ORIGINAL ARTICLE

Impact of insulin resistance on contrast induced nephropathy in patients undergoing percutaneous coronary intervention

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Abstract Contrast-induced nephropathy (CIN) is a common complication following percutaneous coronary intervention (PCI). Contrast-induced nephropathy after emergency PCI in subjects with insulin resistance (IR) has not been studied before. In this prospective study we determined the relation between IR on CIN, among those undergoing PCI due to acute coronary syndrome. One hundred twenty four consecutive acute coronary syndrome patients with diabetes (N=44), insulin resistance (N=38) and normal glycemic metabolism (N=42) were included in the study. They were all treated with PCI. Pre- and post procedural creatinines were measured and independent predictors of CIN were analyzed. IR was defined as a HOMA level (HOMA-IR= Serum Glucose (mg/dL) X Plasma Insulin (micro unit/mL) / 405 >2.5. Patients with IR or diabetes had significantly higher levels of creatinine after procedure, serum cholesterol, glucose, contrast volume, hospital stay and HOMA. Female gender, frequency of CIN and multivessel disease were also higher in these patients. On the other hand they had signifi-cantly lower ejection fraction. Logistic regression analysis showed that HOMA was the single independent risk factor for CIN in patients with acute coronary syndrome treated with PCI. Insulin resistance is an independent risk factor for CIN in patients with acute coronary syndrome treated with PCI. It carries a similar risk with diabetes and proper prophylaxis should be performed.

Keywords Acute coronary syndrome · Insulin resistance · Contrast induced nephropathy

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Introduction

Contrast-induced nephropathy (CIN) is a common complication post-percutaneous coronary intervention. The grow-ing number of coronary angiographic procedures requiring contrast media has triggered a parallel increase of CIN [1, 2]. CIN is defined as an increase in serum creatinine by either≥0.5 mg/dl or by≥25 % from baseline within the first 2–3 days after contrast medium administration, when alternative explanations for renal impairment have been excluded [3, 4]. The incidence of CIN can be increased to>50 % in patients at high risk for CIN [5, 6]. The development of CIN has been associated with increased in-hospital and long term morbidity and mortality, prolonged hospitalization, and long term renal impairment [2, 5]. Chronic renal insufficiency, diabetes mellitus, congestive heart failure, intravascular volume depletion, and the use of a large contrast medium amount are considered to be important predisposing factors [7]. Insulin resistance (IR) is a pathological condition characterized by a lack of physiological response of peripheral tissues to insulin action, leading to the metabolic and hemodynamic disturbances [8]. The importance of CIN after emergency PCI in patients with acute coronary syndrome and IR has not been well examined [4]. The purpose of this prospective study was to determine the relation between IR on CIN, in patients undergoing PCI due to ACS.

Methods

Study population

The present study included patients (N=124) with acute ST-segment elevation myocardial infarction or unstable angina/ non–ST-segment elevation myocardial infarction undergo-ing emergency PCI between January 2011 and June 2011. Patients were divided into three groups: DM (N=44), insulin resistance (N=38) and control group (N=42). Control group had contained patients with acute coronary syndrome with-out IR/DM. We enrolled consecutive patients with baseline Cr <1.5 mg/ dL admitted to our hospital undergoing PCI.

Percutaneous coronary intervention

The patients were eligible for inclusion if they had been admitted within 24 h of the onset of chest pain that had lasted for>30 min with ST-segment elevation of>0.2 mV in>2 contiguous leads and cardiac markers elevation. Patients were also enrolled if they had had an episode of ischemic chest pain of >10 min with transient or persistent ST-segment depression (> 0.5 mm), T-wave inversion (>1 mm), and/or elevation of troponin T greater than the upper limit of nor-mal, thus presenting with refractory angina or hemodynamic instability despite maximum drug therapy within>24 h of admission. Emergency PCI was performed by a 24-h, on-call, interventional team, according to standard clinical prac-tice, using the femoral approach and 6 F guiding catheters. Target lesions were predilated using conventional angioplas-ty balloons followed by stent implantation.

After contrast medium exposure, physiologic (0.9 %) sa-line was given intravenously at a rate of 1 ml/kg/h for 12 h. In patients with left ventricular dysfunction (ejection fraction <40 %) the hydration rate was reduced to 0.5 ml/kg/h.

Clinical definitions and follow-up

According to the American Diabetes Association Practice Guidelines, DM was defined as a fasting blood glucose concentration >126 mg/dL, two hour postprandial plasma glucose level greater than 200 mg/dL or a clinical diagnosis of DM with dietary, oral hypoglycemic agents or insulin treatment [9]. IR was defined as a HOMA level (HOMA-IR=Serum Glucose (mg/dL) X Plasma Insulin (micro unite/mL) / 405 >2.5 and control group as a fasting serum glucose<126 mg/dl and HOMA level <2.5. HOMA indice was calculated using both the fasting insulin (FI) and fasting blood glucose levels. Multivessel involvement was defined as the presence of two or more major coronary arteries with intraluminal diameter narrowing of at least 70 %. Contrast induced nephropathy was defined as was defined as an absolute increase in Cr >0.5 mg/dl on the second day after coronary intervention [10].

