The relationship between glycosylated hemoglobin and perioperative glucose control in patients with diabetes

La relation entre l'hémoglobine glyquée et le contrôle glycémique périopératoire chez les patients diabétiques

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Received: 27 August 2009 / Accepted: 7 January 2010 / Published online: 3 February 2010
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Abstract

Purpose Hyperglycemia and elevated glycosylated hemoglobin (HbA_{1c}) are associated with perioperative morbidity in patients with diabetes, but the relationship between long-term glycemic control and perioperative glucose control is unknown. The purpose of this study was to determine the relationship between glycosylated hemoglobin (HbA_{1c}) and perioperative glucose in fasting patients with type 2 diabetes undergoing elective non-cardiac surgery.

Methods This was a prospective observational study of 244 adult patients with type 2 diabetes who were evaluated before elective non-cardiac surgery at a preoperative medicine clinic in a tertiary care medical centre during the period September 2004 to May 2005. Preoperative HbA_{1c} levels were determined, and preoperative and

postoperative glucose values were measured on the day of surgery. The primary outcome variables were preoperative and postoperative blood glucose values.

Results Half of all study patients had an $HbA_{1c} \geq 7\%$, including 23% of patients with $HbA_{1c} \geq 8\%$. HbA_{1c} levels predict preoperative glucose levels, and preoperative glucose levels and duration of surgery predict postoperative glucose levels. Glucose levels in one-third of the patients with type 2 diabetes decreased during surgery without administration of insulin or glucose-regulating medications.

Conclusion HbA_{1c} values may serve as biomarkers for glucose control during the immediate perioperative period in patients with type 2 diabetes undergoing elective surgery.

Résumé

Objectif L'hyperglycémie et une hémoglobine glyquée (HbA_{1c}) élevée sont associées à une morbidité périopératoire chez les patients diabétiques, mais la relation entre le contrôle glycémique à long terme et le contrôle glycémique périopératoire est inconnue. L'objectif de cette étude était de déterminer s'il existait une relation entre l'hémoglobine glyquée (HbA_{1c}) et le glucose périopératoire chez les patients à jeun souffrant de diabète de type 2 et subissant une chirurgie non urgente et non cardiaque.

Méthode Cette étude observationnelle prospective a porté sur 244 patients adultes souffrant de diabète de type 2, lesquels ont été évalués avant une chirurgie non urgente et non cardiaque dans une clinique de médecine préopératoire dans un centre médical de soins tertiaires entre septembre 2004 et mai 2005. Les niveaux préopératoires de HbA_{1c} ont été déterminés, et les valeurs glycémiques préopératoires et postopératoires ont été mesurées le jour de la chirurgie. Les

Institution to which the work should be attributed: University of Chicago. The work of this manuscript should be attributed to the University of Chicago Department of Anesthesiology and Critical Care.

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critères d'évaluation principaux étaient les valeurs glycémiques préopératoires et postopératoires.

Résultats La moitié des patients à l'étude avaient une HbA_{1c} $\geq$ 7 %, dont 23 % des patients avec une HbA_{1c} $\geq$ 8 %. Les niveaux de HbA_{1c} prédisent les niveaux glycémiques préopératoires; et les niveaux glycémiques préopératoires et la durée de la chirurgie sont des prédicteurs des niveaux glycémiques postopératoires. Les niveaux glycémiques d'un tiers des patients souffrant de diabète de type 2 ont diminué pendant la chirurgie sans administration d'insuline ou de médicaments régularisant la glycémie.

Conclusion Les valeurs de HbA_{1c} pourraient servir de biomarqueurs pour assurer le contrôle glycémique pendant la période périopératoire immédiate chez les patients souffrant de diabète de type 2 et subissant une chirurgie non urgente.

The glycosylated fraction of hemoglobin A (HbA_{1c}) is a reflection of longer-term glucose control. Although preoperative hyperglycemia is associated with poor outcome, there are no data examining the prospective use of HbA_{1c} to predict blood glucose in fasting patients with diabetes during the perioperative period.¹⁻³ Glycemic control during the perioperative period is difficult to predict and manage because multiple factors affect blood sugar and pancreatic function, including the stress of surgery, acute illness, anorexia, anesthetic masking of hypoglycemic symptoms, and nil per os (NPO) status.

