



Association of preoperative glycemic variability with surgical-site infection and anastomotic complications following elective colorectal cancer surgery

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Abstract

Background: Chronic hyperglycaemia is a known post-colorectal surgery risk factor for poor outcomes; however, the significance of short term variations in blood glucose is poorly understood. The current study aimed to investigate if there is an independent association between preoperative glycemic variability and surgical-site infection and anastomosing complications. **Methods:** A prospective observational cohort of 312 patients with elective colorectal resection was created. The glycemic variability was measured using serial preoperative capillary and venous glucose measurements, using coefficient of variation and the mean amplitude of glycemic excursion as quantitative measurements. Patients were divided into low and high variability groups. Multivariable logistic regression that was adjusted for age, body mass index, diabetes status, glycated haemoglobin, tumour stage and operative approach. **Results:** 18.9% of the patients developed S-SI, and anastomotic complications were observed in 9.6%. HGV was independently associated with surgical-site infection and anastomotic complications; independent of mean glucose and glycated haemoglobin. **Conclusion:** Glycemic variability is an independent and potentially modifiable peri-operative risk factor for infective and anastomotic morbidity after elective CRC surgery and should be added to peri-operative risk assessment.

Keywords: *Glycemic variability, Surgical-site infection, Anastomotic leak, Colorectal cancer, Perioperative glucose*

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1. Introduction

The global burden of Colorectal cancer is still increasing due to population ageing, diet change and growing screening programs that find the patients at resectable stages of the disease ([Sung et al., 2021](#)). With more patients advancing to elective surgery, the risks involved in an operation and its benefits in the long term become more and more important for patient and health systems. Overall, decreasing avoidable morbidity has become a major goal of contemporary colorectal surgery, and knowing about modifiable risk factors that can be reduced preoperatively is an important step to achieving this goal.

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Colorectal cancer (CRC) is still one of the most common cancers globally and an important contributor to surgical capacity in both high and middle income health systems. The main surgical option for the treatment of non-metastatic disease is surgical resection which has a significant risk of post-surgical morbidity. Either surgical-site infection or anastomotic complications are the significant complications most strongly affecting recovery, hospital stay and oncological outcome, and anastomotic complications include clinically apparent leakage, contained collections and delayed healing of the subsequent bowel reconstruction site (McDermott *et al.*, 2015). These events are associated with extended hospital stay, and reoperation risk, as well as delaying adjuvant therapy and have been consistently associated with lower long-term survival rates (Mrak *et al.*, 2016). The prevention of anastomotic leak is a first order priority during colorectal oncological surgery as it can be fatal in the short term and is a risk factor for local recurrence. It is therefore of great clinical importance to identify those patients who are at increased risk of these complications preoperatively to decide on the amount of optimisation needed and to plan other considerations such as fashioning a protecting stoma intraoperatively.

The operative metabolic setting has now been established as a surgeries tool that can be switched to improve the outcomes. Hyperglycaemia directly affects neutrophils, their chemotaxis, phagocytosis, and oxidative bactericidal activity, it affects the integrity of the collagen synthesis and microvascular perfusion, and it stimulates the local inflammatory response, all relevant to wound integrity and integrity of the anastomosis (Turina *et al.*, 2005; Jackson *et al.*, 2012). As a result, both mean perioperative glucose levels and glycated haemoglobin (HbA1c) have been used in risk-stratification guidelines and improved-recovery programs (Gustafsson *et al.*, 2019). These static indicators, however, only reflect the central level of glucose exposure and are unable to see the time-series of glycaemia.

Anastomotic healing is a very delicate procedure. Successful attachment of the bowel to the bowel is dependent on metabolic integrity of tissue, organized deposition and cross-linking of collagen, and a controlled inflammatory process. Defective host defence renders the bowel wall more susceptible to infective breakdown and impaired microcirculation and the abnormal function of the fibroblasts necessary to bring the healing process under control puts the bowel wall at risk for leakage during hyperglycaemic conditions. The metabolically very early postoperative days may have a high biological relevance since the first and most fragile phase of anastomotic healing is in this period.

