.

2.3. Outcomes

Hyperglycemia was defined as the occurrence of at least one intra- or post-operative measurement of BG > 125 mg/dL [4]. Infectious morbidity was defined as any of the following: superficial and deep wound infection, organ/space infection, urinary tract infection, pneumonia, sepsis, and septic shock. The determination of an episode of infection was based on *a priori* definition [10].

In all patients, C-reactive protein, white cell count and body temperature were determined routinely during the postoperative period. Procalcitonin plasma level was assessed only in patients with a suspected infection.

The assessors of infections were trained by the study coordinator to achieve concordance with respect to definitions. Each participating center had 2 independent outcome assessors. The assessors recorded the day and hour of the first clinical manifestation of any infectious complication.

Patients who exhibited a proven anastomotic dehiscence and all blood glucose data obtained from patients during the actual period of infection were excluded from the final analysis. In both cases, hyperglycemia could be the consequence – not the potential cause – of the infectious complication.

The occurrence of postoperative infection was assessed twice a day during hospitalization and for 30 days after the operation. Post-

discharge patient surveillance and follow-up involved weekly outpatient visits. Telephone interviews were also allowed for monitoring the health status of patients.

We also evaluated the potential pre- and intra-operative determinants of hyperglycemia and explored whether raising levels of BG were associated with an increased risk of developing infections.

We scored the severity of complications according to the Dindo-Clavien classification [20].

2.4. Statistics

Descriptive statistics of pre- and intra-operative factors were calculated using median with inter-quartile range for skewed continuous variables and number with percentages for categorical variables. The analysis was carried out stratifying patients in three groups: normoglycemia (all intra- and post-operative measurements < 125 mg/dL), mild hyperglycemia (all measures <160 mg/dL but at least one ≥ 125 mg/dL) and moderate hyperglycemia (at least one ≥ 160 mg/dL). The comparison between the three groups was performed using the Kruskal–Wallis test for continuous variables and the Fisher test or the Chi-squared test for categorical variables.

To quantify the association between intra and post-operative potential determinants of hyperglycemia we fitted a logistic regression model including the following covariates: age, sex, body mass index, BG level at admission >100 mg/dL (threshold identified by the Youden index), target organ (upper gastrointestinal or lower gastrointestinal or genitor-urinary tract), comorbidities (yes or no), laparoscopy (yes or no), cancer (yes or no), ASA score (3 or lower), clean surgery (yes or no), epidural analgesia (yes or no), blood loss, duration of surgery. A similar model was fitted including BG level at admission as a continuous variable in place of the dichotomized one.

To describe the overall risk of developing hyperglycemia and infection in the intra- and post-operative period we estimated the Kaplan–Meier cumulative incidence curves of the two end-points. Subsequently, we assessed the association between the longitudinal measurement of BG over time and the risk of developing an infection, adjusting for the possible confounding effect of pre- and intra-operative factors (age, sex, body mass index, BG level at admission, target organ, comorbidities, laparoscopy, cancer, ASA score, clean surgery, blood loss, duration of surgery). This analysis was performed using the "joint modelling of longitudinal and time-to-event outcomes" methodology [21]. The method simultaneously evaluates the impact of the covariates on the longitudinal outcome (though a mixed-effects model) and on the time-to-event outcome (through a hazard-based model) providing also a measure of the association in the form of a hazard ratio-between the two outcomes [22,23]. The main advantages of this method are the following. First, the evolution over time of the longitudinal variable is described using a (linear) mixed-effect model. Thus, the variable is continuously estimated over time and its values become available also for the time points were the measurement was not taken. In contrast, other methods (e.g. the time varying Cox model) rely on the "last observation carried forward" approach where the value of the longitudinal variable for a patient between two consecutive measurements is assumed constant and equal to the last observed value. Secondly, the model accounts for the random measurement error [24].

In particular, we used a linear random intercept and random slope model for the BG levels and a piecewise-exponential proportional hazards model for the time to infection. The estimated parameters were then used to make cumulative risk predictions of infections during the first month after surgery for a "paradigmatic" patient with BG levels according to 9 different linear profiles: A) decreasing trend starting from 110 mg/dL in the intraoperative to 84 mg/dL at the end of day 3; B) decreasing from 140 to 114; C) decreasing from 180 to 154; D) constant at 80; E) constant at 110; F) constant at 140; G) increasing from 80 to 145; H) increasing from 110 to 175; I) increasing from 140 to 205. With "paradigmatic" patient we mean an hypothetic subject with baseline characteristics equal to the average or the most frequent observed value in our sample. It is worth to note that the BG profiles considered were not derived as a linear interpolation of real values belonging to selected subgroup of patients from the study. They represent a linear approximation of possible trends observable in hypothetical new patients. The predictive ability of the model regarding the risk of event within the first post-operative month was computed using a time-dependent AUC index.

