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Original Paper

Association between Glycosylated Haemoglobin Level and Contrast-Induced Acute Kidney Injury in Patients with Type 2 Diabetes Mellitus

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Key Words
Contrast media · Acute kidney injury · Coronary angiography · Percutaneous coronary intervention · Type 2 diabetes mellitus

Abstract
Background: There are several reports suggesting that admission hyperglycaemia increases the risk of contrast-induced acute kidney injury (CI-AKI). However, it is not clear whether there has been an association between long-standing poor glycaemic control and the incidence of CI-AKI. The purpose of this study was to examine the impact of poor glycaemic control or elevated glycosylated haemoglobin (HbA1c) on the incidence of CI-AKI in patients with type 2 diabetes mellitus (T2DM). ***Methods:*** The present study prospectively enrolled 133 patients with T2DM undergoing elective coronary angiography (CAG) and/or intervention. All patients had an estimated glomerular filtration rate (eGFR) of ≥60 ml/min/1.73 m^2. Patients were divided into two groups: those with an optimal HbA1c (<7%) and those with an elevated HbA1c (≥7%). All had similar baseline characteristics and were hydrated appropriately. The outcome was assessed by the incidence of CI-AKI. ***Results:*** CI-AKI occurred in 2 of 41 patients (4.9%) with optimal HbA1c levels and 5 of 92 patients (5.4%) with elevated HbA1c levels (p = 0.89). The cutoff point of HbA1c was set at 6.5%, but no statistically significant difference between the two groups was observed [1 of 24 patients (4.1%) vs. 6 of 109 patients (5.5%), p = 0.79]. However, despite a high variability in the incidence of CI-AKI, there was no statistically significant difference between the two groups when varying CI-AKI definitions were considered. ***Conclusion:*** An elevated HbA1c level is not associated with a higher incidence of CI-AKI compared to optimal HbA1c levels in patients with T2DM (patients with an eGFR of ≥60 ml/min/1.73 m^2) undergoing CAG and/or intervention.

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Introduction

The incidence of contrast-induced acute kidney injury (CI-AKI) is increasing due to the gradually growing use of coronary angiography (CAG) and percutaneous coronary intervention (PCI) [1]. The increased prevalence of type 2 diabetes mellitus (T2DM), a known significant risk factor of CI-AKI, also contributes to this process. A long-standing hyperglycaemic milieu is considered to be responsible for the increased incidence of CI-AKI in patients with T2DM [2]. Several studies have reported that acute hyperglycaemia also increases the risk of CI-AKI and therefore mortality [3–5]. This has been associated with the pathophysiological similarity of the adverse effects of both hyperglycaemia and iodinated contrast media (CM) on kidneys (oxidative stress, endothelial dysfunction and vasoconstriction) [6–8]. However, there are no adequate clinical studies to demonstrate whether long-standing poor glycaemic control further increases the risk of CI-AKI. Accordingly, in this study, we investigated whether the risk of developing CI-AKI differs in T2DM patients with and without an elevated level of glycosylated haemoglobin (HbA1c, i.e., marker of glucose control of the last 2–3 months).

Methods

Patient Population

Eligible consecutive patients with T2DM (n = 133) undergoing CAG and/or PCI from January 2012 to January 2013 were enrolled in this study. Exclusion criteria were age <20 years, history of dialysis, acute ST segment elevation myocardial infarction (STEMI), known allergy to CM, recent exposure to CM within the previous 3 days, use of nephrotoxic drugs within the previous 7 days, pregnancy or breast-feeding, uncontrolled arterial hypertension (blood pressure >180/110 mm Hg), AKI of alternative aetiology, and those for whom volume expansion is contraindicated such as hypervolemic hyponatraemia or active decompensated heart failure. Patients with a serum creatinine (SCr) of >1.5 mg/dl or an estimated glomerular filtration rate (eGFR) of <60 ml/min/1.73 m^2 were also excluded. None of the patients was black [a variable for the calculation of eGFR by the re-expressed Modification of Diet in Renal Disease (MDRD) formula]. The study was approved by the institutional review board, and all patients gave informed consent.

