The Effect of Elevated A1C on Immediate Postoperative Complications: A Prospective Observational Study

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IN BRIEF This study examined whether elevated A1C in patients with diabetes is associated with a higher incidence of postoperative infections and other complications. Researchers followed 50 noncardiac surgical patients for 7 postoperative days. Half of the patients had an A1C <7% and the other half had an A1C ≥7%. The two groups were otherwise comparable except that the higher-A1C group had significantly higher pre-induction and postoperative blood glucose levels, with wider variability in the first 24 hours after surgery. During the first postoperative week, 11 patients developed complications, of whom 10 were in the higher-A1C group. Elevated A1C, unlike a single preoperative blood glucose value, may predict difficult postoperative glucose control and postsurgical complications.

Infection or impaired wound healing in the immediate postoperative period leads to poor surgical outcomes and increased health care costs. Hyperglycemia has been shown to be a significant factor associated with postoperative infection (1–3). Chronic complications of diabetes such as neuropathy and nephropathy have been attributed to poor long-term control of blood glucose (4). Prolonged exposure to high glucose levels causes glycosylation of proteins, which impairs the activity of neutrophils and fibroblasts, leading to poor wound healing and infection (5).

A1C is formed by irreversible glycation of the amino acids in the hemoglobin molecule and reflects glycemic control over the previous 8–12 weeks. It is used as one of the diagnostic criteria for diabetes, and the American Diabetes Association recommends an A1C level <7% as an acceptable glycemic target for most people (6). During the past decade, there have been suggestions that better long-term glycemic control may play a significant part in abating postoperative complications (7–10). However, the evidence is not conclusive (11).

The purpose of this prospective, observational pilot study was to determine whether elevated A1C is associated with a higher incidence of surgical wound problems, surgical site infection, or infection elsewhere within the first postoperative week. The secondary objective was to compare glycemic control and blood glucose variability during the immediate postoperative period.

Research Design and Methods

All adult patients with diabetes who were scheduled for elective surgery were eligible to be enrolled into this institutional review board–approved, prospective, observational study. The subjects were identified from the daily operating-room schedule. Patients having cardiac surgery or a surgical procedure expected to take <1 hour were excluded, as were those with preexisting infection and those taking antibiotics, steroids, chemotherapy, or immunosuppressive medications.

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The plan for this pilot study was to enroll all eligible, consecutive patients throughout a 6-month period until at least 25 subjects (a convenience sample) were enrolled in each of two groups: Group A, having an A1C <7% and Group B, having an A1C ≥7%. A1C was assessed for all of the patients within 2 weeks of their surgery.

The data collected for each patient included demographic details (age, sex, weight, height, and comorbidities); diabetes details (type of diabetes, antidiabetic medications, and A1C); type and duration of surgery; all blood glucose values measured during the perioperative period; and the average of all blood glucose values measured during the first postoperative 24-hour period. Additional data collected focused on complications during the first postoperative 7 days, including surgical site infection or infection elsewhere (pyrexia or inflammation of the surgical site that resulted in administration of prophylactic antibiotic was recorded as postoperative infection); surgical wound problems (any inflammation, excessive oozing, delayed healing, or dehiscence of the surgical incision was recorded as a surgical wound problem); and other morbidity or mortality.

Statistical Methods

All continuous variables were analyzed by Mann–Whitney U test, and discrete variables were analyzed by Fisher's exact test. Descriptive statistics are reported as mean ± SD. Statistical analysis was conducted using R Project for Statistical Computing (The R Foundation, Vienna, Austria). *P* values <0.05 were considered significant.

Results

During the study period, all consecutive patients with diabetes who were scheduled for elective, noncardiac surgery were selected. After excluding 13 subjects based on the exclusion criteria (6 for surgical duration <1 hour, 2 for systemic steroid use, 4 for taking antibiotics, and 1 for preexisting infection), 25 subjects were enrolled into each study group (Group A for those with an A1C <7% and Group B for those with an A1C ≥7%).

Patient Demographics

The two groups were comparable with respect to age, BMI, sex, associated comorbidities, and duration and type of surgical procedures (Table 1). Group B had significantly higher pre-induction glucose levels (*P* <0.0001), higher A1C levels (*P* <0.0001), and more patients on insulin (*P* = 0.02), whereas more patients in Group A were on metformin (*P* = 0.039).