Reducing perioperative hyperglycemia in patients with diabetes has been targeted as a national quality improvement initiative by the Centers for Medicare and Medicaid Services.⁴ Several studies show that perioperative hyperglycemia is associated with morbidity.^{5,6} An association between baseline glucose regulation and hyperglycemia in critically ill patients has been reported.⁷ In trauma patients, there is a relationship between HbA_{1c} and hyperglycemia after a stress response. There are no reports of the relationship between long-term glucose control and perioperative glucose control in non-cardiac surgery.

Identification and treatment of patients in advance of surgery may prevent the acute hyperglycemia associated with poor outcomes. We hypothesized that a preoperative HbA_{1c} value is a biomarker for perioperative glucose control.

Methods

This was a prospective observational study of surgical patients with type 2 diabetes performed at the University of

Chicago Medical Center, Chicago, IL, USA, an urban tertiary care teaching hospital.

Participants

During the period September 2004 to May 2005, adults with a diagnosis of type 2 diabetes scheduled for elective non-cardiac surgery and evaluated at the preoperative medicine clinic before surgery were eligible for enrolment. We categorized patients with type 2 diabetes by reported history from the patient or from their primary care physician. Patients taking insulin were asked whether they had experienced episodes of diabetic ketoacidosis, which is uncommon in patients with type 2 diabetes. Patients with a history of diabetic ketoacidosis were excluded.

All patients were scheduled to come from home on the day of surgery, and written informed consent was obtained from the patients at the time of their enrolment in the preoperative clinic. The University of Chicago Medical Center Institutional Review Board approved the protocol.

Data collection

The sample size was a convenience sample, and 271 patients were enrolled in our study. The analytic sample ($n = 244$) excluded 27 patients who had taken insulin, steroids, or oral hypoglycemic agents on the day of surgery. An additional 23 patients who were treated with insulin, glucose, or steroids during surgery were excluded from all analyses of postoperative blood glucose values, including those evaluating preoperative to postoperative change in glucose. These patients were excluded because the interventions were not standardized, and they likely would have influenced postoperative glucose values.

Demographic data, including age, race/ethnicity, gender, body mass index (BMI), duration of diabetes, and diabetic medications, were obtained from the computerized preoperative record. Race/ethnicity was self-reported through the use of open-ended questions from the researcher. On the day of surgery, we collected the following: American Society of Anesthesiologists (ASA) physical status; duration of fasting; pre- and intraoperative administration of steroids; type of anesthesia, i.e., general, sedation, centronoaxial or peripheral nerve blocks; and time of day of glucose draws. We noted the duration and type of procedure and administration of glucose-containing intravenous fluids or insulin.

We used the Hopkins Risk Score, which was developed to evaluate the invasiveness of the procedure as a predictor of surgical risk, to address the differences in the anticipated stress response. The Hopkins risk system classifies surgeries into five categories by evaluating invasiveness, fluid shifts, blood loss, entry into specific body areas (intrathoracic,

Table 1 Patient demographics and clinical characteristics ($n = 244^a$)

		Median (IQR)	Range
Age (yr)		63 (17)	26 – 94
BMI		32 (10)	17 – 83
Diabetes duration (yr)		6 (8.5)	2 mth – 38 yr
HbA _{1c} (%)		7 (1.6)	4.1 – 12.4
		Frequency	%
Age group (yr)	25 – 49	47	19
	50 – 59	45	18
	60 – 69	86	35
	70 – 79	44	18
	80 – 94	22	9
Gender	Male	97	40
	Female	147	60
Race	African American	131	54
	White	101	42
	Other ^b	10	4
BMI level (kg·m ⁻²)	< 25	24	10
	25 – 29.9	72	30
	30 – 39.9	101	41
	≥ 40	47	19
HbA _{1c} (%)	< 6.5	67	27
	6.5 – 6.9	54	22
	7 – 7.9	68	28
	≥ 8	55	23
ASA physical status	2	22	9
	3	142	58
	4	80	33
Treatment regimen	diet	20	8
	1 oral medication	135	55
	2-3 oral medications	62	25
	insulin +/- oral meds ^c	27	11