All the analyses were performed using the R software version 3.4.3 and in particular with the "JM" package [25].

3. Results

During the study period, 770 patients were screened for eligibility. After applying the exclusion criteria, 498 subjects were enrolled in the study. Two-hundred and seventy-two patients were excluded for the following reasons: past medical history of diabetes (n = 76), or pancreatic disease (n = 70), denied consent (n = 33), preoperative weight loss >10% (n = 30), fasting glucose level >125 mg/dL (n = 21), ASA >3 (n = 20), previous infections (n = 15), and ongoing corticosteroid therapy (n = 7). Forty-six patients were excluded due to anastomotic leak or because hyperglycemia occurred after the onset of infection, leaving 452 cases for the final analysis. In these patients, we obtained 6078 BG measures distributed among different time points of assessment with an average of 13.45 per subject.

The cumulative incidence of patients having at least one episode of hyperglycemia was 69.7% (315/452). Most of the episodes (72.7%; 229/315) of hyperglycemia occurred within 24 h. The overall 30-day infection rate was 16.1% (73/452).

The trends over time of intra- and post-operative BG is illustrated in Fig. 1.

The Kaplan–Meier curves of the cumulative risk of hyperglycemia and infection in time are shown in Fig. 2. As graphically

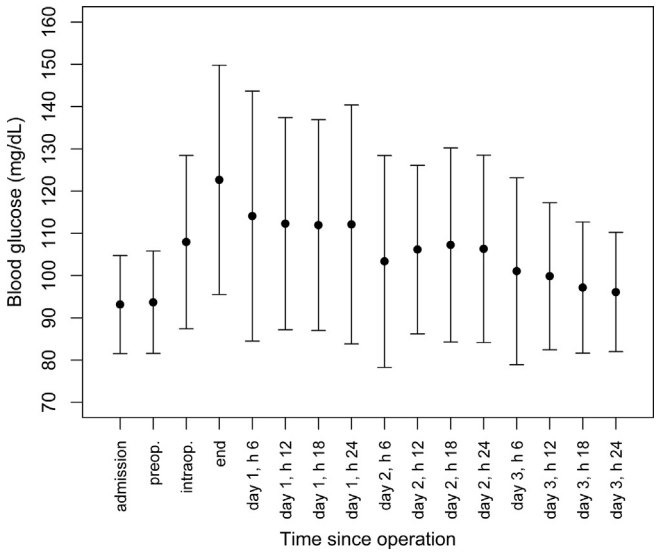

Fig. 1. Trends of blood glucose levels over time. Numbers are means ± standard deviations.

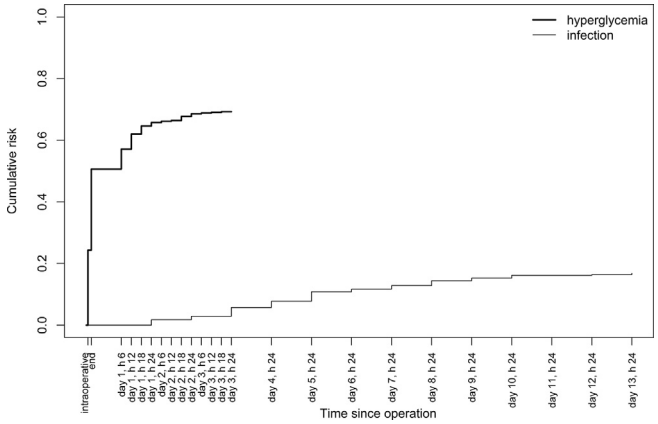

Fig. 2. Kaplan–Meier curves describing the cumulative risk of hyperglycemia and infection over time.

depicted, the occurrence of hyperglycemia preceded the clinical awareness of infections.

The baseline characteristics and the surgical details after stratification of the cohort into 3 groups are described in Table 1. Although the groups were not homogenous for several variables, the results of the multiple logistic regression model showed that the only significant risk factor for having at least one intra- or post-operative episode of hyperglycemia was the baseline BG level (Table 2). Notably, there was a nearly 3-fold increased risk of having intra- or post-operative hyperglycemia if the BG level at admission was >100 mg/dL compared to BG $\leq$ 100 mg/dL (OR = 2.986, 95% CI: 1.671–5.333, P < 0.001). According to the model, the risk of hyperglycemia increased by 28% for each increase of 10 mg/dL (OR = 1.283, 95%CI: 1.067–1.544, P = 0.008) when the baseline BG was considered as a continuous variable.