We used nonionic low-osmolality contrast medium (Iohexol; Omnipaque 350 mg/50 ml, GE Healthcare Bio-Sciences, Amersham Health Inc. Cork, Ireland) for all pa-tients. They received aspirin and clopidogrel in the coronary care unit and continued to take aspirin and clopidogrel after the procedure. In addition, the patients received a bolus of 5,000 U heparin in the coronary care unit, followed by a bolus of 5,000 U heparin just before the procedure. Prior to PCI, metformin was routinely withheld. Serum creatinine concentration (Cr) was measured before coronary interven-tion and on the second day of follow-up. The risk factors for CIN were recorded: including age, gender, left ventricular ejection fraction (LVEF), fasting plasma glucose (FPG), and volume of contrast media, basic levels of serum creatinine and the number of treated vessels. Glomerular filtration rate (GFR) were calculated.

In-hospital and short-term clinical outcomes were recorded, including procedure-related complications, major adverse car-diac events, length of hospital stay and CIN requiring haemodialysis. We performed an echocardiographic evalua-tion of the left ventricular ejection fraction (LVEF) in all individuals within 24 h from hospital admission. Volume of contrast media was recorded for all patients during catheterization.

Exclusion criteria included sepsis, cardiogenic shock, known acute renal failure, end-stage renal disease requiring dialysis, administration of nephrotoxic agents within 3 days before the procedure, contrast load within the previous 6 days or the following 2 days, known allergy to contrast media and pregnancy. Patients were excluded if emergency bypass grafting was required or if the coronary anatomy was not suitable for PCI. The ethical committee of our institution approved the study, and all patients provided written in-formed consent.

Statistical analysis

Statistical Package for Social Sciences software (SPSS 12, Chicago, IL, USA) was used for analysis. Descriptive param-eters were shown as mean±standard deviation or in percent-ages. Comparisons of continuous variables of the three groups were performed by one-way analysis of variance (ANOVA) with multiple Scheffe-type comparisons. Category variables were analyzed using the Chi square test. Logistic regression analysis was done in two different models in order to under-stand independent determinants of CIN. STEMI, Multivessel disease, contrast volume, gender, ejection fraction, cholesterol and HOMA were covariates in model 1 and contrast volume, DM, STEMI, heart failure, HOMA, gender and glomerular filtration rate were covariates in model 2. A $P<0.05$ was considered significant.

Table 1 Comparisons of clinical characteristics of patients with diabetes, insulin resistance and normal glycemic metabolism

	Normal (N=42)	IR (N=38)	DM (N=44)	P Value
Age	61±9	60±10	63±10	0.458
Gender (female)	6 (14)	13 (34)	21 (48)	0.004
Hypertension	14 (33)	17 (45)	26 (59)	0.056
Multivessel disease	18 (43)	16 (42)	33 (75)	0.002
STEMI	20 (48)	23 (60)	31 (70)	0.005
Contrast induced nephropathy	0 (0)	6 (16)	7 (16)	0.0204
ACE	5 (12)	7 (18)	13 (30)	0.304
Beta blocker	1 (2)	8 (21)	2 (5)	0.006
Calcium channel blocker	2 (5)	2 (5)	4 (9)	0.803
Diuretic	1(2)	0 (0)	3 (7)	0.081
Cholesterol (mg/dl)	176±26	184±24	198±29	0.001
Low-density lipoprotein (mg/dl)	112±25	123±28	134±33	0.038
High-density lipoprotein (mg/dl)	46±18	42±15	39±11	0.046
Triglycerides (mg/dl)	121±35	133±39	147±46	0.033
Glucose(mg/dl)	100±11	105±11	232±113	<0.001
Hemoglobin (g/dl)	14.1±1.5	14.4±1.3	14.1±1.5	0.623
LVEF, %	51±9	47±9	42±8	<0.001
Contrast volume, ml	193±38	213±55	222±56	0.02
Baseline Creatinine, (mg/dl)	0.83±0.14	0.86±0.15	0.86±0.17	0.661
Control creatinine, (mg/dl)	0.87±0.17	1.21±0.7	1.43±1.11	0.004
Change in creatinine, (mg/dl)	0.04±0.16	0.35±0.69	0.57±1.09	0.006
Change in creatinine, %	5.29±19.65	43.00±92.96	67.07±125.34	0.009
Insulin, (μU/ml)	4.54±2.33	17.94±13.21	16.66±15.50	0.001
HOMA	1.15±0.57	4.69±3.30	8.39±5.94	<0.001
eGFR (ml/min/1.73 m^2)	99.9±22.2	96.7±25.1	94.3±23.7	0.47

STEMI ST elevation myocardial infarction, LVEF left ventricle ejection function, HOMA homeostasis model assessment, GFR glomerular filtration rate

Results

One hundred twenty four consecutive patients (84 male and 40 female, mean age 62±10 years) were included in the study.