Clinical Definitions

CI-AKI was defined as ≥25% relative or ≥0.5 mg/dl absolute increase in SCr from baseline at 48 h after administration of CM in the absence of an alternative aetiology. T2DM was defined as onset at >20 years of age and treatment with an oral antihyperglycaemic agent and/or insulin prior to hospital admission. Anaemia was defined as a baseline haemoglobin value of 13 g/dl in men and 12 g/dl in women. Systolic dysfunction was defined as left ventricular ejection fraction (EF) <40%. Hyperuricaemia was defined as serum uric acid level of ≥6 mg/dl in men and ≥8 mg/dl in women.

Study Protocol

Patients were divided into two groups: those with an optimal HbA1c (<7%, n = 41) and those with an elevated HbA1c (≥7%, n = 92). A cutoff point of 7% was chosen because it is the recommended target of glycaemic control for T2DM to reduce complications [9]. All patients were hydrated intravenously [isotonic saline (0.9% NaCl) at a rate of 1 ml/kg/h for 12 h before and 12 h after administration of CM] or orally (spring or tap water starting at least 12 h earlier before the procedure until the last 2 h, and then in the first 12 h following the procedure), as appropriate. For patients with a history of congestive heart failure or systolic dysfunction, the rate of isotonic saline infusion was set at 0.5 ml/kg/h and oral fluids were restricted to 1.5–2 liter/day in order to prevent decompensation of patients. The total volume intake was recorded in all patients. Serum glucose, HbA1c, SCr, potassium and sodium were measured just before the beginning of the volume expansion to avoid dilution effect. Postprocedure SCr measurements were not random but standardized at exactly 48 h which suggests that delayed onset (>48 h) elevation of SCr might be overlooked; however, this approach was preferred since the number of this class of patients was expected to be low and the risk of renal atheroembolism presenting as a confounding factor would be increased beyond 48 h [10]. Calculation of eGFR was performed with the following re-expressed MDRD formula: $[(175 \times SCr^{-1.154}) \times (age^{-0.203}) \times (0.742$ if

female) × (1.212 if black)]. Diuretics were withheld on the day of CM administration. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers were not withheld due to the contradictory results in the literature and their known positive effects on ventricular remodelling in patients with coronary artery disease and/or congestive heart failure [11]. Metformin was continued because of the low risk of developing lactic acidosis in patients with an eGFR of ≥60 ml/min/1.73 m^2 [12]. N-acetylcysteine was not used since it has been shown to be ineffective in the well-designed (multicentre, prospective, randomized, and large-scale) Acetylcysteine for Contrast-Induced Nephropathy Trial (ACT) [13]. Ascorbic acid was also not used. Prophylactic haemodialysis or haemofiltration was performed in none of the patients. Additional measurements were carried out in all patients with a postprocedural SCr increase. The same CM (non-ionic low osmolar iopromide, 370 mg iodine per millilitre) was used in all procedures. The CI-AKI risk score was calculated according to the definition of Mehran et al. [14]. To identify patients receiving a high CM load, the formula by Cigarroa et al. [15] [5 × body weight (kg)/SCr (mg/dl)] was used. The contrast ratio was determined by dividing the actual amount of CM received by the calculated maximum CM dose. The maximum CM dose was considered exceeded if the ratio was >1. The total amount of iodine intake was calculated to obtain comparability with other studies using a different kind of CM. Data on mortality and need for dialysis within 30 days were obtained from hospital records or by interviewing (directly or by phone) patients or their families.

Outcomes

The primary outcome was the incidence of CI-AKI. The secondary outcome was a composite of death and need for dialysis within 30 days.

Statistical Analysis

All data are presented as mean ± SD or median (interquartile range) for parametric variables and as percentages for categorical variables. Continuous variables were checked for the normal distribution assumption using the Kolmogorov-Smirnov statistics. Categorical variables were tested by Pearson's χ^2 test and Fisher's exact test, as appropriate. Differences between the groups were evaluated using the Kolmogorov-Smirnov test or ANOVA test, as appropriate. Correlations between two continuous variables were assessed with Pearson's test. A two-tailed p value of <0.05 was considered statistically significant. All statistical studies were carried out using the Statistical Package for Social Sciences software (SPSS 16.0 for Windows, SPSS Inc., Chicago, Ill., USA).