^a = Missing values: race (2);^b = Asian (1), Hispanic (7), Middle Eastern (1), Other (1);^c = Insulin only (11), insulin and oral medications (16)IQR = interquartile range; BMI = body mass index; HbA_{1c} = hemoglobin A1c or glycosylated hemoglobin; ASA = American Society of Anesthesiologists

intracranial), physiological changes, and need for intensive care monitoring.^A In our study, the Hopkins criteria were modified according to Donati *et al.*; consequently, levels 1 and 2 were combined to form minor surgery, level 3 was moderate surgery, and levels 4 and 5 became major surgery.⁸

HbA_{1c} tests were ordered in the preoperative clinic by the anesthesiologist. We accepted HbA_{1c} values if they were drawn within three months of surgery. Perioperative glucose values were determined by finger prick testing and bedside glucometry and were derived from capillary samples. The Lifescan SureStepFlexx, Professional Blood Glucose Management System, (LifeScan Inc, Milpitas, CA, USA) was used to analyze blood samples. Preoperative blood glucose was obtained from the patient in the preoperative area. Postoperative blood glucose values were

obtained immediately upon the patient's arrival in the postoperative anesthesia care unit. All patients underwent monitored anesthesia care (sedation), general and/or regional (i.e., centroneuraxial and peripheral nerve blocks) anesthesia. On the day of surgery, the anesthesiologist chose the type of anesthesia and was not limited in the selection of drugs or fluid management. Since we did not control the timing or scheduling of cases, the duration of fasting and timing of measurements varied. Typically, patients were instructed not to eat after midnight, to discontinue oral hypoglycemics and insulin on the morning of surgery, and to maintain their regular drug schedules until the evening of the day before surgery.

Outcomes and measurements

The primary outcomes of interest were preoperative and postoperative capillary blood glucose values.

^A Pasternak LR. Preanesthesia evaluation of the surgical patient. ASA Refresher Courses in Anesthesiology 1996; 24: 205-19.

Statistical analysis

The primary objective of the analysis was to evaluate HbA_{1c} as a predictor of perioperative blood glucose control, alone, and controlling for patient and surgical characteristics. Preoperative and postoperative glucose values and the primary covariate of interest, HbA_{1c}, were analyzed as continuous variables. Whether HbA_{1c} would be predictive of postoperative glucose after controlling for the preoperative level of control was of particular interest.

The relationships between perioperative blood glucose and HbA_{1c} were evaluated using a multivariable linear model. Exploratory data analysis suggested a log transform as a variance stabilization transformation for the pre- and postoperative glucose values. Additional covariates considered were patient demographics (age, gender, race/ethnicity), clinical characteristics (BMI, ASA physical status, duration of diabetes), and perioperative variables (duration of fasting, time of preoperative blood glucose

measurement, surgical risk class, type of anesthesia, surgery start time, and duration of surgery). Age, gender, and BMI were analyzed because of their association with fasting, hyperglycemia, or impaired fasting glucose.⁹⁻¹³ Data on race/ethnicity were collected because differences in insulin sensitivity have been reported among different ethnicities.¹⁴ Duration of fasting was included in the analysis because the administration of carbohydrates preoperatively has been shown to reduce postoperative insulin resistance. Surgical risk class, duration of surgery, and type of anesthesia were considered because minimally invasive surgery and epidural anesthesia have been proposed to reduce perioperative insulin resistance and hyperglycemia.^{15,16} Time of day was considered because of the potential for diurnal variations in fasting glucose values.¹⁷ A logarithmic transformation was applied to duration of fasting, which was markedly skewed with large outliers. Univariate analysis was performed on the covariates shown in Tables 3 and 4. Variables, which were statistically

