Glycosylated Hemoglobin levels and the Risk for Contrast-Induced Nephropathy in Diabetic Patients Undergoing Coronary arteriography/Percutaneous Coronary Intervention

hong Zhang

Tianjin Chest Hospital

han Fu

Tianjin Medical University

jing Zhang

Tianjin Chest Hospital

peng Zhang

Tianjin Chest Hospital

shicheng Yang

Tianjin Chest Hospital

xiaofeng Fu

Tianjin Medical University

zhican Zeng

Tianjin Medical University

naikuan fu (✉ cdrfnk@163.com)

Tianjin Chest Hospital

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Abstract

Backgrounds: Diabetes mellitus is an independent risk factor for Contrast-induced nephropathy (CIN) in patients undergoing Coronary arteriography (CAG)/percutaneous coronary intervention (PCI).

Glycosylated hemoglobin (HbA1c) is the gold standard to measure blood glucose control, which has important clinical significance for evaluating blood glucose control in diabetic patients in the past 3 months. This study aimed to evaluate whether preoperative hemoglobin a1c levels in diabetic patients who received CAG/PCI had an impact on the occurrence of postoperative CIN.

Methods: We reviewed the incidence of preoperative HbA1c and postoperative CIN in 670 patients with CAG/PCI from January 1, 2020 to October 30, 2020, and divided the preoperative HbA1c levels into 5 groups. Blood samples were collected at admission, 48h and 72h after operation to measure the Scr value of patients. Categorical variables were compared using a chi-square test, and continuous variables were compared using an analysis of variance. Fisher's exact test was used to compare the percentages when the expected frequency was less than 5. Multivariable logistic regression analysis was used to exclude the influence of confounding factors and P for trend was used to analyze the trend between HbA1c levels and the increased risk of CIN.

Results: Patients with elevated HbA1c had higher BMI, FBG and LDL-C, and they were more often on therapy with hypoglycemic agents, Insulin and PCI. They also had higher basal, 24h and 48h Scr. (Table 1) The incidence of CIN in the 5 groups of patients were: 9.8%, 11.9%, 15.2%, 25.3%, 48.1%. ($p < 0.0001$) The multivariate analysis confirmed that in the main high-risk subgroup, patients with elevated HbA1C levels ($\geq 8.8\%$) had a higher risk of CIN disease. (Figure 2) Trend test showed the change of HR (1.000, 1.248, 1.553, 2.625, 5.829). (Table 2)

Conclusions: Studies have shown that in diabetic patients undergoing CAG/PCI, elevated HbA1C is independently associated with the risk of CIN, and with the increase of HbA1C level, the incidence of CIN gradually increases.

Introduction

Contrast-induced nephropathy (CIN) is reversible acute renal failure observed after administration of iodinated contrast media (CM) during angiographic or other medical procedures and is defined as an increase of 25% or more, or an absolute increase of 0.5 mg/dL or more in serum creatinine (Scr) from baseline value, at 48 to 72 hours following the exposure to CM. (1, 2) The exact mechanism of CIN is unclear, and it may be related to hemodynamic effects, the formation of reactive oxygen species (ROS) and renal tubular cytotoxicity. (3) In addition, studies have shown that inflammation, immune response, and the decrease in the number of endothelial progenitor cells (EPCs) will also affect the occurrence of CIN. (4–6) Many risk factors may contribute to the development of contrast nephropathy, such as age, glomerular filtration rate, preoperative hyperglycemia at blood cholesterol admission, and elevated glycosylated hemoglobin, both associated with CIN. (7, 8) The key to reducing the incidence of CIN is to