Table 3 summarizes the results of the "joint model" describing the estimated association between baseline covariates, BG levels over time, and the risk of infection. The likelihood of developing an infection increased 0.65% for each 10 mg/dL increase in BG over time. In addition to the kinetics and levels of BG, the magnitude of surgical stress (i.e. blood loss and duration of operation) and surgical field contamination significantly affected the risk of infection.

The "joint model" provided a means of estimating the cumulative risk of infection according to the increasing, decreasing or stable trends of BG over time (keeping the baseline covariates as constant and equal to normal values of a prototypical patient). Considering the overall risk in the month following surgery, we observed an increased risk of infection only in those patients who experienced an increase of BG levels unrelated to the mean BG (Fig. 3A–I).

The details and severity of infectious complication, graded per the Clavien-Dindo classification, are reported in the Supplementary Table 1. The median time (IQR) for onset of infection was 5.0 (3.7–8.0) days in the BG < 125 mg/dL group, 4.0 (3.0–6.0) days in the BG 125–160 mg/dL group and 4.0 (3.0–7.0) in the BG > 160 mg/dL group (p = 0.650).

The overall incidence of infections was 14.5% (20/137) in the BG < 125 mg/dL group, 16.6% (35/211) in the BG 125–160 mg/dL group and 18.2% (19/104) in the BG > 160 mg/dL group (P = 0.678). The group with BG > 160 mg/dL had significantly more abscesses and more severe infectious complications. The latter group was also

Table 1
Analysis of pre- and intra-operative factors according to blood glucose levels.

	Normoglycemia BG < 125 N = 137	Mild hyperglycemia 125 ≥ BG < 160 N = 211	Moderate hyperglycemia BG ≥ 160 N = 104	P value
Age, years	69.0 [59.0, 75.0]	70.0 [58.0, 74.0]	70.0 [54.5, 76.0]	0.843
Sex, male	80 (58.4)	117 (55.5)	55 (52.9)	0.707
Body mass index	25.0 [23.0, 27.3]	25.3 [23.1, 27.7]	25.3 [23.5, 27.7]	0.719
Fasting blood glucose at admission, mg/dL	89.0 [84.0, 98.0]	93.0 [84.0, 102.0]	95.0 [86.0, 104.0]	0.016
Hemoglobin, g/dL	13.0 [11.7, 14.6]	12.8 [11.5, 14.7]	12.9 [11.3, 14.4]	0.806
Albumin, g/dL	3.9 [3.6, 4.1]	3.8 [3.4, 4.0]	3.9 [3.7, 4.2]	0.277
Creatinine, mg/dL	0.90 [0.80, 1.02]	0.90 [0.75, 1.10]	0.90 [0.72, 1.08]	0.722
C-reactive protein, mg/L	0.65 [0.20; 1.63]	0.72 [0.23; 1.32]	1.31 [0.25; 2.91]	0.015
Number of comorbidities				0.240
0	51 (37.2)	87 (41.2)	48 (46.2)	
1	47 (34.3)	62 (29.4)	23 (22.1)	
2	24 (17.5)	47 (22.3)	23 (22.1)	
≥3	15 (10.9)	15 (7.1)	10 (9.6)	
Cancer	117 (85.4)	174 (82.5)	91 (87.5)	0.513
ASA physical status classification				0.626
1–2	99 (72.2)	159 (75.3)	80 (76.9)	
3	38 (27.8)	52 (24.7)	24 (22.1)	
Target organ for operation				0.853
Upper GI	41 (29.9)	64 (30.5)	34 (32.7)	
Lower GI	72 (52.6)	112 (53.3)	49 (47.1)	
Urology and gynecology	24 (17.5)	34 (16.2)	21 (20.2)	
Laparoscopy	49 (40.8)	85 (40.3)	40 (38.5)	0.717
Type of surgery				0.095
Clean	47 (34.3)	77 (36.5)	33 (31.7)	
Clean-contaminated	88 (64.2)	124 (58.8)	68 (65.4)	
Contaminated	2 (1.5)	20 (4.7)	3 (1.9)	
Epidural analgesia	60 (43.7)	95 (45.0)	45 (43.3)	0.612
Intraoperative hypothermia	3 (2.2)	4 (1.9)	8 (7.7)	0.029
Blood loss, mL	160 [150, 200]	155 [100, 250]	230 [150, 300]	<0.001
Duration of surgery, min	165 [140, 200]	170 [140, 210]	165 [145, 230]	0.631

Data as numbers (%) for categorical variables or median [IQR] for continuous variables.
BG: Blood glucose; Upper GI (stomach, liver, esophagus); Lower GI (colon, rectum); Urology and gynecology (kidney, prostate, bladder, uterus/ovary).
Fisher test (Chi-square test) p-value for categorical variables, Kruskal–Wallis test p-value for continuous variables.

