Pre-operative Glycosylated Hemoglobin Level and Fasting Blood Sugar as Markers for Risk of Acute Kidney Injury in the Immediate Post-Operative Period Among Type 2 Diabetic Patients After Elective Abdominal Surgery

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Abstract

Objectives. The study aimed to identify whether pre-operative glycosylated hemoglobin level (HbA1c) and fasting blood sugar (FBS) can be used as markers for the development of acute kidney injury (AKI) in the immediate post-operative period of type 2 diabetic patients after elective abdominal surgery.

Methods. This retrospective cohort pilot study included seventy-four diabetic patients who underwent elective abdominal surgery from 2015 to 2018. HbA1c and FBS, demographic data, comorbidities, type and indication of surgery, and treatment history were correlated with the development of AKI using logistic regression analysis.

Results. In this cohort, 12% of subjects developed AKI. Univariate and multivariate logistic regression analysis, however, showed that neither HbA1c and FBS nor other studied factors were predictive for the occurrence of AKI (OR 2.55, p= 0.26 and OR 0.64, p= 0.72 respectively).

Conclusion. Pre-operative HbA1c and one-time FBS values in diabetic patients undergoing elective abdominal surgery procedures were not statistically predictive of AKI in the present data. However, the observed trend towards the risk of AKI among the elevated HbA1c subset of patients should drive further studies with a greater sample size and of a prospective nature looking at other metabolic factors contributing to AKI.

Keywords: Pre-operative Glycosylated Hemoglobin level, Fasting Blood Sugar, Acute Kidney Injury

Introduction

The increasing number of diabetic patients undergoing elective abdominal surgeries warrants the identification of a marker or markers that can help physicians assess who are at a greater risk of AKI post-operatively. Surgical diabetic patients have a 23% to 37% increase in 30-day mortality and in-hospital morbidity compared with patients without diabetes.[1] One complication associated with significant morbidity and mortality across all settings is the occurrence of AKI.[2] The incidence of post-operative AKI accounts for up to 36% of all hospital-acquired AKI events.[3,4]

Despite an exhaustive literature search, none of the currently available literature studied the risk of AKI among an exclusively diabetic population. Furthermore, the little existing literature shows conflicting results regarding the utility of HbA1c, a parameter of long-term glucose concentrations in the past three months, as a predictor of post-operative complications. For example, in the study of Acott et al., diabetics were at a significantly increased risk for complications such as surgical site infection, dysrhythmia, heart failure, urinary tract infection, stroke, pneumonia, bleeding, and AKI. However, this increased risk was not directly correlated with elevated pre-operative glycosylated hemoglobin. Therefore, delay of surgical procedures may not be warranted simply because of poor long-term glycemic control. [5] Similarly, Abdelmalak et al. found that the