Table 2 Fasting blood glucose and perioperative variables ($n = 244^a$)

a. Fasting Blood Glucose		Median (IQR)	Range
Preoperative glucose (mmol·L ⁻¹)		7.56 (2.75)	3.38 – 23.7
Postoperative glucose ^b (mmol·L ⁻¹)		8.63 (4.07)	3.33 – 18.26
Pre- to postoperative percent change in glucose ^b		11.36 (41.33)	–2.61 – 11.32
b. Preoperative and Surgical Variables		Median (IQR)	Range
NPO duration (hr)		12.1 (4.4)	6.8 – 86.0
Time of preoperative glucose ^c		8.9 (3.7)	6.6 – 15.8
Surgery start time ^c		10.3 (4.5)	7.5 – 17.3
Length of surgery (hr)		1.95 (2.0)	0.1 – 10.2
		Frequency	%
Length of surgery (hr)	< 1	52	22
	1 – 1.9	73	30
	2 – 3.9	80	33
	≥ 4	35	15
Surgical risk	minor	81	33
	moderate	127	52
	major	36	15
Type of anesthesia	General anesthesia ^d	179	73
	Other ^e	65	27
Intraoperative Treatment ^f	Glucose	9	4
	Insulin	7	3
	Steroids	9	4

^a Missing values: preoperative glucose (2), postoperative glucose (5); NPO (nil per os) duration (5 missing, 18 missing but replaced with time from midnight to preoperative glucose measurement); Time of preoperative glucose measurement (5), surgery start time (2), length of surgery (4), intraoperative glucose (4), intraoperative insulin (4), intraoperative steroids (4)

^b Excludes 23 patients who received insulin, glucose, or steroids during surgery

^c Hours since midnight

^d General anesthesia alone (167), with peripheral nerve block anesthesia (9), with epidural (3)

^e Other anesthesia: sedation (49), peripheral nerve block (10), spinal (1), local (1), combination (4)

^f Glucose and steroids (1), glucose and insulin (1)

IQR = interquartile range; NPO = nil per os

Table 3 Univariate analysis and final model selection for preoperative glucose

Parameter	Univariate analysis			
	Estimate	95% confidence interval	P value	
Surgical Risk moderate	-0.07	-0.15	0.02	0.12
Surgical Risk major	-0.04	-0.16	0.08	0.52
Age (yr)	0.002	-0.002	0.01	0.12
Race African American	-0.26	-0.69	0.18	0.24
Race White	-0.26	-0.70	0.17	0.23
Race Hispanic	-0.25	-0.74	0.24	0.31
Race Middle Eastern	-0.08	-0.83	0.67	0.82
Race Other	-0.31	-1.06	0.44	0.41
Female	0.05	-0.03	0.13	0.20
BMI (kg·m ⁻²)	-0.001	-0.005	0.003	0.77
DM duration (yr)	0.003	-0.003	0.01	0.23
ASA physical status 3	-0.13	-0.27	0.02	0.07
ASA physical status 4	-0.12	-0.27	0.03	0.10
HbA _{1c} (%)	0.07	0.04	0.10	<0.001
Log NPO duration	-0.06	-0.16	0.04	0.22
Surgery Start time	-0.02	-0.04	-0.01	0.01
Final model				
Intercept	1.51	1.30	1.72	<0.001
HbA _{1c}	0.07	0.04	0.10	<0.001

BMI = body mass index; ASA = American Society of Anesthesiologists; DM = diabetes mellitus; NPO = nil per os; HbA_{1c} = hemoglobin A1c or glycosylated hemoglobin

Univariate analysis and the final model. Model selection was performed on this model, and the final model consisted only of HbA_{1c}

significant in the univariate analysis, were used in the multivariate analysis and model selection. We employed the Least Absolute Shrinkage and Selection Operator (LASSO) for model selection using the Bayesian information criterion (BIC) as the model selection approach.^{18,19} For the models, the residuals were checked for any aberrations and for the assumption of normality.

Results

HbA_{1c}, which reflects long-term glucose control, is a strong predictor of preoperative glucose levels, and it predicts immediate postoperative glucose values in the absence of a preoperative glucose value. Additionally, an immediate preoperative glucose value also predicts postoperative glucose.

For preoperative glucose values, the model selection criteria chose HbA_{1c} as the sole predictor. For postoperative glucose values, preoperative glucose was chosen as the only predictor. In the absence of preoperative glucose as an explanatory variable, a second model chose covariates that were available or could be estimated prior to the day of surgery, i.e., HbA_{1c} and duration of surgery.