Results

Relevant clinical, demographic and biochemical features of the patients are summarized in tables 1 and 2. The two groups were comparable regarding age, gender, frequencies of hypertension, history of heart failure, previous coronary artery disease, anaemia and hyperuricaemia. Baseline SCr and eGFR were comparable between the two groups, whereas the serum glucose level was significantly higher in the group with elevated HbA1c. The total volume of hydration and the volume of CM used were not statistically different between the two groups. The contrast ratio was exceeded in only 1 patient; however, CI-AKI did not occur in this patient. CI-AKI was found in 2 of 41 patients (4.9%) in the optimal HbA1c group and in 5 of 92 patients (5.4%) in the elevated HbA1c group (p = 0.89). When the cutoff point of HbA1c was set at 6.5%, again, there was no statistically significant difference between the two groups [1 of 24 patients (4.1%) vs. 6 of 109 patients (5.5%), p = 0.79]. The levels of HbA1c were not correlated with the incidence of CI-AKI in the study population.

Procedure-related complications were similar in the two groups (data not shown). None of the patients developed major bleeding or cardiogenic shock, and no need for intra-aortic balloon pump or cardiopulmonary resuscitation was encountered. A 66-year-old man with an HbA1c level of 8.6%, haemoglobin value of 11.5 g/dl, moderate mitral valve regurgitation and EF of 45–50%, as well as pre-procedure SCr of 1.2 mg/dl died at the hospital following AKI requiring dialysis. No other patient required dialysis during the hospitalization period or in the first 30 days.

Table 1. Clinical, demographic and biochemical data of the patients

	HbA1c <7 (n = 41)	HbA1c ≥7 (n = 92)	p value
Age, years	64.1±12.1	61.1±11.8	0.36
≥70	19 (46)	29 (31)	0.11
Female gender	12 (29)	33 (36)	0.46
BMI	28.2±5.1	29.9±4.5	0.17
Indication for procedure			
Non-ST elevation myocardial infarction	26 (63)	73 (80)	
Unstable angina pectoris	7 (17)	1 (12)	0.12
Stable angina pectoris	8 (19)	8 (9)	
Systemic hypertension	30 (73)	66 (72)	0.87
History of heart failure	4 (10)	3 (3)	0.21[a]
LVEF, %	46±12	48±11	0.24
<40%	13 (31)	18 (20)	0.19
Previous PCI	13 (32)	28 (30)	0.89
Previous CABG	6 (14)	21 (23)	0.28
Anaemia	15 (37)	30 (33)	0.66
Hyperuricaemia	5 (12)	8 (9)	0.53
Drugs			
Aspirin	41 (100)	85 (92)	0.23
Angiotensin-converting enzyme inhibitor	30 (73)	70 (76)	0.72
Angiotensin II receptor blocker	3 (7)	8 (9)	0.95[a]
Calcium channel blocker	10 (24)	25 (27)	0.74
β-Blocker	28 (68)	75 (82)	0.09
Oral anti-hyperglycaemic agent	7 (17)	5 (6)	0.03
Insulin	11 (26)	60 (65)	0.01
Performed procedure			
Coronary angiography	22 (53)	36 (39)	0.51
PCI	11 (26)	13 (14)	0.50
CI-AKI risk score			
≤5	24 (59)	61 (66)	
6–10	15 (37)	29 (32)	0.55
11–15	2 (5)	2 (2)	
≥16	0	0	
SCr, mg/dl			
Baseline	0.90 (0.35)	0.90 (0.35)	0.14
After 48 h	1.0 (0.40)	0.90 (0.30)	0.13
eGFR, ml/min/1.73 m^2			
Baseline	83.5±23.6	88.8±22.7	0.22
After 48 h	80.2±23.4	85.6±25.4	0.25
Serum glucose, mg/dl			
Baseline	145±50	222±81	0.01
After 48 h	125±36	191±71	0.01

Values are presented as mean ± SD or as n (%). Calculation of eGFR was performed with the re-expressed MDRD formula [(175 × $SCr^{-1.154}$) × ($age^{-0.203}$) × (0.742 if female) × (1.212 if black)]. CABG = Coronary artery bypass graft surgery. BMI = Body mass index; LVEF= left ventricular ejection fraction.