The overall in hospital mortality rate in the entire population was 4,8 % (6). A total of 3 patients with DM died (1 from refractory heart failure, 1 from multiorgan failure, 1 from cardiogenic shock) and 2 patients with IR died (1 from cardiogenic shock, 1 from refractory heart failure) and 1patient with normal group died (from refractory heart failure). Culprit of left anterior descending coronary artery (54), circumflex coronary artery (33), right coronary artery (37). In 26 patients were multivessel disease. Over 95 % of pa-tients were treated with statins.

Comparisons of clinical characteristics of the patients were shown in Table 1. Patients with IR or DM had significantly higher levels of creatinine after procedure, serum cholesterol, glucose, contrast volume, and HOMA. Female sex, frequency of CIN and multivessel disease were also

Table 2 Logistic regression analysis showing independent predictors of contrast induced nephropathy (model 1)

Variables	Odds Ratio	95%CI	P value
Contrast volume, ml	1.010	0.995–1.026	0.194
ST wave elevation MI	0.422	0.065–2.733	0.365
Gender, women	0.784	0.116–5.293	0.803
LVEF, %	0.895	0.788–1.016	0.086
Cholesterol, (mg/dl)	1.013	0.979–1.048	0.475
HOMA	1.380	1.127–1.690	0.002
Multivessel disease	0.533	0.065–4.362	0.557

Table 3 Logistic regression analysis showing independent predictors of contrast induced nephropathy (model 2)

Variables	Odds Ratio	95%CI	P value
contrast volume, ml	1.013	0.999–1.027	0.079
DM	0.228	0.032–1.616	0.139
ST wave elevation MI	0.478	0.094–2.437	0.374
Heart failure	0.224	0.040–1.239	0.086
HOMA	1.418	1.201–1.675	0.001
Gender, women	0.500	0.073–3.430	0.481
GFR (ml/min/1.73 m^2)	1.008	0.971–1.047	0.671

higher in these patients. On the other hand they had significantly lower ejection fraction. Logistic regression analysis in two different models showed that HOMA was the single independent risk factor for CIN in patients with acute coronary syndrome treated with PCI (Tables 2–3).

Discussion

The present study showed that insulin resistance was an independent predictor of CIN in acute coronary syndrome patients treated with primary percutaneous intervention. Pre-existing renal disease, DM, advanced age, nephrotoxic agent administration, hypovolaemia, large doses of contrast agent or use of ionic hyperosmolar contrast agent and congestive heart failure is strongly associated with CIN. Among all predisposing factors for CIN, diabetic patients with pre-existing renal disease constitute the group at highest risk for CIN [11]. However, for the first time we report that, IR was a risk for CIN.

Several mechanisms have been suggested as etiological factors for CIN, most of which are associated with DM and pre-diabetic stage. They include medullary hypoxia due to decreased renal blood flow secondary to renal artery vasoconstriction and direct tubular toxicity by contrast media. Bakris et al. [12] showed that intrarenal injection of radiocontrast medium resulted in transient vasoconstriction and a persistent decline in glomerular filtration rate due to increased oxygen free radical generation. Furthermore, patients with underlying diabetes or renal insufficiency have higher baseline levels and a greater tendency to increase endothelin after contrast exposure, which contributes renal vasoconstriction [13]. Impaired endothelial function, increased endothelin-1 (ET-1) and angiotensin II levels, and altered nitric oxide-dependent renal vasodilatation are seen in diabetic nephropathy, which may contribute to CIN [14–16]. Our findings showed that, these changes at the molecular stage might have been altered in patients with IR. This hypothesis was supported by several reports. Correlation between ET-1 levels and HOMA (index of insulin resistance) has been shown in different studies [17, 18]. Furthermore, better antioxidant defense prevents increase in endothelin level in insulin-resistant subjects characterized by increased HOMA [19].

The incidence of CIN is usually <2 % in the general population who do not have any risk factor for CIN, and in patients with DM and stages 3–4 chronic kidney disease the incidence of CIN has ranged from 10 % to 80 % [20, 21]. CIN is a frequent complication after emergency PCI for ACS, and the risk of these patients developing CIN is high; reported to affect 19 %–28 % of all patients undergoing emergency PCI for acute myocardial infarction and is a strong predictor of in-hospital mortality (31 %) [2, 12].

The treatment of established CIN is limited to supportive measures and dialysis. Therefore, screening for high-risk patients before coronary angiography and initiating the appropriate prophylactic regimens are important in reducing CIN [22]. Acute coronary syndrome patients with insulin resistance should be on the list of prophylaxis beside diabetics.

Limitations of the study

The proven risk factors for CIN including contrast volume, lower LVEF, STEMI were not significant in our cohort. The reason could be due to the small sample size. Impaired fasting glucose and impaired glucose tolerance which pose a high risk for CIN were not measured.

Conclusion

Insulin resistance is an independent risk factor for CIN in patients with acute coronary syndrome treated with PCI. It carries a similar risk with diabetes and proper prophylaxis should be performed.

Conflict of interest None declared.

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