If preoperative glucose values are not considered, one could still predict preoperative glucose using HbA_{1c} and then use this predicted value to estimate postoperative glucose using the first model with a marginal increase in the standard error of the prediction rather than estimate the duration of surgery for the second model.

Patient demographic and clinical characteristics are shown in Table 1. Ninety-seven percent of patients in our study had HbA_{1c} tested within one month (31 days) of surgery. Patient characteristics were notable for a mean BMI of 34. Fifty-one percent of patients had an HbA_{1c} $\geq 7\%$, with 23% of patients having an HbA_{1c} $\geq 8\%$.

Blood glucose and perioperative variables are summarized in Table 2. Preoperative glucose values exceeded 6.10 mmol·L⁻¹ in 80% of patients and 9.99 mmol·L⁻¹ in 16% of patients. Postoperative glucose values exceeded 6.10 mmol·L⁻¹ in 84% of patients and 9.99 mmol·L⁻¹ in 38% of patients.

Preoperative blood glucose

HbA_{1c} was a strong predictor of preoperative glucose levels in univariate and multivariable analysis (Figure 1). Patient characteristics, such as age, race, gender, BMI, duration of diabetes, diabetes medication regimen, and fasting duration were not significant. In univariate analysis, earlier time of day of glucose measurement was associated with higher preoperative glucose. Only HbA_{1c} remained significant in multivariable analysis.

Postoperative blood glucose

An immediate preoperative glucose value was a highly significant predictor of an immediate postoperative glucose value (Table 4). HbA_{1c} was also predictive of postoperative glucose in the absence of a preoperative glucose value. In addition to HbA_{1c} and preoperative glucose, length of surgery was a significant predictor of postoperative glucose in univariate and multivariable analysis. Patient and surgical characteristics, such as age, race, gender, BMI, duration of diabetes, diabetes medication regimen, type of anesthesia, surgical risk classification, and fasting duration were not significant.

Discussion

In this study, we found that long-term glucose control affected perioperative glycemic control in patients with diabetes who underwent elective non-cardiac surgery. We investigated the relationship of HbA_{1c} and patient and surgical characteristics on perioperative blood glucose control in patients undergoing non-cardiac surgery.

Table 4 Univariate analysis and final model selection for postoperative glucose

Parameter	Univariate Analysis			
	Estimate	95% confidence interval		P value
Surgical Risk moderate	0.20	0.12	0.29	<0.001
Surgical Risk major	0.29	0.17	0.41	<0.001
Age (yr)	−0.003	−0.01	0.001	0.09
Race African American	−0.33	−0.78	0.12	0.14
Race White	−0.27	−0.72	0.18	0.24
Race Hispanic	−0.14	−0.65	0.36	0.58
Race Middle Eastern	−0.19	−0.96	0.58	0.62
Race Other	−0.54	−1.31	0.23	0.16
Female	0.01	−0.08	0.09	0.89
BMI (kg·m ^{−2})	0.01	0.001	0.01	0.03
DM duration (yr)	0.01	−0.001	0.01	0.07
ASA physical status 3	−0.15	−0.30	−0.01	0.04
ASA physical status 4	−0.08	−0.23	0.08	0.31
HbA _{1c} (%)	0.08	0.05	0.12	<0.001
Time of day for preoperative glucose	−0.02	−0.04	0.00	0.03
Log preoperative glucose	0.26	0.14	0.38	<0.001
Surgery start time	−0.02	−0.04	0.00	0.02
Anesth (GA/Regional)	0.20	−0.16	0.56	0.28
Anesth (GA/Epidural)	−0.23	−0.33	−0.13	<0.001
MAC	−0.13	−0.33	0.08	0.21
Regional	−0.37	−0.99	0.25	0.23
Spinal	−0.29	−0.92	0.33	0.34
Combo Anesth	−0.08	−0.39	0.24	0.62
log NPO duration	−0.001	−0.01	0.003	0.70
Surgery duration (hr)	0.06	0.04	0.08	<0.001
	Final model			
Intercept	1.62	1.34	1.86	<0.001
Log preoperative glucose	0.26	0.14	0.38	<0.001