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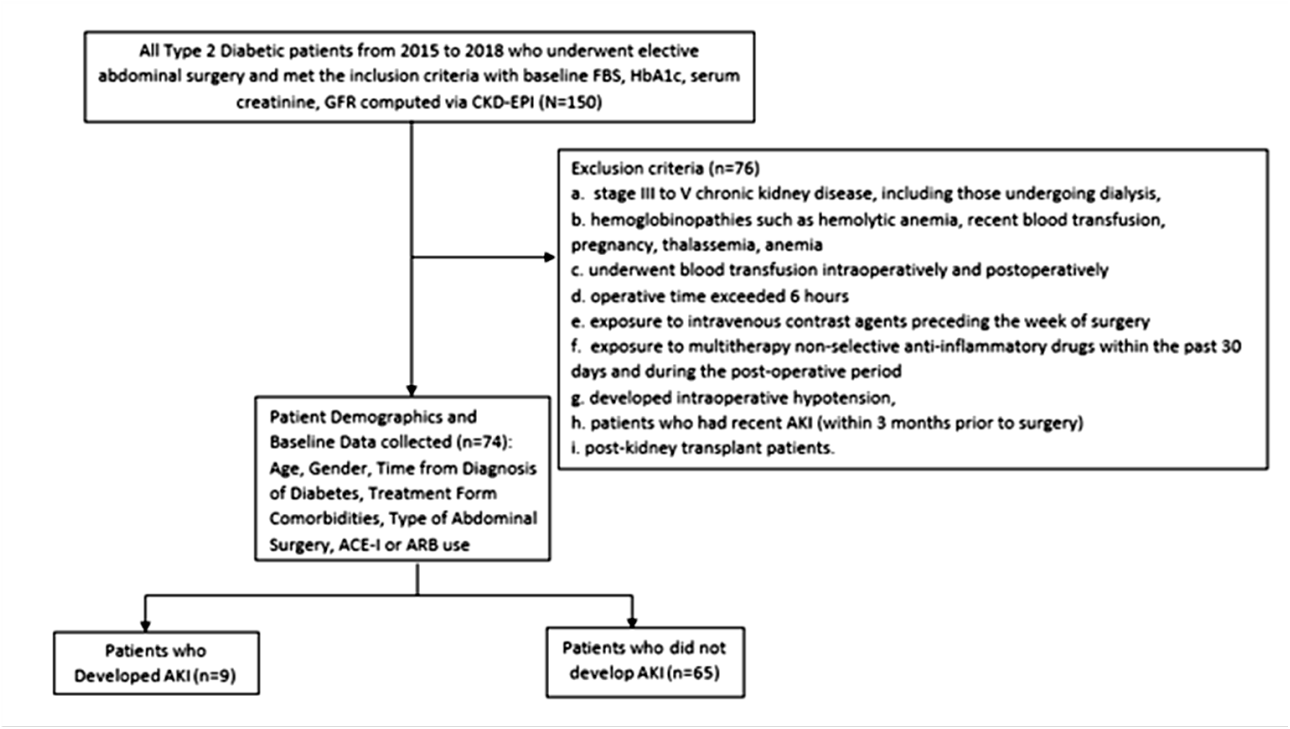

Figure 1. Study procedures followed in this study

relationship between pre-operative FBS and the probability of post-operative complications (including AKI) did not significantly differ between patients with and without diabetes mellitus.[6] On the contrary, Gustafsson et al. suggested that elevated pre-operative HbA1c may be used to identify patients at higher risk of poor post-operative glycemic control and post-operative complications after major abdominal surgery.[7] This study did not evaluate the utility of HbA1c as a predictor of AKI post-operatively, which this current study will further evaluate.

Therefore, this pilot study aimed to identify whether pre-operative HbA1c and FBS could be used as markers for the development of AKI in the immediate post-operative period of type 2 diabetic patients after elective abdominal surgery in a pilot setting. Understanding which patients are at risk of AKI can help the clinicians anticipate which subset of patients warrant intensive pre-operative preparations and more vigilant post-operative renal function monitoring.

Methods

This pilot retrospective cohort study included patients with type 2 diabetes admitted for elective abdominal surgery from January 2015 to December 2018 at a single tertiary center who satisfied the inclusion criteria. This study was approved by the local Institutional Review Board (MMC IRB no. 2018-101) and was conducted following the Declaration of Helsinki and the Guidelines for Good Clinical Practice.

Patient data including age, gender, significant comorbidities, type of surgery, pre-procedural and post-procedural serum creatinine, GFR (computed via CKD-EPI equation), and use of ACEi/ ARBs were collected and analyzed. The patients were further analyzed according to their HbA1c and FBS results. The occurrence of AKI was assessed using the criteria in the 2012 KDIGO guidelines as evidenced by an increase in the serum creatinine by 0.3 mg/dl within 48 hours or increase in serum creatinine $\geq$ 1.5 times baseline or decrease in urine output $\leq$ 0.5 ml/kg body weight/hour for 6 hours).[8] Pre-operative serum creatinine, FBS and HbA1c should be collected within two months before surgery while post-operative serum creatinine or decrease in urine output should have been documented up to one week post-operatively. The study methodology is illustrated in *Figure 1*.