The amplitude and frequency of changes in blood glucose concentration with time (glycemic variability) has become a new focus of interest as an independent metabolic phenotype (Suh and Kim, 2015). Wide glucose fluctuation has been shown to be associated with oxidative stress, endothelial dysfunction and increased mortality, some of which may be independent of the absolute glucose concentration in critically ill population and cardiac surgical patients (Krinsley, 2008; Subramaniam *et al.*, 2014). The biological arguments are powerful – intermittent hyperglycaemic and hypoglycaemic fluctuations create reactive oxygen species, and lead to more regular endothelial damage than values which are persistently and stably hyperglycaemic (Monnier *et al.*, 2006). Experimental studies have shown that fluctuations in glycaemia increase more the expression of inflammatory cytokines and markers of oxidative stress than a constant high glucose concentration (Ceriello *et al.*, 2008), giving a mechanistic insight into the different pathological roles of glycaemia fluctuations from those of hyperglycaemia. However, little attention has been paid to glycemic variability as a complication of colorectal surgery, let alone to the role of glycemic variability before surgery.

Another missing concept is the association between glycemic variability and diabetes. Although this is often thought to apply to those patients who have a known diagnosis of diabetes, metabolic instability is now commonly appreciated in people who do not have an actual diagnosis of diabetes – especially during the surgical stress response, insulin resistance associated with specific malignancy and neoadjuvant therapy-associated catabolic state (Frisch *et al.*, 2010). The clinical relevance of variability measurements would go far beyond the diabetic sub-population with whom glucose surveillance is currently targeted if variability is a predictor of complications in patients, regardless of whether they have diabetes or not. The colorectal patient population allows a useful study to address this question, as a significant proportion of patients in this population is not diabetic, but nevertheless confronted with a demanding metabolic challenge from major abdominal surgery.

Much of the evidence comes from intra- or postoperative measurements of glucose levels, and hence cannot be applied to preoperative optimisation. Pre-op metabolic instability, if it occurs, could be a target variable if it

is itself predictive of bad outcome, and allow time for intervention between initial diagnosis and operation. This current study sought to identify if the glucose swings before surgery (glycemic variability obtained via routine pre-operative glucose measurements) were an independent risk of both surgical-site and anastomotic infection and bleeding following elective colorectal cancer surgery over and above known risk factors such as diabetes status and glycated haemoglobin. A secondary aim was to see if such association, if any, was the same in diabetic and non-diabetic patients and to examine the incremental value of glycaemic variability compared to conventional static evaluation of glycaemia.

2. Materials and methods

2.1. Study design

A prospective observational cohort study performed in a tertiary referral centre Department of General and Colorectal Surgery for 30 months. The study design and reporting were based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort studies (von Elm et al., 2007). The protocol was approved by the Institutional Ethics Committee, and written informed consent was acquired from all of the subjects before entry into the study. All procedures were following the principles of the Declaration of Helsinki.

2.2. Participants and eligibility criteria

Eligible consecutive patient series of adult patients undergoing elective resection of histologically proven colorectal adenocarcinoma were identified. Eligible patients were those at least 18 years of age with the diagnosis of segmental colectomy, anterior resection or restorative proctocolectomy with primary anastomosis for curative purposes. Patients who had emergency surgery, palliative or purely diverting surgery with no anastomosis, disseminated metastatic disease which precluded any chance of a cure, active systemic infection on admission, were on chronic corticosteroid or immunosuppressive therapy, had end-stage renal disease and/or dialysis, or an incomplete set of glucose data in the pre-operative period were excluded. To obtain a reliable estimate of the variability, patients with fewer than 4 glucose measurements before surgery were also excluded.

2.3. Sample size estimation

Sample size was based on an expected surgical-site infection rate of ~12% for the low-variability group. A sample size of 300 patients was required to detect a clinically meaningful increase in the high-variability group, with 80% statistical power, at a significance level (alpha) of 0.05, considering an anticipated group ratio and a projected drop-out rate of 10%. This was used as a cut-off for recruitment, which was continued until this was surpassed.