Glucose Levels and Postoperative Complications

One patient from Group A and 10 from Group B had pre-induction glucose values >200 mg/dL, and 4 of these patients, all from Group B, developed postoperative infections. For each patient, all glucose values measured during the first 24 hours after surgery were averaged, and glucose variability was calculated. Average glucose during the first 24 hours was higher in Group B (*P* = 0.0016), as

TABLE 1. Patient Demographics

	Group A (A1C <7%) (*n* = 25)	Group B (A1C ≥7%) (*n* = 25)	*P*†
Age (years)*	62.4 ± 10.1	63.9 ± 11.8	0.76
Sex (male/female)	14/11	17/8	0.56
BMI (kg/m^2)*	36.5 ± 10.1	36.2 ± 5.9	0.61
Duration of surgery (hours)*	2.9 ± 2.1	3.5 ± 2.6	0.40
A1C (%)*	6.2 ± 0.4	8.4 ± 1.1	**<0.0001**
Pre-induction glucose (mg/dL)*	123.5 ± 31.2	189.8 ± 60.6	**<0.0001**
Comorbidities (*n*)			
Hypertension	18	22	0.29
Coronary artery disease	10	7	0.55
Obstructive sleep apnea	14	17	0.56
Malignancy	5	6	1.00
Chronic kidney disease	1	6	0.10
Medications (*n*)			
Insulin	5	14	**0.020**
Metformin	20	12	**0.039**
Other antidiabetic drugs	11	12	1.00
Antihypertensive drugs	20	22	0.70
Chronic pain medications	6	13	0.08
Anticoagulants	7	3	0.29
Surgical procedure (*n*)			
Gynecological	1	3	0.60
Orthopedic	9	6	0.54
Colorectal	7	5	0.74
Spinal	4	6	0.72
Urological	2	2	1.00
Head and neck	1	3	0.60
Vascular	1	0	1.00

**Mean ± SD. †Bold indicates statistical significance.*

TABLE 2. Postoperative Glucose and Infection Details

	Group A (A1C <7%) (*n* = 25)	Group B (A1C ≥7%) (*n* = 25)	*P*†
Glucose on postoperative day 1 (mg/dL)*	152.7 ± 32.4	183.0 ± 40.4	**0.0016**
Glucose variability on postoperative day 1 (mg/dL)*	22.8 ± 12.3	43.0 ± 32.2	**0.02**
Mean glucose >200 mg/dL on postoperative day 1 (*n*)	5	13	**<0.05**
Infection (at surgical site or elsewhere) or surgical wound problems (drainage, hematoma, dehiscence) (*n*)	1	10	**0.0046**
Other complications (*n*)			
Acute renal failure	0	1	—
Postoperative ileus	1	0	—
Systemic lupus erythematosus flare-up	1	0	—
Supraventricular tachycardia	0	1	—

**Mean ± SD. †Bold indicates statistical significance.*

was glucose variability (P = 0.02) (Table 2). During the first postoperative day, of the 18 patients (5 from Group A and 13 from Group B) who had glucose values >200 mg/dL (Table 2), 4 from Group B developed infections.

During the first postoperative week, nine patients developed surgical site infections or surgical wound problems, one developed a urinary tract infection, and one had hospital-acquired pneumonia. Of these 11 patients, 10 were in Group B, and 1 was in Group A (Table 2). This translates to a relative risk of 10.0 for a person with an A1C ≥7% to develop postoperative complications. The one patient from Group A who developed surgical wound hematoma had an A1C of 6.9%. There were no significant differences in the distribution of surgical procedures or the type of diabetes between those who did and did not develop postoperative wound problems. Apart from these 11 patients, 4 developed other complications (Table 2), all of which were self-limiting.

A subgroup analysis of those who developed postoperative complications showed that they had significantly higher A1C levels (P = 0.0021) and pre-induction glucose levels (P = 0.01), as well as a longer duration of intubation and lengthier intensive care unit stay (Table 3). Although glucose levels on the first postoperative day were comparable between groups, variability in glucose levels was significantly greater among those who developed complications (P = 0.04). Because reliable information about patients' duration of diabetes was not available, use of insulin was taken as a surrogate marker for severity of diabetes. Of the 14 patients in Group B who were on insulin, only 6 developed complications, whereas 4 of the 11 patients who were not on insulin developed complications. This was not a significant difference (P = 0.74).