Table 2
Multivariate logistic regression model performed to assess pre- and intra-operative determinants of hyperglycemia.

Determinants	Odd Ratio (95% CI)	P value
Age, per 10 years	0.897 (0.749; 1.074)	0.236
Sex (male vs. female)	0.825 (0.528; 1.289)	0.399
Body mass index, per 5 units	0.995 (0.735; 1.346)	0.972
Blood glucose at admission, per 10 mg/dL[a]	1.283 (1.067; 1.544)	0.008
Blood glucose at admission ≥ 100 mg/dL	2.986 (1.671; 5.333)	<0.001
Target organ, upper GI (vs. lower GI)	1.040 (0.609; 1.775)	0.887
Target organ, others (vs. lower GI)	0.906 (0.482; 1.704)	0.760
Comorbidities (yes vs. no)	1.125 (0.702; 1.804)	0.624
Laparoscopy (yes vs.no)	0.774 (0.453; 1.322)	0.348
Cancer (yes vs. no)	0.995 (0.527; 1.877)	0.987
ASA (1/2 vs. 3)	0.616 (0.384; 1.089)	0.093
Surgery (clean vs. not clean)	1.072 (0.671; 1.714)	0.770
Epidural analgesia (yes vs. no)	1.130 (0.691; 1.847)	0.627
Blood loss, per 100 mL	1.104 (0.974; 1.252)	0.121
Duration of surgery, per h	1.122 (0.885; 1.422)	0.342

GI: Gastrointestinal.
[a] The effect of blood glucose level at admission, considered as a continous variable, was assessed in another multivariate logistic model including all the other determinants with the exception of the dichotomized BG level at admission (<100 or ≥100 mg/dL).

more likely to be admitted to the intensive care unit (16.3%; 17/104) than the BG 125–160 mg/dL group (7.6%; 16/211) and BG < 125 mg/dL group (6.6%; 9/137) (P = 0.023). A similar trend was observed for 30-day overall mortality rates (3.8% in the BG > 160 mg/dL group, 0.5% in the BG 125–160 mg/dL group, and 0.7% in the BG < 125 mg/dL group; P = 0.061).

4. Discussion

Early hyperglycemia in patients without diabetes occurring during and after major operations is the consequence of a boost release and synthesis of glucose (glycogenolysis and gluconeogenesis), and to a much higher probability to the reduced glucose utilization and uptake mediated by insulin resistance and blunt insulin sensitivity [26–28]. The primary contributing factor for this glucose metabolism is surgery-related tissue injury, followed by an immediate release of insulin-regulating inflammatory mediators and hormones [29].

The consequence of hyperglycemia after elective surgery remains controversial [30]. Temporary and reversal increase in blood glucose concentrations may simply represent a crucial physiological response to injury to maintain vital organ functions. However, persistent hyperglycemia has been repeatedly shown to blunt several key immune defense mechanisms that are indispensable to protect the host from the risk of infections [31,32].

Glucose dyshomeostasis is observed quite frequently and early in stress conditions and can be easily identify through the measurement of circulating glucose concentration. Consistent with previous results [4,33] we observed close to a 70% cumulative incidence of hyperglycemia episodes and the vast majority of the events were observed during surgery and within 24 h after operations. This observation highlights the need of monitoring BG levels predominantly during this timeframe and most likely with a lower intensity during the later postoperative periods.

Our analysis advocates that the only significant predictor of hyperglycemia occurring during and after surgery is the fasting BG concentration at admission. More specifically, the risk of having hyperglycemia was amplified by nearly 30% for each 10 mg/dL increase in BG at baseline. This risk increased almost 3-fold when the baseline BG concentration was dichotomized at 100 mg/dL. This results are highly consistent with previous findings [16] and with some theories postulating that high BG during surgery is an indirect sign of previously undiagnosed glucose intolerance that is eventually revealed in the setting of surgical stress [6]. Another potential explanation lies in a subclinical inflammatory state as shown by the increased baseline levels of C-reactive protein found in patients who experienced moderate hyperglycemia. It is possible that a "second inflammatory hit" such as surgical injury [34] may worsen the host glucose metabolism which is already compromised by chronic inflammation. These results imply that in this subgroup of patients without diabetes, BG levels should be more carefully monitored.