identify patients at high risk of CIN and to adopt appropriate prevention programs. Studies have found that patients with diabetes have a higher risk of CIN. Diabetic nephropathy has been identified as a powerful and independent risk factor for CIN. (9) Both diabetes and the administration of iodinated radiocontrast agents are both associated with marked alterations of renal physiology, including changes in GFR and renal hemodynamics, enhanced tubular transport activity and oxygen expenditure and intensification of medullary hypoxia, and ROS generation.(10) Long-term hyperglycemia will cause many pathophysiological changes, such as endothelial and microvascular dysfunction, increased production of vascular inflammatory markers and ROS, and impaired immune response. (11) Measurements of glycosylated hemoglobin (HbA1c) can provide an average blood glucose level for the past 2–3 months and adequately reflect glycemic control in patients with diabetes.(12)Current studies have shown that among patients without diabetes undergoing CAG/PCI elevated HbA1c is independently associated with the risk of CIN. (13)However, there is no more data to confirm whether the level of HbA1c in patients with existing diabetic patients affects the occurrence of CIN, and most prior studies have focused predominantly on the prognostic value of admission glucose, which represents only a single measurement in time. Therefore, compared with previous clinical trials, our study aims to focus on whether the level of HbA1c in diabetic patients undergoing CAG/PCI is related to the risk of CIN, and a prospective trial was conducted in diabetic patients receiving CAG/PCI.

Method

Study population

We initially assessed 833 patients who underwent CAG/PCI. Inclusion criteria were as follows: Patients who meet the diagnostic criteria for diabetes and underwent CAG/PCI. [The American Diabetes Association (ADA) defines Criteria for the diagnosis of diabetes: (1) fasting plasma glucose (FPG) > 126 mg/dL (7.0 mmol/L); (2) 2 h plasma glucose (PG) > 200 mg/dL (11.1 mmol/L) during oral glucose tolerance test (OGTT); (3) HbA1c > 6.5% (48 mmol/mol); (4) In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose > 200 mg/dL (11.1 mmol/L)]. (14)Exclusion criteria were acute ST-segment elevation myocardial infarction (STEMI) receiving emergency PCI, receiving CM 14 days before PCI, hypotension (systolic blood pressure < 90 mmHg), using any renal toxicity drugs during the perioperative period, severe renal insufficiency (creatinine clearance < 30 mL/min) or severe cardiac insufficiency (left ventricular ejection fraction (LVEF) < 30%), cardiogenic shock and heart failure, hypersensitivity to CM, severe liver damage, autoimmune diseases, malignant tumor, infectious diseases or fever. We also exclude other conditions that may affect HbA1c: hemoglobinopathy, pregnancy, uremia, blood transfusion and hemolytic anemia.(15) (Fig. 1) The present study was approved by the Ethics Committee of the Tianjin Chest Hospital and written informed consent was obtained from all participants before enrollment.

Figure 1. CAG: HbA1c: glycosylated hemoglobin; Coronary arteriography PCI; percutaneous coronary intervention; Scr: serum creatinine; CIN: contrast-induced nephropathy.

Study protocol

We finally evaluated 670 diabetic patients undergoing CAG/PCI. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. Patients were stratified into 5 pre-procedural HbA1c groups: <6.5%; 6.5–8%; 8–9.5%; 9.5–11%; >11%. Because related studies have proved that hydration in the perioperative period is effective in preventing the occurrence of CIN(16, 17), all patients received isotonic saline (0.9% sodium chloride) 12 hours before and after surgery and supplemented with standard hydration solution (at least 1,000 mL) at a rate of 1 mL/kg/h. Hydration rate was reduced to 0.5 mL/kg/h for patients with LVEF $\leq$ 45%. All patients were given aspirin and clopidogrel loading dose 300 mg before surgery. Clinicians can decide whether to use the following medicines based on clinical requirements or guidelines, including β -blockers, angiotensin converting enzyme inhibitors (ACEIs)/angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs), diuretics, and statin.