2.4. Glucose measurement protocol and definition of glycemic variability

A standardised preoperative programme for glucose monitoring was instituted in all the patients that were admitted prior to surgery. Single Point-of-care valid blood Glucose (PoC) readings were obtained prior to each of the three major meals and at bedtime, whilst Fasting venous Plasma Glucose (FPG) readings were taken on the morning of admission and the day before surgery. In the cases admitted for the shorter interval monitoring continued to produce at least four distinct measurements for a minimum of 48 hours. High-

Table 1: Definitions of the glycemic-variability indices applied in the study		
Index	Definition	Role in study
Coefficient of variation	Standard deviation of all preoperative glucose values divided by the mean glucose, expressed as a percentage	Primary index
Mean amplitude of glycemic excursion	Arithmetic mean of glucose excursions exceeding one standard deviation of the mean glucose	Secondary index
High-variability threshold	Coefficient of variation ≥ 36%, per international consensus	Group definition

performance liquid chromatography was used to measure glycated haemoglobin at a single point in time at enrolment. Two complementary glycemic indices were used to quantify glycemic variability. Coefficient of variation of glucose (SD of all the glucose pre-operative values/mean glucose x 100) was the primary index. The secondary index was the glycemic excursion mean amplitude, which is the arithmetic mean of the glucose excursions that fell outside one standard deviation of the mean glucose. Both indices were independently calculated by the two blinded investigators; discrepancies were sorted out by re-calculation. CV=36% was defined as an a priori cut-off point as used internationally for the CV threshold between stable and unstable glycaemia ([Danne et al., 2017](#)). Patients were then divided into low variability (CV<36%) group and high variability (CV≥36%) group.

2.5. Surgical procedure and perioperative care

Operations were carried out by consultant colorectal surgeons with standardised techniques of open or minimally invasive operations as per tumor location and surgeon's preference. Mechanical bowel preparation and oral antibiotic was given according to the institution's protocol. All received intravenous prophylactic antibiotics within 60 minutes of skin incision with additional doses if procedures were lengthy or for excessive blood loss. Our operating surgeon's choice of anastomosis construction method was stapled or hand-sewn. A shared insulin protocol was used to control glucose within 6-10 mmol/L in patients with diabetes, and an enhanced-recovery pathway was followed for postoperative care (common for all patients).

2.6. Outcome definitions

The primary outcome was Surgical-Site Infection (SSI) within 30 days of surgery, which included superficial incisional infection, deep incisional infection, and organ/space infection, in accordance with the definition of Centers for Disease Control and Prevention (CDC) [13]. Anastomotic complication was defined as co-primary outcome and classified according to classification of ISG of rectal cancer ([Rahbari et al., 2010](#)). Outcomes were adjudicated by 2 blinded clinicians who were not involved in the operating room.

2.7. Data collection and covariates

The pervasive research data collection method used were structured case-report forms which were used to collect baseline demographic, clinical, and operative data. Pre-recorded variables included the age, sex, body mass index, smoking status, American Society of Anesthesiologists physical status, pre-existing diabetes mellitus, glycated haemoglobin, tumour location and stage using the tumour-node-metastasis classification, operative approach, length of surgery and amount of blood loss. Data were double-entered into a secure electronic database and checked against each other to minimise any transcription errors. All glucose measurements were made with the same calibrated point-of-care analyzer, duplicate outcome-blinded investigators generated the variability indices and outcome adjudication was performed by outcome-blinded clinicians.

2.8. Statistical analysis

The continuous variables were described using mean ± SD or median + IQR and analyzed using independent-samples t-test and Mann-Whitney U-test, while categorical variables were described as frequencies and percentages and were analyzed using chi-square and Fisher exact test. Multivariable logistic regression was used to evaluate the independent relationship of glycemic variability with each outcome. Model discrimination and calibration were evaluated employing area under receiver operating characteristic curve and Hosmer-Lemeshow test. Statistical significance set at p value < 0.05 (two sided).