A predetermined cut-off level for HbA1c 7% as recommended by ADA cut-off and as used by similar studies used this ADA cut-off. [9, 10] Meanwhile, the cut off level of FBS was set at 100 mg/dl, reflecting normal levels for the general population as set by the ADA. [10]

Inclusion and Exclusion Criteria. Patients aged 18 years and older who were diagnosed with type 2 diabetes mellitus and were admitted for elective abdominal surgery. They underwent HbA1c and FBS determination at Makati Medical Center using the Abbott Architect c800 whole blood (national glycohemoglobin standardization program certified) and the Chemiluminescence Method (Abbott, Illinois) respectively. The said tests must be done before surgery. In addition, they must have available results for serum creatinine pre-operatively, post-operatively, and whose urine output was documented. Those with normal kidney function or mild impairment

Table I. Patient Characteristics and Presence or Absence of Acute Kidney Injury (n= 74)

Characteristic	Frequency	AKI absent (n=65)	AKI present (n=9)	*p-value*
Age (average, years)		63	65	
Gender				
Male	47	40 (85%)	7 (15%)	0.472 [b]
Female	27	25 (93%)	2 (7%)	
Years since Diagnosis of diabetes				
< 5 years	19	17 (89%)	2 (11%)	0.905[c]
5 - 10 years	26	22 (85%)	4 (15%)	
> 10 years	29	26 (90%)	3 (10%)	
Type of treatment for Type 2 Diabetes Mellitus				
None	2	2 (100%)	0	0.541 [c]
OHA treatment [a]	63	56 (89%)	7 (11%)	
Insulin Treatment	2	2 (100%)	0	
Combined Treatment	7	5 (71%)	2 (29%)	
Comorbidities				
none	24	22 (92%)	2 (8%)	0.004* [c]
CKD	4	3 (75%)	1 (25%)	
Hypertension	38	35 (92%)	3 (8%)	
past AKI	1	1 (100%)	0	
obstructive uropathy	2	2 (100%)	0	
Nephrolithiasis	1	1 (100%)	0	
multiple	4	4 (100%)	0	
Type of Abdominal Surgery				
Colorectal	10	7 (70%)	3 (30%)	0.162 [c]
Upper Gastrointestinal	18	16 (89%)	2 (11%)	
Urologic	17	16 (94%)	1 (6%)	
Splenectomy	3	2 (77%)	1 (33%)	
Exploratory Laparotomy	9	7 (78%)	2 (22%)	
Total Abdominal Hysterectory	3	3 (100%)	0	
Laparoscopic	14	14 (100%)	0	
HbA1c				
< 7%	44	39 (89%)	5 (11%)	0.735 [c]
≥ 7%	30	26 (87%)	4 (13%)	
FBS				
< 100 mg/dl	9	8 (89%)	1 (11%)	1.000 [c]
≥ 100 mg/dl	65	57 (88%)	8 (12%)	
ACE-Inhibitors and ARB use				
None	34	30 (88%)	4 (12%)	1.000 [c]
Present	40	35 (87%)	5 (13%)	

[a]Oral hypoglycemic agent treatment [b] t-test [c] Fisher's exact test *statistically significant

(CKD stages I and II whose eGFR is ≥ 60 ml/min/ 1.73 m^2) were included.

Meanwhile, patients were excluded if they belonged to stage III (eGFR 30 to 59 ml/min/ 1.73 m^2), stage IV (eGFR 15 to 29 ml/min/1.73 m^2), and stage V (eGFR less than 15 ml/min/1.73 m^2) of chronic kidney disease, including those undergoing dialysis, or if they have one of the following comorbidities, medication exposures, and intra- and post-operative complications as detailed in *Figure 1*.