The risk of CIN is related to CM osmotic pressure. Iodine contrast agents include low-osmotic contrast media (LOCM), iso-osmotic contrast media, and high-osmotic contrast media. (18) Isotonic contrast agents are more effective than LOMC in reducing the incidence of CIN in patients. (19) Therefore, patients with normal and mildly abnormal Scr levels (Scr $\leq$ 177 μ mol/L) before surgery are treated with iopromide (LOCM). Compared with other CMs, iodixanol (isotonic contrast agent) has less nephrotoxicity, lower risk of cardiovascular adverse events, and thermal discomfort and is used in patients with moderately and severely abnormal Scr level (Scr > 177 μ mol/L) (20, 21) There was no statistically significant difference in the number of patients using contrast media between the five groups. (P = 0.261)

Study endpoints

Blood samples were collected at admission, 48 h and 72 h after operation to measure the Scr value of patients. The primary study end point was CIN, diagnosed by the highest Scr concentrations 48 and 72 hours after CM exposure. Additional clinical endpoints included: Adverse events during hospitalization and 14-day follow-up, included all-cause mortality, hypotension or severe decrease in blood pressure, acute heart failure, coronary artery bypass, and graft cerebrovascular events.

Statistical analysis

Results are expressed as numbers (%) or mean $\pm$ SD. Compare means between five groups: categorical variables were compared using a chi-square test, and continuous variables were compared using an analysis of variance. Fisher's exact test was used to compare the percentages when the expected frequency was less than 5. Multivariable logistic regression analysis was used to exclude the influence of confounding factors, and to evaluate whether the association between pre-procedural HbA1c values and CIN persisted after adjustment for other patient characteristics and potential confounders. P for trend was used to analyze the trend between HbA1c levels and the increased risk of CIN. All statistical data were analyzed by SPSS software 22.0.

Results

Baseline clinical characteristics

There were no significant differences between the five groups in the baseline characteristics (Age, Male, Smoking, LVEF, Hypertension, Contrast volume, Hemoglobin, TG, TC, HDL-C, Hydration amount, Aspirin, Clopidogrel, b-blockers, ACEI/ARB, Diuretics, CCBs) before operation. Patients with elevated HbA1C levels had higher LDL levels ($p = 0.010$), BMI ($p < 0.001$) and Preoperative FBG ($p < 0.001$). In addition, patients with higher levels of HbA1C were more often on therapy with hypoglycemic agents ($p = 0.033$), Insulin ($p = 0.011$) and PCI. ($p = 0.027$) (Table 1)

Table 1
Comparisons of baseline characteristics between the two groups.

Variables	HbA1c<6.5% (n = 82)	HbA1c6.5–8% (n = 236)	HbA1c8–9.5% (n = 197)	HbA1c9.5% to 11% (n = 99)	HbA1c>11% (n = 27)	P
Age (years)	66.61 ± 7.13	67.78 ± 6.08	67.06 ± 7.42	66.55 ± 7.51	68.93 ± 5.78	0.296
Male (%)	43(52.4)	112(47.5)	101(51.3)	44(44.4)	13(48.1)	0.767
Smoking (%)	59(72.0)	157(66.5)	126(64.0)	60(60.6)	17(63.0)	0.778
LVEF	61.12 ± 6.52	59.81 ± 7.29	60.50 ± 6.96	59.87 ± 7.31	61.63 ± 5.97	0.445
Hypertension (%)	40(48.8)	24.62 ± 2.28	129(54.7)	118(59.9)	65(65.7)	16(74.1)
BMI (kg/m ²)	24.62 ± 2.28	129(54.7)	118(59.9)	65(65.7)	16(74.1)	< 0.0001 ^a
Contrast volume (mL)	168.90 ± 58.44	24.90 ± 2.09	25.27 ± 1.85	25.63 ± 1.80	26.45 ± 1.70	0.734
TG (mmol/L)	1.77 ± 1.02	166.61 ± 52.07	170.91 ± 62.12	175.76 ± 70.34	175.19 ± 45.27	0.512
TC (mmol/L)	4.55 ± 0.39	1.75 ± 0.91	1.85 ± 1.10	1.75 ± 0.86	2.06 ± 0.87	0.364
HDL-C (mmol/L)	1.30 ± 0.38	4.52 ± 0.41	4.61 ± 0.57	4.52 ± 0.52	4.57 ± 0.50	0.509
LDL-C (mmol/L)	2.46 ± 0.55	1.24 ± 0.33	1.28 ± 0.33	1.28 ± 0.40	1.26 ± 0.25	0.010 ^a
Preoperative FBG	6.63 ± 1.37	2.49 ± 0.61	2.50 ± 0.51	2.54 ± 0.49	2.89 ± 0.72	< 0.0001 ^a
Hydration amount (mL)	1305.5 ± 257.28	7.15 ± 1.51	7.95 ± 1.50	8.81 ± 1.54	10.09 ± 1.83	0.430
Aspirin (%)	77(93.9)	1322.4 ± 244.99	1277.4 ± 277.21	72(72.7)	25(92.6)	0.642
Clopidogrel (%)	41(50.0)	204(86.4)	191(97.0)	81(81.8)	19(70.4)	0.132
β-antagonist (%)	7(8.5)	137(58.1)	151(76.6)	49(49.5)	24(88.9)	0.950
ACEI/ARB (%)	10(12.2)	20(8.5)	172(87.3)	7(7.1)	2(74.1)	0.978
Diuretics (%)	25(30.9)	24(10.2)	91(46.2)	11(11.1)	3(11.1)	0.033 ^a
CCB (%)	6(7.3)	93(39.4)	13(6.6)	40(40.4)	13(48.1)	0.011 ^a
Hypoglycemic agents (%)	45(54.8)	19(8.1)	21(10.7)	16(16.2)	7(25.9)	0.027 ^a
Insulin (%)	101.60 ± 15.03	141(59.7)	81(41.1)	69(69.7)	23(85.2)	< 0.0001 ^a
PCI (%)	113.46 ± 16.46	102.14 ± 14.35	20(10.2)	109.94 ± 15.66	112.02 ± 12.45	