In the present study we selected patients without diabetes to limit the potential differences in the mechanisms and consequences of hyperglycemia on infectious morbidity. In fact, the results of a recent meta-analysis by Martin et al. [35] supported the consideration of diabetes as an independent risk factor for surgical site infections, other authors showed an irrelevant role of diabetic status [1,3,4], whereas Kwon et al. [5] and Kotagal et al. [6] found a paradox effect with patients with diabetes being at lower risk than nondiabetic ones for the occurrence of infections.

A defining feature of this study is our employment of a sound statistical methodology. This approach allows for the jointly modeling of the effect of covariates on both a longitudinal (BG trend over time) and a time-to-event outcome (appearance of infection) and a risk of the event [21–24]. The model provides a solid framework to assess the association between the two outcomes and to evaluate the impact of a particular profile over time of the longitudinal factor on the prediction of the absolute risk of event. By evaluating more than 6000 BG measures (average of

Table 3
Joint model of continuous and longitudinal blood glucose measures and risk of infection by the hazard model.

Factors	Hazard Ratio (95% CI)	P value
Age, per 10 years	1.002 (0.982; 1.021)	0.880
Sex (male vs. female)	1.272 (0.778; 2.081)	0.338
Body mass index, per 5 units	1.279 (0.959; 1.706)	0.094
Blood glucose at admission, per 10 mg/dL	1.076 (0.883; 1.312)	0.465
Target organ, upper GI (vs. lower GI)	0.879 (0.497; 1.556)	0.659
Target organ, urology/gynecology (vs. lower GI)	1.187 (0.635; 2.217)	0.592
Comorbidities (yes vs. no)	1.154 (0.700; 1.904)	0.711
ASA (1/2 vs. 3)	1.024 (0.601; 1.738)	0.928
Cancer (yes vs. no)	0.915 (0.481; 1.738)	0.786
Laparoscopy (yes vs. no)	0.688 (0.368; 1.289)	0.243
Type of surgery (not clean vs. clean)	1.752 (1.004; 3.059)	0.048
Blood loss, per 100 mL	1.128 (1.015; 1.236)	0.025
Duration of surgery >3 h	1.841 (1.140; 2.975)	0.013
Time dependent intra-post-operative BG level, per 10 mg/dL	1.065 (1.001; 1.113)	0.045

BG: Blood glucose; GI: Gastrointestinal.