Statistical Analysis. All patients from the database fulfilling the inclusion criteria were included in this pilot study. However, the required sample size was computed to ensure the power of the study. The required sample size of 66 was computed using the open-source calculator, G*Power, Version 3.1.9.7 (Dusseldorf University, Germany). A medium effect size of 0.7 was chosen based on the association of diabetes and AKI reported in Brienza et al.[3]. The margin of error used was 10%, with a 95% confidence interval and a power of 80%.

Descriptive statistics such as mean and standard deviation were used to present data on the demographic and clinical profile of the recruited subjects. Frequency and percentages were used to present categorical data. Differences in characteristics were compared using Student's T-test if continuous variables and Fischer's Exact Test if categorical variables were present. Statistically significant associations were subjected to post-hoc analysis using pairwise Fisher's exact test using Benjamini-Hochberg FDR method for multiple hypothesis testing at a 5% cut-off. Simple logistic regression was done to determine the variables that probably have a significant association with having AKI. All variables, including demographic data, comorbidities, type and indication of surgery, and treatment history, were also included in the multiple logistic regression analysis to determine the association of each variable while accounting for the confounding effect of other variables. P values <0.05 were considered statistically significant. All statistical tests were carried out using IBM SPSS Statistics for Windows, Version 24.0 (Armonk, NY) and R statistical computing (Vienna, Austria).

Results

Participants. A total of 150 type 2 diabetic patients underwent elective abdominal from 2015 to 2018 at the Makati Medical Center. The following patients were excluded (n=76) from the study: (a) CKD stage III to V (n= 16), (b) presence of hemoglobinopathies (n= 12), (c) underwent blood transfusion intraoperatively and post-

operatively (n=10), (d) operative time exceeded 6 hours (n= 15), (e) exposed to intravenous contrast agents preceding the week of surgery (n=9), (f) exposed to multitherapy non-selective anti-inflammatory drugs within the past 30 days and during the post-operative period (n= 9), (g) developed of intraoperative hypotension (n=5).

Overall, 74 diabetic patients were included in this study. *Table I* describes their baseline characteristics composition in further detail.

Occurrence of Acute Kidney Injury. Nine patients (12%) of subjects developed AKI in this cohort. The occurrence of AKI did not vary significantly when patients were stratified according to the patient's age, gender showing the homogeneous distribution of AKI among these factors. The occurrence of AKI however varied significantly across the comorbidities as shown in *Table I*. This significance was not seen in the post-hoc analysis when comorbidities were considered individually. Similarly, the occurrence of AKI did not increase when patients were grouped according to time from diagnosis of diabetes, treatment

Table II. Simple and Multiple Logistic Regression of Variables in Association with the Occurrence of Acute Kidney Injury

	Univariate Analysis			Multivariate analysis		
	Odds Ratio	95% C. I.	*p-value*	Odds Ratio	95% C. I.	*p-value*
Age	1.01	0.95 – 1.09	0.582	1.05	0.97 – 1.15	0.221
Gender						
Male	*Reference*			*Reference*		
Female	0.46	0.09 – 2.38	0.352	0.14	0.02 – 1.14	0.066
Time from Diabetes						
Less than 5 years	*Reference*			*Reference*		
5 to 10 years	1.55	0.25 – 9.46	0.638	1.49	0.21 – 10.42	0.691
More than 10 years	0.98	0.15 – 6.50	0.984	0.74	0.08 – 6.79	0.789
HbA1c (in %)						
< 7	*Reference*			*Reference*		
≥ 7	1.28	0.31 – 5.22	0.731	2.55	0.50 – 13.06	0.260
FBS (in mg/dl)						
< 100	*Reference*			*Reference*		
≥ 100	1.12	0.12 – 10.20	0.918	0.64	0.05 – 13.06	0.724
Serum creatinine Pre-operative	0.10	0.00 – 4.42	0.230	0.02	0.00 – 1.81	0.087
ACEi/ARB	1.07	0.26 – 4.35	0.923	1.42	0.29 – 6.90	0.665