Basal Scr (mmol/L)	HbA1c<6.5% (n = 82)	HbA1c6.5–8% (n = 236)	HbA1c8–9.5% (n = 197)	HbA1c9.5% to 11% (n = 99)	HbA1c>11% (n = 27)	P
48 h Scr(mmol/L)	109.82 ± 16.25	114.18 ± 17.82	127.42 ± 15.55	138.16 ± 9.74		0.0001 ^a
72 h Scr (mmol/L)	109.82 ± 16.25	124(62.9)	104.32 ± 11.48	119.29 ± 15.55	125.22 ± 13.84	< 0.0001 ^a
			119.96 ± 15.67			
			116.61 ± 14.47			

Table 1. Data are expressed as mean ± SD or n (%). ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; BMI: body mass index; TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; LVEF: left ventricular ejection fraction; CCB: calcium channel blockers; FBG: fasting blood glucose; PCI: Percutaneous Coronary Intervention.

Comparison of Scr level and CIN incidence in each group

Patients with elevated HbA1C had higher basal Scr ($p < 0.0001$), higher Scr values at 48 h and 72 h after CAG/PCI ($p < 0.0001$, Table 1). Multivariable logistic regression analysis was used to analyze the factors affecting CIN. CIN was taken as the dependent variable, and factors that may affect the development of CIN (male, age, LVEF, Contrast volume, Hydration amount, ACEI/ARB, Diuretics, CCBs) were taken as independent variables. CIN was used as the dependent variable to exclude confounding factors. (OR = 2.019(1.362–3.209), $p = 0.001$)

The multivariate analysis confirmed the association between HbA1C and the risk of CIN after adjustment for baseline confounding factors. The results showed that patients with elevated HbA1C (above the median value 8.75%) in the main high-risk subgroup had a higher risk of CIN, such as BMI (BMI > 23.9 kg/m²: adjusted OR = 1.909(1.196–3.047), $p = 0.007$; BMI ≤ 23.9 kg/m²: adjusted OR = 2.631(0.922–7.512), $p = 0.071$), LDL (LDL > 2.59 mmol/L: adjusted OR = 1.797(0.949–3.403), $p = 0.072$; LDL ≤ 2.59 mmol/L: adjusted OR = 2.314(1.312–4.084), $p = 0.004$), FBG (FBG > 7.1 mmol/L: adjusted OR = 1.592(0.973–2.604), $p = 0.064$; FBG ≤ 7.1 mmol/L: adjusted OR = 2.017(0.780–5.216), $p = 0.148$), PCI (PCI: adjusted OR = 1.688(1.032–2.762), $p = 0.037$; No PCI: adjusted OR = 3.007(1.198–7.549), $p = 0.019$). (Fig. 2)

Figure 2. 8.8% is the median elevated HbA1C levels. BMI: body mass index; LDL-C: low-density lipoprotein cholesterol; FBG: fasting blood glucose; PCI: Percutaneous Coronary Intervention.