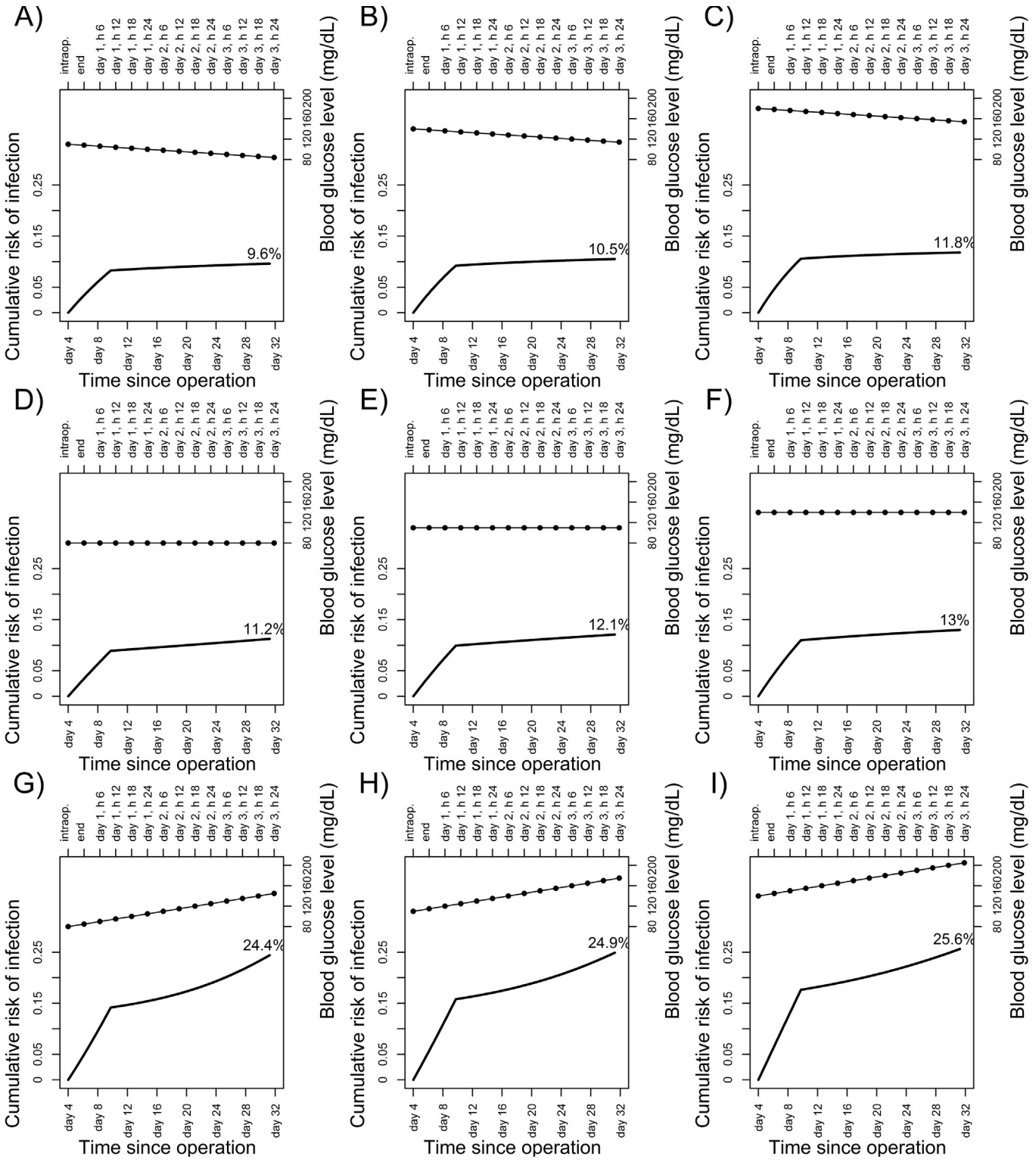

Fig. 3. Predicted cumulative risk of infection for a "paradigmatic" patient according to different blood glucose profiles. For each scenario, the overall risk of infection during the first month after surgery is also shown. A) decreasing trend of blood glucose starting from 110 mg/dL in during surgery to 84 mg/dL at the end of day 3; B) decreasing from 140 to 114; C) decreasing from 180 to 154; D) constant at 80; E) constant at 110; F) constant at 140; G) increasing from 80 to 145; H) increasing from 110 to 175; I) increasing from 140 to 205.

13.45 per subject), we found that the rapidity and the risk of infection onset increased by 0.65% for each 10 mg/dL increase of the BG level. Despite exhibiting statistical significance, the clinical meaning of this augmented hazard may be negligible since i.e. for a robust increment of 40 mg of BG, the absolute risk escalates of 2.6%.These finding are in contrast with previous reports showing an increased risk of 30% for each 40-point increase of plasma glucose concentration [1]. The most relevant and remarkable result of the present investigation is the lack of statistical association between the concentration of glucose measured during the first 3 days after surgery and the 30-day risk of infectious complications. In contrast, several other studies [2–6,12]

advocated a strong association between hyperglycemia and likelihood of infections. However, all these studies were retrospective and evaluated sporadic or even isolated BG measures, obtained at different time-points during operation or within the first days after surgery or they evaluated the mean BG among all measures or the highest value retrieved. Thus, an accurate evaluation of the effect of glucose variability and trends over time could not be meaningfully achieved. The important differences in results between our and those previous trials may partially explained by the sample size of the studies. In fact, the lack of difference in infection rates among the subgroups of the our cohort could have been driven by a type II error. Moreover, the patients in present study were kept without source of glucose for two days after surgery to avoid the interference of an exogenous origin of derangement of glucose homeostasis. This potential confounder was not assessed in other studies.

Our findings suggest that the risk of having an infection after the operation was mostly driven by the fluctuation of BG rather than by the absolute concentration, since regardless the initial levels of BG, the risk of infection was mainly driven by trends over time. Our statistical modeling allowed to predict the risk of infection in a paradigmatic patient with different BG starting levels and trends over time. All BG profiles that exhibited an incremental tendency were associated with high and overlapping calculated risk of infection irrespective of the initial BG concentrations. These profiles may likely represent patients who develop true insulin resistance in the postoperative course. In contrast, the BG profiles having constant or spontaneously declining slopes over time lead to a comparably and low risk regardless the initial glucose concentration. These finding suggest that the adverse consequences of hyperglycemia may arise only in specific cohorts of subjects and these are the one who consequently may require tight glucose control and probably insulin therapy even at BG level lower than 180 mg/dL [16] as previously recommended [18]. Consistent with our previous data [10], and taken together the present findings suggest that mild to moderate hyperglycemia is not a major determinant for the development of infectious complications notwithstanding we observed a significant increase of the severity of infection in patients moderate hyperglycemia. However, our previous trial was not designed to study the effect of BG fluctuation and time trends. In that context, the use of preoperative carbohydrate loading was effective in blunting insulin resistance and maintaining BG levels within the normal range after operations. Thus, the present results strengthen the validity of this therapeutic approach as the use of preoperative carbohydrate enriched drinks may limit the occurrence of persisting and incremental hyperglycemia over time.