GA = general anesthesia; NPO = nil per os; ASA = American Society of Anesthesiologists; DM = diabetes mellitus; BMI = body mass index; HbA_{1c} = hemoglobin A1c or glycosylated hemoglobin; MAC = monitored anesthesia care

Univariate Analysis and the final model. Model selection was performed on this model, and the final model consisted only of log-preoperative glucose

Patients with poor glycemic control (HbA_{1c} ≥ 7%) had mean preoperative glucose levels 2.09 mmol·L^{−1} higher and postoperative glucose levels 1.86 mmol·L^{−1} higher than patients with good glucose control (HbA_{1c} < 7%). While this difference may seem insignificant, data suggest that increases in glucose as small as 1.11 mmol·L^{−1} among cardiac surgery patients are associated with a 34% increase in the likelihood of a perioperative complication, such as infection, delirium, need for mechanical ventilation, or death.⁶ While preoperative glucose is clearly the stronger predictor of postoperative control, HbA_{1c} has the advantage of being available before the day of surgery.

Duration of surgery has been associated with postoperative complications.²⁰ In our study, duration of surgery was

a significant predictor of elevated postoperative blood glucose. We hypothesize that patients who underwent longer surgeries were more likely to have had a more robust stress response. Although glucose values increased on average from the pre- to the postoperative period, glucose levels decreased in one-third of our patients in the perioperative period without glucose-regulating medications.

The literature supporting short-term tight glucose control in the operating room and the intensive care unit is controversial.^{21–23} Results from the only randomized controlled trial of intraoperative glucose management indicated that targeting lower glucose values in the operating room did not confer benefit.²² At the same time, a large body of evidence shows an association between

Fig. 1 HbA_{1c} % vs log-preoperative glucose

perioperative hyperglycemia and poor outcomes, suggesting that perioperative glucose levels are a marker of morbidity.^{5,24} If treatment of glucose values in the immediate perioperative or critical care period does not confer benefit, perhaps the goal should be to achieve improved control of diabetes in anticipation of elective surgery. In this context, Dunkelgrun *et al.* suggested that an oral glucose tolerance test (OGTT) might be useful to stratify perioperative risk.²⁵ We have shown that an HbA_{1c} can be useful to identify patients with diabetes who may be at risk for poor perioperative glucose control during elective surgeries. Obtaining an HbA_{1c} is less costly, cumbersome, unpleasant, and time consuming than undergoing an OGTT. Additionally, most perioperative physicians can order and interpret an HbA_{1c} result easily. Several studies have considered the difficulty of achieving intraoperative normoglycemia.^{26,27} It may be prudent, safer, and more effective to improve glucose control, and therefore, decrease HbA_{1c} well before surgery.

Our study has several limitations. We did not screen our patients for conditions that may affect HbA_{1c} values, such as transfusions, high erythrocyte turnover in hemolysis, or hemoglobin variants. Since our patients were scheduled for elective surgeries, there was a low likelihood of recent transfusions or significant hemolytic conditions. We did not standardize the length of time between HbA_{1c} determination and the day of surgery, but all values were drawn within three months of surgery, with 97% of values drawn within 31 days. We did not standardize the duration of fasting or the timing of perioperative blood glucose determination, and we included a variety of surgeries and all types of anesthesia. The study design was purposeful and pragmatic and reflected common clinical situations.

In conclusion, a significant number of patients who have elective surgery have poor glucose control. We have shown that HbA_{1c} can identify diabetic patients who are at higher risk of elevated perioperative glucose levels. In addition, patients who arrive at the hospital with elevated preoperative blood glucose values on the day of surgery are at greater risk for high blood glucose levels postoperatively. Our study identifies specific characteristics, such as HbA_{1c} and length of surgery, as correlates of poor glucose control in the immediate perioperative period. Our data highlights risk factors associated with surgical hyperglycemia, but not causality. Further studies are needed to delineate whether intensive glucose control in advance of elective surgery improves outcomes in patients with and without diabetes.

Acknowledgement Dr. Moitra had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The authors would like to thank Sally Kozlik for her editorial assistance.

Financial support None.

Competing interests None declared.

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