3. Results

3.1. Participant flow

A total of 361 patients were screened during study period. Forty-nine of them were excluded; 21 were emergency conversion and/or non-elective, 12 underwent palliative or diversionary surgery without a primary anastomosis, 9 lacked a complete set of pre-operative glucose data, 4 had been on chronic immunosuppressive therapy and 3 were actively infected on admission. All 312 other patients (analytic cohort) had no loss to follow-up during the entire 30-day outcome window.

3.2. Baseline characteristics

A total of 312 patients were selected for the analytic cohort, and they all met all eligibility criteria. The mean age for the cohort was 62.4 years and 57.4% were male. 34.6% of patients had preexisting diabetes mellitus. 118 patients (37.8%) of the total cohort were allocated to the high-variability group and 194 (62.2%) patients were classified into the low-variability group. The two groups were broadly similar in terms of age, gender and tumour stage; the high variability group had a higher diabetes prevalence and higher glycated haemoglobin values and mean glucose concentrations. This body mass index was slightly elevated in the high variability group but conventionally not significantly so. The comparable distribution of tumour sites, disease stage, surgical procedures and physical state are significant, as they minimize the possibility that the differences in outcome outlined below are due to differences in disease severity or surgical complexity and not to the metabolic state (Table 2).

Table 2: Baseline demographic and clinical characteristics by glycemic-variability group

Characteristic	Low variability (n = 194)	High variability (n = 118)	p-value
Age, years, mean (SD)	61.8 (10.6)	63.3 (11.1)	0.234
Male sex, n (%)	110 (56.7)	69 (58.5)	0.762
Body mass index, kg/m ² , mean (SD)	25.9 (3.8)	26.7 (4.2)	0.087
Current smoker, n (%)	38 (19.6)	27 (22.9)	0.481
Diabetes mellitus, n (%)	48 (24.7)	60 (50.8)	< 0.001
Glycated haemoglobin, %, mean (SD)	6.1 (0.9)	7.3 (1.4)	< 0.001
Mean preoperative glucose, mmol/L	6.4 (1.1)	8.1 (1.9)	< 0.001
ASA III-IV, n (%)	52 (26.8)	41 (34.7)	0.140
Rectal tumour location, n (%)	71 (36.6)	45 (38.1)	0.789
TNM stage III, n (%)	70 (36.1)	44 (37.3)	0.831
Minimally invasive approach, n (%)	121 (62.4)	68 (57.6)	0.402
Note: SD, standard deviation; ASA, American Society of Anesthesiologists; TNM, tumour-node-metastasis.			

3.3. Incidence of outcomes

Overall, 59 out of the 312 patients had SSI (incidence 18.9%). These included 34 superficial incisional, 15 deep incisional and 10 organ/space infections. 30 patients (9.6%) had anastomotic complications, including 21 patients who had anastomotic leak. These two outcomes were significantly increased in the high-variability group. In the high-variability group, 30.5% developed Surgical-Site Infection (SSI) versus 11.9% in the low-variability group, whereas 15.3% versus 6.2% of the respective groups developed anastomotic complications. Unadjusted comparisons of both differences statistically significant (Table 3).

The same trend was observed for the secondary outcomes. Within 30 days, a reoperation was required in 11.9% of high-variability patients vs. 4.6% of low-variability patients; patients with high variability had a 3-day longer median length of stay. That this difference exists is in keeping with the higher proportion of infective and anastomotic events in that group and provides a warning of the resource implications of a preoperative metabolic instability.