TABLE 3. Comparison of Patients Stratified by Development of Postoperative Complications

	Developed Complications (*n* = 11)	Had No Complications (*n* = 39)	*P*†
Age (years)*	66.6 ± 15	62.2 ± 9.5	0.21
BMI (kg/m^2)*	34.9 ± 6.5	36.8 ± 8.6	0.70
Duration of surgery (hours)*	4.7 ± 3.2	2.8 ± 1.9	0.1
Duration of intubation (hours)*	14.5 ± 22	3.7 ± 2.0	**0.04**
Length of intensive care unit stay (days)*	1.0 ± 1.5	0.1 ± 0.4	**0.0023**
A1C (%)*	8.5 ± 1.5	7.0 ± 1.2	**0.0021**
Median A1C (%)	7.9	6.5	
Pre-induction glucose (mg/dL)*	194.9 ± 65.6	145.9 ± 52	**0.01**
Glucose on postoperative day 1*	159.9 ± 48.5	168.8 ± 50.3	0.59
Glucose variability on postoperative day 1*	43.0 ± 41.3	19.6 ± 19.0	**0.04**

**Mean ± SD. †Bold indicates statistical significance.*

Discussion

In this observational study, patients with diabetes who had an A1C ≥7% had a higher incidence of postoperative infection and surgical wound problems than those with an A1C <7%. These patients also showed higher blood glucose levels with wider variability in the postoperative period.

Hyperglycemia leads to glycation of intracellular and extracellular proteins, which subsequently form advanced glycation end-products (AGEs), and this process has an important role in the pathophysiology of the chronic complications of diabetes such as nephropathy, neuropathy, and retinopathy. AGEs cause release of proinflammatory molecules such as tumor necrosis factor-α that can limit wound closure (12). In diabetic mice, AGEs have also been shown to affect the functioning of fibroblasts, leading to reduced collagen deposition, reduced proliferation of endothelial cells, and impaired angiogenesis (13).

Although it is widely accepted that hyperglycemia in the perioperative period is associated with surgical site infections and other complications after surgery (1,2,10), tight glycemic control in the postoperative period may act as a double-edged sword, increasing the risk of hypoglycemia and its associated higher mortality (14). Thiessen et al. (15) have suggested that, in patients undergoing cardiopulmonary bypass, accepting glucose values up to 180 mg/dL would be prudent to avoid hypoglycemia in the pursuit of achieving normoglycemia.

In this study, postoperative glucose levels and their variability were both significantly higher among those with an A1C ≥7% (Table 2), despite efforts to keep blood glucose levels to <180 mg/dL, per institutional guidelines. In the subgroup analysis comparing patients who developed postoperative complications to those who did not, A1C levels and glycemic variability were significantly higher among those who developed complications, whereas mean glucose on the first postoperative day did not differ significantly (Table 3). This could suggest that factors other than hyperglycemia may be contributing to postoperative complications.

Knapik et al. (9), in a retrospective study, looked at the prevalence of elevated A1C and its association with postoperative complications such as stroke, renal failure, wound infection, and perioperative myocardial infarction in 2,665 patients undergoing coronary artery surgery. Of the 782 who had diabetes (29%), 283 (38%) had an A1C >7%. The only association they found with elevated A1C was a higher incidence of perioperative myocardial infarction (9). Halkos et al. (8) showed that A1C >8.6% was associated with a fourfold increase in mortality in patients undergoing coronary artery bypass surgery. Acott et al. (11) in a retrospective review of nearly 39,000 patients undergoing major surgery, observed that of the 2,960 patients with diabetes, 780 (26%) developed one or more complications. They showed that patients with diabetes were at increased risk for complications and death after surgery compared to those who did not have diabetes, but the risk did not correlate with A1C levels.

As the prevalence of diabetes increases in the population, it seems likely that there will be a corresponding increase in the number of people with diabetes who need scheduled surgery (16). The important socioeconomic question, then, is whether A1C levels should be measured preoperatively in all patients with diabetes. A1C is a measure of glycemic control, and the cause of poor glycemic control could be multifactorial, encompassing both noncompliance to treatment and poor response to treatment. An elevated A1C result, unlike a single preoperative glucose value, could predict difficulty in achieving postoperative glycemic control and the development of complications. Although the evidence showing an association between elevated A1C and postoperative complications is inconsistent (15,17,18), the authors of a recent editorial (19) argue that a preoperative A1C screening for all patients with diabetes is justified by the fact that a relatively inexpensive test can identify candidates for increased surveillance to prevent a potentially serious complication.

This prospective study, in which a small sample of patients with diabetes were observed for adverse outcomes in the immediate postoperative period, has resulted in more questions than answers. Among these questions are:

1. Is postoperative morbidity the result of hyperglycemia or of poor long-term glycemic control or both? The fact that the mean glucose value on the first postoperative day was comparable between those who developed complications and those who did not (Table 3) suggests that hyperglycemia may not be the only relevant factor for wound complications. In a patient with poor long-term glycemic control, the development of postoperative complications could either be a consequence of glycosylation of tissue proteins and impaired neutrophil activity or a direct consequence of elevated A1C. Either way, however, an elevated A1C could be an easily measured marker.
2. Should elective surgery in a patient with an elevated A1C be rescheduled? If so, what would be an acceptable A1C level for surgery? In this study, the median A1C among patients who developed complications was 7.9%, compared to 6.5% among those who did not have complications.