[a] Fisher's exact test was used.

Table 2. Comparison of relevant variables in patients with and without CI-AKI

	CI-AKI (n = 7)	No CI-AKI (n = 126)	p value
SCr, mg/dl			
Baseline	0.90 (0.50)	0.90 (0.22)	0.11
After 48 h	1.50 (0.70)	0.90 (0.30)	0.01
eGFR, ml/min/1.73 m^2			
Baseline	73.3±18.8	87.9±23.3	0.11
After 48 h	46.2±16.5	86.1±23.5	0.01
Total volume of hydration, ml	3,110±550	3,120±1,130	0.95
Oral volume supplementation	2 (29)	65 (51)	0.28[a]
Volume of contrast media, ml	95±25	110±73	0.56

Values are presented as median (interquartile range), mean ± SD or as n (%).

[a] Fisher's exact test was used.

Discussion

The main result of this study was that elevated HbA1c levels were not associated with CI-AKI in patients with T2DM (patients with an eGFR of ≥60 ml/min/1.73 m^2). Indeed, it is known that CI-AKI is more common in patients with T2DM, which is assumed to be caused mainly by a long-standing hyperglycaemic milieu. Studies have demonstrated that elevated glucose levels are known to increase oxidative stress and the amount of free radicals in kidneys, prevent vasodilation by decreasing nitric oxide levels, impair endothelial function and increase ischemic and reperfusion injury [16–18]. These mechanisms are involved in the development of CI-AKI in a similar manner, further aggravating the adverse effects of CM on kidneys. Moreover, hyperglycaemia might cause hypovolaemia by increasing the osmotic diuresis.

Prior Studies

Two studies on intensive care unit patients have demonstrated that the incidence of AKI in various clinical settings reduced after obtaining relatively normal glucose levels with insulin therapy [19, 20]. Similarly, several studies have demonstrated that admission hyperglycaemia in patients with STEMI increased the incidence of AKI, cardiac failure and mortality even in the absence of a history of T2DM [21–24]. The results of two recent studies regarding the relationship of admission hyperglycaemia and CI-AKI are particularly interesting. These studies have demonstrated similar rates of CI-AKI development in T2DM patients with and without admission hyperglycaemia [3, 4]. However, the development of CI-AKI was more common in non-diabetic patients with admission hyperglycaemia compared to those without admission hyperglycaemia. The difference might possibly be explained by the administration of a more aggressive insulin therapy in patients with T2DM during hospitalization, a better hydration of these patients since T2DM is known to be a risk factor for CI-AKI, and the need for a greater stress factor in association with its secondary adverse effects in non-diabetics which generate a comparably high level of glucose.

To date, there have been two studies on the relationship between long-standing poor glycaemic control and CI-AKI. In their retrospective study, Ding et al. [25] have reported higher glycated albumin and HbA1c levels in patients with CI-AKI compared to those without

Table 3. Incidence of CI-AKI according to varying definitions

	HbA1c <6.5 (n = 24)	HbA1c ≥6.5 (n = 109)	p value	HbA1c <7 (n = 41)	HbA1c ≥7 (n = 92)	p value
SCr increase ≥25%	1 (4.1)	6 (5.5)	0.99	2 (4.9)	5 (5.4)	0.89
SCr increase ≥0.5 mg/dl	0	4 (3.7)	0.99	1 (2.4)	3 (3.2)	0.99
SCr increase ≥50%	0	3 (2.8)	0.99	1 (2.4)	2 (2.2)	0.99
SCr increase ≥0.3 mg/dl	1 (4.1)	6 (5.5)	0.99	2 (4.9)	5 (5.4)	0.99
eGFR decrease ≥25%	4 (16.7)	12 (11.0)	0.49	5 (12.2)	11 (11.9)	0.97[a]

Values are presented as n (%). Variables were tested by Fisher's exact test unless stated otherwise.
[a] Pearson's χ^2 test was used.