3.4. Multivariable analysis

High glycemic variability was independently associated with surgical-site infection (adjusted odds ratio 2.41

Table 3: Unadjusted incidence of study outcomes by glycemic-variability group

Outcome	Low variability (n = 194)	High variability (n = 118)	p-value
Surgical-site infection, n (%)	23 (11.9)	36 (30.5)	< 0.001
Superficial incisional	15 (7.7)	19 (16.1)	0.021
Deep incisional	5 (2.6)	10 (8.5)	0.017
Organ/space	3 (1.5)	7 (5.9)	0.031
Anastomotic complication, n (%)	12 (6.2)	18 (15.3)	0.007
Anastomotic leak	8 (4.1)	13 (11.0)	0.017
Reoperation within 30 days, n (%)	9 (4.6)	14 (11.9)	0.015
Length of stay, days, median (IQR)	7 (5-9)	10 (7-14)	< 0.001

[95% confidence interval 1.38–4.21] ($p = 0.002$) after adjusting for age, body mass index, diabetes status, glycated haemoglobin, mean preoperative glucose, tumour stage, and operative approach. A similar independent relationship was found with anastomotic complications (aOR 2.08 95% CI 1.02–4.24; $p = 0.043$). Importantly, glycated haemoglobin or mean preoperative glucose were no longer independently associated with either outcome when both were considered in the model as the pattern of glucose fluctuation provided information additional to an absolute glycaemia. The other variables that remained were Body Mass Index (BMI), which was found to be an independent predictor of surgical-site infection; and length of operation,

Table 4: Multivariable logistic regression for the association between glycemic variability and study outcomes

Variable	Adjusted OR	95% CI	p-value
<i>Outcome: Surgical-site infection</i>			
High glycemic variability	2.41	1.38–4.21	0.002
Diabetes mellitus	1.29	0.71–2.34	0.402
Glycated haemoglobin (per %)	1.11	0.86–1.43	0.421
Body mass index (per kg/m ²)	1.08	1.01–1.16	0.028
Age (per year)	1.02	0.99–1.04	0.183
<i>Outcome: Anastomotic complication</i>			
High glycemic variability	2.08	1.02–4.24	0.043
Rectal tumour location	1.94	0.96–3.92	0.065
Glycated haemoglobin (per %)	1.07	0.79–1.45	0.663
Male sex	1.41	0.66–3.01	0.375
Operative time (per hour)	1.28	1.03–1.59	0.026

which is a normal surgical correlation and an independent predictor of anastomotic complications. This effect was independent of the diabetic group as a whole, as variability, but not the diagnosis of diabetes, per se, was predictive, supporting the hypothesis that it is the variability and not the diabetic diagnosis per se that induces the response (Table 4).

3.5. Subgroup and sensitivity analyses

The prespecified subgroup analysis revealed that the correlation of high glycemic variability with SSI remained in both patients with and without diabetes with ORs of 2.29 and 2.58, respectively, and no significant interaction term (p for interaction = 0.71), suggesting that the impact of variability was not meaningfully different in patients with and without diabetes. There were also no significant differences found in anastomotic complications. For every 10% unit rise in CV, there was a corresponding 34% rise in the adjusted odds of SSI (adjusted OR 1.34, 95% CI 1.12-1.60). Consistent estimates for both direction and magnitude were observed when using the mean amplitude of glycemic excursion to replace the coefficient of variation in the sensitivity analysis, which lent strength to the primary findings using a different measure of variability.

Table 5: Association between high glycemic variability and outcomes, stratified by diabetes status			
Subgroup	Adjusted OR	95% CI	p (interaction)
<i>Outcome: Surgical-site infection</i>			
Patients with diabetes	2.29	1.09–4.81	0.71
Patients without diabetes	2.58	1.18–5.64	
<i>Outcome: Anastomotic complication</i>			
Patients with diabetes	1.97	0.84–4.62	0.68
Patients without diabetes	2.21	0.86–5.68	

3.6. Model performance

Discrimination for surgical-site infection by the multivariable model was acceptable (area under the ROC curve, 0.74) and that for anastomotic complications was 0.71. All discrimination was greater with glycemic variability incorporated compared to a model including only conventional covariates where the area under the curve for surgical-site infection was 0.68. However, there was no significant difference between the actual and the predicted probability of events for both the models as shown by Hosmer–Lemeshow goodness of fit test with p value of 0.36 and 0.52 respectively.