Table III. Individual Patient Characteristics of those who Developed Acute Kidney Injury

Patient Number	Age	Gender	Medications used for diabetes	Duration of Diabetes	Comorbidity	HbA1c (%)	FBS (mg/dl)	Surgery
1	79	Male	Oral Hypoglycemic Agents	More than 10 years	Chronic Kidney disease stage I	8.76	273	Exploratory Laparotomy
2	57	Male	Oral Hypoglycemic Agents	5 to 10 years	None	8.69	218	Splenectomy
3	57	Male	On Insulin	5 to 10 years	Hypertension	5.9	90	Open Colorectal surgery
4	47	Male	Combined Oral Hypoglycemic Agents and insulin	5 to 10 years	Hypertension	6.61	157	Open Cholecystectomy
5.	65	Male	Oral Hypoglycemic Agents	5 to 10 years	None	7.15	184	Open Colorectal Surgery
6.	50	Male	Combined oral Hypoglycemic Agents and insulin	More than 10 years	Hypertension	6.86	157	Exploratory Laparotomy
7.	83	Female	Oral Hypoglycemic Agents	More than 10 years	Hypertension	8	165	Open Cholecystectomy
8.	59	Male	Oral Hypoglycemic Agents	Less than 5 years	Hypertension	5.3	129	Open Colorectal Surgery
9.	84	Female	Oral Hypoglycemic Agents	Less than 5 years	Hypertension	6.9	163	Open Nephrectomy

for diabetes used among patients, type of abdominal surgery, and use of ACEi/ARB (*Table I*).

Predictive Factors for the Development of Acute Kidney Injury. Possible predictors for the development of AKI in the immediate post-operative setting, namely HbA1c and FBS, were subjected to further univariate and multivariate analysis. In addition, other possible predictors from literature, such as age, gender, duration of diabetes mellitus, pre-operative serum creatinine, and use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, were likewise included in the model.

The variables mentioned above were subjected to simple and multiple logistic regression (*Table II*). While none of the examined variables were statistically significant predictive of AKI, a trend for an increased incidence of AKI was observed among patients with elevated HbA1c (OR 2.55, $p = 0.260$). Notwithstanding, elevated FBS was not associated with an increased risk for AKI (OR 0.64, $p = 0.724$). Conversely, a trend for the decreased incidence of AKI was observed for the female gender (OR 0.14, $p = 0.066$) and normal pre-operative serum creatinine (OR 0.02, $p = 0.087$).

Using the 7% HbA1c predetermined cut-off level was likewise not predictive for the development of AKI (p-= 0.799). Furthermore, using a predetermined cut-off FBS level of 100 mg/dl was also not predictive for the development of AKI (p-value 0.918). Therefore, patients with higher HbA1c or FBS did not necessarily exhibit an increased risk of developing AKI.

Summary of Clinical Characteristics of Patients who developed AKI. Table III summarizes the clinical characteristics of patients who developed AKI after undergoing abdominal surgeries. All patients who developed AKI were above 47 years of age, while the majority were male (78%), on oral antidiabetic medications (89%), and had diabetes for more than five years (78%). In addition, they were hypertensive patients with fairly-controlled HbA1c and elevated FBS levels.

Discussion

In this retrospective cohort of 74 patients who underwent elective abdominal surgery, AKI was observed in 12% of patients. This finding falls within the previous studies[4], where post-operative AKI was associated with various predictive factors. In particular, this study looked at HbA1c and FBS and their association with AKI development.

HbA1C and FBS as predictors for development of AKI. HbA1c has been utilized to measure diabetic control over the preceding months. Good control has been equated with reduced incidence and slower progression of diabetes-related complications, myocardial infarction, and stroke. The present study showed a non-significant trend towards the development of AKI among diabetic patients, with as much as twice the number of patients developing AKI among the poor glycemic control (i.e., elevated HbA1c) compared to the group with good glycemic control (OR 2.55). This trend did not reach statistical significance and may be attributable to the fact that HbA1c is more reflective of the chronic blood glucose control, which may not be significantly contributory in determining renal function in the acute setting.