Several limitations of this study should be acknowledged. We design a study to limit potential intra- and postoperative confounding interventions that could affect the BG concentration. One of these was the 2-day fasting after surgery that may be not adherent to new standards of care such as the enhanced recovery programs. Another shortcoming was the avoidance of administering steroids that are largely used to prevent nausea and vomiting, and again the use of intravenous dextrose during the time of observation. In addition, the role of high glucose levels could not be ruled out from the design of the study. It may be that in these patients the risk of infection is actually increased as reported by others [2,3,6,16]. Furthermore, the study was not designed to evaluate the mechanistic understanding by which persistent or rising hyperglycemia over time may affect the occurrence of infections. To minimize this drawback, we excluded patients who exhibited a proven anastomotic leak and all blood glucose data obtained from patients during the actual period of infection were excluded from the final analysis.

In conclusion, our data suggest that most of the hyperglycemia episodes occur during surgery and within the first 24 h after the operation. The persistence of hyperglycemia over time and the variation – as opposed to the absolute concentration – of blood glucose are major determinants of the risk of postoperative infections. These findings helped to determine the appropriate interval for blood glucose measurements in the perioperative period and in the future to direct the allocation of resources to at-risk patients.

Authors' contribution

Luca Gianotti: study supervisor and management, literature search, study design, data interpretation, writing.

Marta Sandini: study management, patient recruitment, literature search, data analysis, data interpretation, writing.

Roberto Biffi: patients recruitment, study design, data interpretation, writing.

Daniele Marrelli: patient recruitment, study design, data interpretation, writing.

Andrea Vignali: patient recruitment, study design, data interpretation, writing.

Sebastian K.S. Begg: study design, literature search, data interpretation, writing.

Davide P. Bernasconi: study design and management, statistical analysis, data analysis, figure drawing, data interpretation, writing.

All the authors read and approved the final version of the manuscript.

Sources of funding

None.

Conflicts of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2018.07.028.

References

[1] Ramos M, Khalpey Z, Lipsitz S, Steinberg J, Panizales MT, Zinner M, et al. Relationship of perioperative hyperglycemia and postoperative infections in patients who undergo general and vascular surgery. Ann Surg 2008;248:585–91.
[2] Ata A, Lee J, Bestle SL, Desemone J, Stain SC. Postoperative hyperglycemia and surgical site infection in general surgery patients. Arch Surg 2010;145:858–64.
[3] Jackson RS, Amdur RL, White JC, Macsata RA. Hyperglycemia is associated with increased risk of morbidity and mortality after colectomy for cancer. J Am Coll Surg 2012;214:68–80.
[4] Kiran RP, Turina M, Hammel J, Fazio V. The clinical significance of an elevated postoperative glucose value in nondiabetic patients after colorectal surgery: evidence for the need for tight glucose control? Ann Surg 2013;258:599–604.
[5] Kwon S, Thompson R, Dellinger P, Yanez D, Farrohki E, Flum D. Importance of perioperative glycemic control in general surgery: a report from the surgical care and outcomes assessment program. Ann Surg 2013;257:8–14.
[6] Kotagal M, Symons RG, Hirsch IB, Umpierrez GE, Dellinger EP, Farrokhi ET, et al. Perioperative hyperglycemia and risk of adverse events among patients with and without diabetes. Ann Surg 2015;261:97–103.
[7] Ceriello A, Esposito K, Piconi L, Ihnat MA, Thorpe JE, Testa R, et al. Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients. Diabetes 2008;57:1349–54.
[8] Mathioudakis N, Golden SH. A comparison of inpatient glucose management guidelines: implications for patient safety and quality. Curr Diab Rep 2015;15:13.
[9] Dhatariya K. Does dexamethasone-induced hyperglycaemia contribute to postoperative morbidity and mortality? BJA 2013;110:674–5.