4. Discussion

The present prospective cohort in patients with elective CRC surgery demonstrated that glycemic variability is independently linked to surgical site infection and mainly anastomotic complications. However, this association remained significant even after adjusting for diabetes, glycated haemoglobin and the mean preoperative glucose level, adding weight to the fact that the dynamic nature of glycaemia provides prognostic information beyond what is provided by static variables. This discovery puts the evaluation of metabolism before surgery in a different perspective – not just is it how high the patient's glucose is, but it seems how much it swings before surgery counts. This finding holds for all the diabetic and non-diabetic subgroups and indicates that the variability is not only a matter for persons with diabetes and that it is a generalisable and hence metabolic characteristic.

4.1. Biological mechanisms

The biological plausibility of this relationship is well supported. Hyperglycaemic euglycaemic (or hypoglycaemic) fluctuation leads to increased oxidative stress, in particular increasing the production of reactive oxygen species, activation of protein kinase C and endothelial dysfunction than stable hyperglycaemia

(Ceriello *et al.*, 2008). These processes reduce microvascular perfusion, as well as the function of the leukocytes at the surgical wound and the anastomotic border, where tissue integrity plays a key role for the outcomes studied here (Kwon *et al.*, 2013). This finding of the loss of the “independent predictive value” of glycated haemoglobin when variability was modelled is compatible with the notion that the pertinent tissue injury was driven not only by the chronic exposure, but also by the variability.

This explanation at the tissue level involves the sequential biology in wound repair. Neutrophils and macrophages are required for the inflammatory phase, fibroblasts for the proliferative phase and ordered cross-linking of collagen for the remodelling phase. Any shifts in glucose will affect these phases and impairs the respiratory burst of phagocytes during relative hyperglycaemia, and can cause transient hypoperfusion during fast declines in glucose. Overall, this leads to a healing environment which is compromised occasionally but which may have a net effect of causing greater damage when it is episodically unstable than it would at a stable, albeit elevated, glucose concentration. Moreover, the frequent fluctuations in glycaemic values result in the production of advanced glycation end products and periodically trigger a low level pro-inflammatory state which has an impact on the orderly evolution of these healing phases, adding to the mechanical fragility of the anastomotic edge during the vulnerable early postoperative period.

4.2. Comparison with existing literature

Results from highest body of evidence written in critical care/cardiac surgical setting has been extrapolated to colorectal arena. Among intensive-care patients, large fluctuations in blood glucose level have been associated with mortality independent of mean blood glucose level, and among cardiac surgical patients' larger fluctuations have been linked to infective and wound complications (Duncan *et al.*, 2010). In general, and gastrointestinal surgery, there is emerging data that suggests that peri-operative variability is associated with complications; however, the majority of these analyses have been performed on either an intra-operative or post-operative measurement window (Kotagal *et al.*, 2015; Cheung *et al.*, 2006). The present study examines the metabolic window before surgery and allows for identification of a signal that is available and can be corrected before surgery – during the time interval in which the clinician has the maximum opportunity for intervention.

The magnitude of association seen here is quite generally consistent with that seen in other neighbouring surgical areas, which have generally seeded adjusted odds ratios for infective complications ranging two- to three-fold in the highest variability strands. The result of non-significant mean glucose and glycated haemoglobin in the presence of variability is also in line with results of studies that demonstrated a superiority of dynamics over statics and support the idea that the two constructs can NOT be used interchangeably which are highly correlated.

It is also evident that the surgical-site infection rate and anastomotic complication rate in this cohort are within those reported for a population underserving elective CRC surgery in the current surgery literature and supports the representativeness of the cohort and the external validity of the observed association. There does not seem to be an over-representation of more advanced disease or complex surgery in the higher rates which were clustered in the high-variability group, but rather these rates seem to result from the metabolic exposure that was being studied. This validity with published incidence rates, along with the internal validity in the primary, subgroup and sensitivity analyses, provides reassurance that the association found is not an idiosyncrasy to the local context.