The trend test was used to further demonstrate the relationship between HbA1C levels and CIN incidence. It can be seen from the changes in Hazard Ratio (HR) (1.000,1.248,1.553,2.625,5.829), with the increase of HbA1C levels, the incidence of CIN increases gradually with a significant trend ($p < 0.0001$). (Table 2)

Table 2
The logistic regression analysis and the trend test

Adjusted Hazard Ratio					
HbA1c	Participants, n	CIN, n	Model 1	Model 2	Model 3
<6.5%	82	9	1.000(Reference)	1.000(Reference)	1.000(Reference)
6.5–8%	236	28	1.450(0.607–3.464)	1.453(0.606–3.482)	1.248(0.512–3.044)
8–9.5%	197	30	2.005(0.844–4.759)	2.015(0.846–4.800)	1.553(0.643–3.804)
9.5% to 11%	99	25	3.642(1.483–8.945)	3.602(1.459–8.894)	2.625(1.025–6.718)
>11%	27	13	9.753(3.268–29.114)	9.791(3.260–29.409)	5.829(1.785–19.034)
P for trend	–	–	<0.0001	<0.0001	<0.0001

Table 2. Model 1 was adjusted for age and male. Model 2 was adjusted for age, male, hypertension, contrast volume and hydration amount. Model 3 additionally was adjusted for BMI, LDL-C and PCI.

Discussion

In this study, we evaluated the relationship between preoperative glycosylated hemoglobin level and CIN incidence in patients undergoing CAG/PCI. This prospective and controlled trial showed that in diabetic patients undergoing CAG/PCI, elevated HbA1C is independently associated with the risk of CIN, and with the increase of HbA1C level, the incidence of CIN gradually increases. These results are of clinical significance, because Type 2 diabetes mellitus (T2DM) is a major risk factor affecting coronary artery disease (CAD), despite significant advances in the treatment of cardiovascular disease over the past 20 years, cardiovascular disease remains the leading cause of morbidity and mortality in patients with Type 2 diabetes mellitus, 75% of T2DM patients die as a consequence of cardiovascular diseases. (22, 23) With the improvement of PCI-related technology and equipment, PCI indications have become more extensive and complex, and the amount of surgery has increased year by year.(24) Patients who develop CIN have a greater risk for a number of non-renal complications including cardiac, vascular and systemic problems. For patients who develop CIN, treatment is limited to supportive measures until renal

impairment resolves. It is important to evaluate the patient's blood glucose control before surgery and prevent postoperative CIN, which not be viewed as a treatable and acceptable complication of contrast procedures. (25)

Diabetes is an important predisposing factor for CIN, particularly in patients with renal functional impairment. Renal hypoxia, combined with the generation of reactive oxygen species, plays a central role in the pathogenesis of CIN, and the diabetic kidney is particularly susceptible to intensified hypoxic and oxidative stress following the administration of contrast media. This complex pathophysiological mechanism includes a priori enhanced tubular transport activity, oxygen consumption, and the generation of reactive oxygen species. The regulation of vascular tone and peritubular blood flow may also be altered. In addition, microvascular and macrovascular diseases and chronic tubulointerstitial changes further compromise regional oxygen delivery, and renal antioxidant capacity might be hampered. In brief, both diabetes and contrast agents enhance ROS formation. They also hamper renal oxygenation, either directly or through increased generation of ROS.(10)The rat experiment showed that the CM-induced changes in diabetic rats indicate impaired renal function, oxidative stress, vascular dysfunction, and apoptosis, and were significance higher in intensity compared to non-diabetic rats.(26)