In summary, patients with A1C ≥7% have a greater incidence of surgical wound complications and also wider postoperative glycemic variability. Although a standard protocol was used for glycemic control in all of the patients in this study, glycemic control was more difficult to maintain in those with higher A1C values. Given the current trend of implementing a perioperative "surgical home" and reducing postoperative hospital days and readmissions (20), it seems prudent to optimize glycemic control before scheduling patients for elective surgery. A1C could be a valuable indicator in such efforts.

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

Author Contributions

P.C. collected and researched data and wrote the manuscript. K.K.H. helped obtaining patient consent and data collection. C.L.M. helped with institutional

review board submission, patient identification, and obtaining patient consent. A.S.B. helped with statistical analysis of the data. V.T.C. conceived of and planned the study, performed institutional review board submission, researched data, and wrote the manuscript. V.T.C. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Golden SH, Peart-Vigilance C, Kao WH, Brancati FL. Perioperative glycemic control and the risk of infectious complications in a cohort of adults with diabetes. Diabetes Care 1999;22:1408–1414

2. Pomposelli JJ, Baxter JK, Babineau TJ, et al. Early postoperative glucose control predicts nosocomial infection rate in diabetic patients. JPEN J Parenter Enteral Nutr 1998;22:77–81

3. Pozzilli P, Leslie RD. Infections and diabetes: mechanisms and prospects for prevention. Diabet Med 1994;11:935–941

4. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405–412

5. Alba-Loureiro TC, Munhoz CD, Martins JO, et al. Neutrophil function and metabolism in individuals with diabetes mellitus. Braz J Med Biol Res 2007;40:1037–1044

6. American Diabetes Association. Standards of medical care in diabetes—2013. Diabetes Care 2013;36(Suppl. 1):S11–S66

7. Dronge AS, Perkal MF, Kancir S, Concato J, Aslan M, Rosenthal RA. Long-term glycemic control and postoperative infectious complications. Arch Surg 2006;141:375–380

8. Halkos ME, Puskas JD, Lattouf OM, et al. Elevated preoperative hemoglobin A1c level is predictive of adverse events after coronary artery bypass surgery. J Thorac Cardiovasc Surg 2008;136:631–640

9. Knapik P, Ciesla D, Filipiak K, Knapik M, Zembala M. Prevalence and clinical significance of elevated preoperative glycosylated hemoglobin in diabetic patients scheduled for coronary artery surgery. Eur J Cardiothorac Surg 2011;39:484–489

10. Zerr KJ, Furnary AP, Grunkemeier GL, Bookin S, Kanhere V, Starr A. Glucose control lowers the risk of wound infection in diabetics after open heart operations. Ann Thorac Surg 1997;63:356–361

11. Acott AA, Theus SA, Kim LT. Long-term glucose control and risk of perioperative complications. Am J Surg 2009;198:596–599

12. Ahmed N. Advanced glycation endproducts: role in pathology of diabetic complications. Diabetes Res Clin Pract 2005;67:3–21

13. Hennessey PJ, Ford EG, Black CT, Andrassy RJ. Wound collagenase activity correlates directly with collagen glycosylation in diabetic rats. J Pediatr Surg 1990;25:75–78

14. NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009;360:1283–1297

15. Thiessen S, Vanhorebeek I, Van den Berghe G. Glycemic control and outcome related to cardiopulmonary bypass. Best Pract Res Clin Anaesthesiol 2015;29:177–187

16. Jacober SJ, Sowers JR. An update on perioperative management of diabetes. Arch Intern Med 1999;159:2405–2411

17. Goodenough CJ, Liang MK, Nguyen MT, et al. Preoperative glycosylated hemoglobin and postoperative glucose together predict major complications after abdominal surgery. J Am Coll Surg 2015;221:854–861

18. Bock M, Johansson T, Fritsch G, et al. The impact of preoperative testing for blood glucose concentration and haemoglobin A1c on mortality, changes in management and complications in noncardiac elective surgery: a systematic review. Eur J Anaesthesiol 2015;32:152–159

19. Mutter TC, Bryson GL. Choosing wisely and preoperative hemoglobin A1c testing: what should it mean? Can J Anesth 2016;63:1307–1313

20. Shafer SL, Donovan JF. Anesthesia & Analgesia's collection on the perioperative surgical home. Anesth Analg 2014;118:893–895