CI-AKI (8.3 ± 1.6% vs. 7.5 ± 1.2% for HbA1c, respectively, p < 0.001). However, in this study, it might be incorrect to suggest uncontrolled glucose levels as the primary cause of CI-AKI. Since the rate of pre-existing chronic kidney disease (CKD) was statistically significantly higher, the EF was lower, the number of elderly patients was higher and a greater amount of CM was used in patients with CI-AKI compared to those without CI-AKI (p < 0.001, for all). In the other study, Yoshikawa et al. [26] have reported a 5% increase in SCr and a decrease of 4 ml/min/1.73 m^2 in eGFR in patients with an HbA1c of ≥6.5% compared to those with an HbA1c of <6.5% following coronary computed tomography angiography (p < 0.001). However, such a small change in the values neither fits the definition of CI-AKI nor has any known clinical implications.

We found that chronic hyperglycaemia did not affect the incidence of CI-AKI. This result is consistent with several in vitro and animal studies demonstrating that wide variations in glycaemia are associated with worse prognosis, since it causes more oxidative stress and apoptosis than chronic hyperglycaemia [27, 28]. The results of the present study might be explained with the more marked effect of other chronic intra-renal mechanisms on kidneys (i.e., changes in the intra-glomerular haemodynamics modulated in part by local activation of the renin-angiotensin system, biochemical derangements, proteinuria, and hypoxia) compared to the direct effect of hyperglycaemia in terms of the development of CI-AKI in T2DM [18]. Another possible explanation is that the length of time of glycaemic control for the last 2–3 months is not adequate to prevent CI-AKI. Perhaps, a future research in patients with successful glycaemic control for a longer period (≥3 months to years) might demonstrate a relationship between HbA1c and CI-AKI.

Consideration of Varying CI-AKI Definitions

In the present study, although CI-AKI was conventionally defined as ≥25% relative or ≥0.5 mg/dl absolute increase in SCr at 48 h in order to obtain comparability with other studies, this was an arbitrary definition. This definition is different from the suggested definition of AKI [29]. We also determined the incidence of CI-AKI by the other definitions, since patients with more than 0.3 mg/dl but less than 0.5 mg/dl increase in SCr do not fit into the conventional definition but fit actually into stage 1 AKI. However, despite a high variability in the incidence of CI-AKI, there was no statistically significant difference between the two groups when varying CI-AKI definitions were considered (table 3).

Limitations

Our study has several limitations. First, it is a single-centre study. Second, urine albumin was not measured. Since CKD is defined by an eGFR of ≥60 ml/min/1.73 m^2 only in the

presence of albuminuria for patients with T2DM, it can be presumed that some of the patients have CKD and others do not. Accordingly, the results are not generalizable to the patients with stage 3–4 CKD. Third, as patients with acute STEMI cannot receive pre-procedural hydration, extrapolation of the results to these patients may not be appropriate. Fourth, these results might also not be valid for radiological procedures (computerized tomography, etc.) that use the intravenous rather than the intra-arterial route. Fifth, renal atheroembolism could not be completely excluded as the potential cause of AKI, although its risk is quite low at 48 h. Sixth, these results might not be valid for patients with type 1 DM. Finally, 'hospital-induced nephropathy', a newly recognized aspect, described as a substantial day-to-day variation in SCr in hospitalized patients regardless of CM injections, might have been a confounding factor [30].

Conclusion

An elevated HbA1c level is not associated with a higher incidence of CI-AKI compared to an optimal HbA1c level in patients with T2DM (patients with an eGFR of ≥60 ml/min/1.73 m^2) undergoing CAG and/or PCI.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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