[10] Gianotti L, Biffi R, Sandini M, Marrelli D, Vignali A, Caccialanza R, et al. Preoperative oral carbohydrate load versus placebo in major elective abdominal surgery (PROCY): a randomized, placebo-controlled, multicenter, phase III trial. Ann Surg 2018;267:623–30.
[11] Bláha J, Mráz M, Kopecký P, Stríteský M, Lips M, Matias M, et al. Perioperative tight glucose control reduces postoperative adverse events in nondiabetic cardiac surgery patients. J Clin Endocrinol Metab 2015;100:3081–9.
[12] Kao LS, Phatak UR. Glycemic control and prevention of surgical site infection. Surg Infect (Larchmt) 2013;14:437–44.
[13] Awad S, Varadhan KK, Ljungqvist O, Lobo DN. A meta-analysis of randomised controlled trials on preoperative oral carbohydrate treatment in elective surgery. Clin Nutr 2013;32:34–44.
[14] de Vries FE, Gans SL, Solomkin JS, Allegranzi B, Egger M, Dellinger EP, et al. Meta-analysis of lower perioperative blood glucose target levels for reduction of surgical-site infection. Br J Surg 2017;104:e95–105.
[15] Dhatariya KK, Wiles MD. Pre-operative testing guidelines: a NICE try but not enough. Anaesthesia 2016;71:1391–407.
[16] Jones CE, Graham LA, Morris MS, Richman JS, Hollis RH, Wahl TS, et al. Association between preoperative hemoglobin A1c levels, postoperative hyperglycemia, and readmissions following gastrointestinal surgery. JAMA Surg 2017;152:1031–8.
[17] Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. J Clin Endocrinol Metab 2002;87:978–82.
[18] American Diabetes Association. Standards of medical care in diabetes–2010. Diabetes Care 2010;33(Suppl. 1):S11–61.
[19] Braga M, Ljungqvist O, Soeters P, Fearon K, Weimann A, Bozzetti F. ESPEN guidelines on parenteral nutrition: surgery. Clin Nutr 2009;28:378–86.
[20] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205–13.
[21] Rizopoulos D. Joint models for longitudinal and time-to-event data with applications in R. Boca Raton: Chapman and Hall/CRC Biostatistics Series; 2012.
[22] Andrinopoulou ER, Rizopoulos D, Jin R, Bogers AJ, Lesaffre E, Takkenberg JJ. An introduction to mixed models and joint modeling: analysis of valve function over time. Ann Thorac Surg 2012;93:1765–72.
[23] Andrinopoulou ER, Rizopoulos D, Geleijnse ML, Lesaffre E, Bogers AJ, Takkenberg JJ. Dynamic prediction of outcome for patients with severe aortic stenosis: application of joint models for longitudinal and time-to-event data. BMC Cardiovasc Disord 2015;15:28.
[24] Ibrahim JG, Chu H, Chen LM. Basic concepts and methods for joint models of longitudinal and survival data. J Clin Oncol 2010;28:2796–801.
[25] Rizopoulos DJM. A package for the joint modelling of the longitudinal and time-to-event data. J Stat Software 2010;35:1–33.
[26] Dungan KM, Braithwaite SS, Preiser J-C. Stress hyperglycaemia. Lancet 2009;373(9677):1798–807.
[27] Nygren J. The metabolic effects of fasting and surgery. Best Pract Res Clin Anaesthesiol 2006;20:429–38.
[28] Svanfeldt M, Thorell A, Hausel J, Soop M, Rooyackers O, Nygren J, et al. Randomized clinical trial of the effect of preoperative oral carbohydrate treatment on postoperative whole-body protein and glucose kinetics. Br J Surg 2007;94:1342–50.
[29] Lipshutz AK, Gropper MA. Perioperative glycemic control: an evidence-based review. Anesthesiology 2009;110:408–21.
[30] Dhatariya K. Should inpatient hyperglycaemia be treated? BMJ 2013;346:f134.
[31] Turina M, Miller FN, Tucker CF, Polk HC. Short-term hyperglycemia in surgical patients and a study of related cellular mechanisms. Ann Surg 2006;243:845–51.
[32] Qadan M, Weller EB, Gardner SA, Maldonado C, Fry DE, Polk HC. Glucose and surgical sepsis: a study of underlying immunologic mechanisms. J Am Coll Surg 2010;210:966–74.
[33] Frisch A, Chandra P, Smiley D, Peng L, Rizzo M, Gatcliffe C, et al. Prevalence and clinical outcome of hyperglycemia in the perioperative period in noncardiac surgery. Diabetes Care 2010;33:1783–8.
[34] Thorell A, Nygren J, Ljungqvist O. Insulin resistance: a marker of surgical stress. Curr Opin Clin Nutr Metab Care 1999;2:68–78.
[35] Martin ET, Kaye KS, Knott C, Nguyen H, Santarossa M, Evans R, et al. Diabetes and risk of surgical site infection: a systematic review and meta-analysis. Infect Control Hosp Epidemiol 2016;37:88–99.