4.3. Clinical implications

There are two clinical implications. Firstly, preoperative glycemic variability (obtainable from routinely collected glucose values without any extra expense) could be included in existing risk stratification tools in order to further improve prediction of infective or anastomotic morbidity. Patients who present with significant variability may have an indication for specific metabolism optimisation measures pre-op, more intensive surveillance post-op, or (depending on the clinical situation) a more conservative approach to reconstruction (e.g. defunctioning stoma). Second, the result suggests a testable hypothesis that deliberate reduction of the 'spread' of preoperative glucose, rather than simply reducing the mean glucose per se, will be effective in reducing complications. The best way to test this hypothesis will be with an interventional trial (Buchleitner *et al.*, 2012).

Accessibility is a key value from a service-delivery standpoint for variability as a risk marker. The coefficient of variation can be automatically calculated within the electronic record, whilst the generation of serial glucose values occurs already in most surgical inpatients as specialised biomarkers and imaging do not. This also sparked the idea that maybe we can have a kind of flag in the administration that will identify the patients who are at risk before surgery and spare them from further testing, so that we could focus the optimisation efforts of the multidisciplinary team on those people where it's most likely to make a difference as a way of saving lives. But any such use would need to be prospective validated and careful consideration given to increasing the risk of inducing hypoglycaemia with overaggressive glucose control (Umpierrez *et al.*, 2011).

4.4. Future directions

The following three lines of enquiry stem from the preceding results. First, however, multicentre cohorts that include continuous glucose monitoring should be created to validate the relationship with higher temporal resolution and in a variety of practice settings. Second, mechanisms studies using variability indices and measures of tissue oxidative stress and anastomotic perfusion should be conducted to help to establish causal pathways. Third, and most importantly, a randomised controlled trial of a preoperative protocol aimed at minimising glucose fluctuation versus standard care will measure whether the protocol reduces surgical morbidity or not. Such a trial would require a balance of potential benefit for tighter control, and a recognised potential for harm from hypoglycaemia, as well as a definition of variability that could be attained in the pre-operative period and yet that would have potential clinical relevance. However, in the absence of such evidence, the current results should be interpreted as a strong basis for integrating glycemic variability in the preoperative evaluation as well as its use in designing interventional studies.

From the data presented here one can see that there is an increasing awareness about the role of the dynamics of metabolic control, beyond the mean, in determining the outcome of surgery. This idea of a glycemic variability window is juxtaposed against the realities of surgical care, where there is a window of opportunity for glycemic variability optimisation before an elective surgery. Once proven and implemented it would be possible to routinely record the level of preoperative variability, adding it to the risk-assessment armamentarium for colorectal surgery as a low cost, non-invasive, and easily applicable test alongside existing markers to direct valuable optimisation resources to those most likely to benefit.

5. Conclusions

Glycemic variability is an independent risk factor for surgical site infection and anastomosis complications in patients undergoing elective colorectal cancer surgery, irrespective of diabetes diagnosis, glycated haemoglobin and mean glucose value. This association did not differ between diabetic or non-diabetic patients and was not sensitive to alternative definitions of variability, and was associated with increased reoperation rate and longer hospital stay. Glycemic variability is an appealing candidate for inclusion in a perioperative risk assessment score since it can be calculated from commonly collected measures and could possibly be modified preoperatively. Hence these findings argue for more metabolic thinking in the peri-operative setting rather than only average glycaemic control and more an awareness about glycaemic stability. Providers who care for patients in the perioperative period before elective colorectal resection may benefit from an examination of the pattern of blood glucose, rather than just the average, in patients who have blood glucose levels which vary frequently, but with acceptable averages. These findings suggest that future multicentre studies are needed using CGM and ultimately interventional trials of variability reduction for assessing whether stabilisation of the preoperative glycemic state can decrease morbidity of surgery. If the trials are successful, the assessment and correction of preoperative glycemic variability might be added to enhanced-recovery pathways as a simple, low-cost intervention that can be widely applied to improve outcomes following colorectal cancer surgery.

Ethics approval and consent to participate

The study was approved by the Institutional Ethics Committee, and written informed consent was obtained from all participants.

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Data availability

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

Author contributions

All authors contributed to the conception and design of the study, data acquisition, analysis and interpretation, drafting and critical revision of the manuscript, and approved the final version for submission.

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