Clinical studies have proven that for patients with known and unknown diabetes, elevated blood glucose levels before surgery are a powerful and independent risk factor for CIN.(27)However, preoperative blood glucose level can only indicate the current blood glucose status, and is affected by stress and recent diet, which makes it difficult to accurately predict the prognosis. Measurement of HbA1c has been the traditional method for assessing glycemic control. From the existing structure and biosynthesis information, glycosylated hemoglobin is formed by the condensation of glucose and hemoglobin in red blood cells. The accumulation of glycosylated hemoglobin is a reflection of the average glucose concentration of red blood cells during their life cycle. Therefore, it can reflect the patient's recent blood sugar control status, and is not affected by external factors.(28)HbA1c level is closely related to the occurrence and development of coronary heart disease, and is also a prognostic factor for death after acute myocardial infarction(29)Prior to this, Barbieri L et al. have shown that HbA1c level is related to the risk of CIN occurrence in without diabetic patients. (13)On this basis, we further studied whether HbA1c level also has an impact on CIN occurrence in diabetic patients, and obtained positive results.

Limitations

Our research excluded patients with severe renal insufficiency, receiving CM 14 days before operation, severe cardiac insufficiency, heart failure, malignant tumor, fever, and emergency PCI. Also excluded patients with anemia that may affect HbA1c. Although HbA1c remains the reference marker for assessing glycemic control and predicting the risk of development of long-term complications, it is limited in that it cannot detect hypoglycemia or hyperglycemia on a daily basis and does not reflect rapid changes in daily glucose control.(12)Further studies on the pathogenesis and preventive measures are needed to completely prevent CIN.

Conclusions

Studies have shown that in diabetic patients undergoing CAG/PCI, elevated HbA1C is independently associated with the risk of CIN, and with the increase of HbA1C level, the incidence of CIN gradually increases. We consider that for patients with diabetes, controlling hemoglobin level has a preventive effect on postoperative CIN, which is of great significance for patients undergoing elective PCI.

Abbreviations

HbA1c

Glycosylated Hemoglobin

CIN

Contrast-induced nephropathy

CAG

Coronary arteriography

PCI

percutaneous coronary intervention

Scr

serum creatinine

ACEI

angiotensin-converting enzyme inhibitor;

ARB

angiotensin receptor blocker

BMI

body mass index

TC

total cholesterol

TG

triglyceride

HDL-C

high-density lipoprotein cholesterol

LDL-C

low-density lipoprotein cholesterol

LVEF

left ventricular ejection fraction

CCB

calcium channel blockers

FBG

fasting blood glucose

Declarations

Human and animal rights: All procedures performed in research involving human participants comply with the ethical standards of the institution and/or the National Research Council, and comply with the 1964 Declaration of Helsinki and its subsequent amendments or similar ethical standards.

Conflict of interest: There is no conflict of interest to be declared in this study

Informed consent: This study was approved by the Ethics Committee of Tianjin Chest Hospital, and written informed consent of all participants was obtained before registration

Availability of data and materials: The data set used and/or analyzed in the current research can be obtained from the corresponding author upon reasonable request

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Author's contribution: Zhang H completed the data collection and sorting; Fu H was mainly responsible for writing the article; Zhang J conducted the article writing guidance; Zhang P completed the related literature search; Yang S analyzed and explained the data; Fu X and Zeng Z were responsible for the blood sample collection and analysis of all patients. All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

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Figures

Figure 1

CAG: HbA1c: glycosylated hemoglobin; Coronary arteriography PCI; percutaneous coronary intervention; Scr: serum creatinine; CIN: contrast-induced nephropathy.

Risk of CIN OR[95%CI]

Figure 2

The association between HbA1C and CIN risk after adjusting for baseline confounding factors 8.8% is the median elevated HbA1C levels. BMI: body mass index; LDL-C: low-density lipoprotein cholesterol; FBG: fasting blood glucose; PCI: Percutaneous Coronary Intervention.