This trend appears to contradict the systematic review by Rollins et al., which failed to show an association of elevated HbA1c with increased post-operative morbidity or mortality in patients with diabetes mellitus undergoing various surgical, orthopedic, and cardiac procedures.[9] The authors themselves acknowledged that the samples were heterogeneous and included patients from multiple surgical specialties, which could have contributed to their results.

Although not statistically significant, this trend may give credence to the practice that patients who require elective surgical interventions can be given endocrine risk assessment with careful and diligent pre-operative blood sugar monitoring to maintain good glycemic control, manifested by FBS within acceptable limits despite high HBA1c. This tight glycemic control is continued post operatively to ensure good surgical outcomes.

Perioperative hyperglycemia was associated with a higher risk of pneumonia, urinary tract infection, increased hospital stays, bacteremia, and renal failure.[11] This last finding was not replicated in the present study since the cited paper had higher levels of blood glucose pre-operatively compared to our data. The previous study included patients undergoing high-risk vascular surgeries. Conversely, this current study only included a single measurement of FBS pre-operatively. It might have yielded an isolated elevated blood glucose level compared to stable serial blood glucose monitoring. Corollary to this, 11% of patients with elevated FBS developed AKI compared to the 5% in the HbA1c group. This emphasizes the practical need for serial glucose monitoring in the immediate pre-operative period and cautions against using one-time measurement of FBS or relying on long-term glucose control and measurement of HbA1c, as previously also seen in other studies.[11, 12]

Univariate analysis of 30-day post-operative morbidity (which included: cardiac, respiratory, cerebrovascular, limb loss, sepsis, and wound complications, and renal events-acute renal failure and renal impairment) among diabetic patients with FBS level of 108 mg/dl ($\pm$ 28 mg/dl) revealed no significant predictive value of pre-operative FBS to the occurrence of AKI in a previous study.[13] Furthermore, in another study, a higher pre-operative random glucose was associated with increased cardiovascular mortality in patients undergoing non-cardiac and nonvascular surgery. Renal insufficiency, meanwhile, was only considered as a confounding factor.[14] In the present study, FBS was not an independent predictor for AKI post-operatively.

Despite an exhaustive literature search, none of the currently available literature studied the risk of AKI among an exclusively diabetic population undergoing abdominal surgeries. Current systematic reviews only

deal with diabetic patients across a wide spectrum of surgical, orthopedic, and cardiac procedures.[9] Even the currently available risk propensity scoring for AKI (Kheterpal et al.) among patients undergoing general surgery included a small number of diabetic patients but was not specifically developed for them.[2] It is a recommendation of this study to further examine the risk of AKI among diabetics in specific undergoing abdominal surgeries.

While HbA1c and FBS were not found to be independent predictors for the development of AKI in the post-operative setting; many other factors (e.g., the presence of ascites, congestive heart failure, and undergoing emergency surgery) that were not included in the present study are likely to contribute to the multifaceted problem of the development of post-operative AKI and its various sequelae, as suggested by a computed pseudo R^2 of 0.12. Therefore, these factors must also be evaluated among diabetic patients specifically.

Conclusion

Pre-operative HbA1c and one-time FBS values in diabetic patients undergoing elective abdominal surgery procedures were not statistically predictive of AKI given the present data available. However, the observed trend towards the elevated risk of AKI should drive further studies with greater sample size and of a prospective nature looking at other metabolic factors contributing to AKI and examining the effect of HbA1c at varying levels of control are recommended as future directions, among the poorly-researched population of diabetic patients undergoing surgery.

Pre-operative assessment should emphasize serial glucose monitoring and the overall clinical picture rather than single HbA1c and FBS measurements, with due diligence to various non-renal post-operative events.

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