Impact of diabetic and pre-diabetic state on development of contrast-induced nephropathy in patients with chronic kidney disease

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Abstract

Background. The aim of the present study was to assess the influence of diabetic and pre-diabetic state on the development of contrast-induced nephropathy (CIN) in chronic kidney disease patients undergoing coronary angiography.

Methods. A total of 421 patients with Cockcroft clearance between 15 and 60 ml/min were divided into three groups [diabetes mellitus (DM), n = 137; pre-diabetes (pre-DM), n = 140; and normal fasting glucose (NFG), n = 144]. CIN was defined as an increase of ≥25% in creatinine over baseline within 48 h of angiography, DM as glucose ≥126 mg/dl, pre-DM as glucose between 100 and 125 mg/dl and NFG as glucose <100 mg/dl.

Results. CIN occurred in 20% of the DM (relative risk (RR) 3.6, P = 0.001), 11.4% of the pre-DM (RR 2.1, P = 0.314) and 5.5% of the NFG group. The decrease of glomerular filtration rate (GFR) was higher in DM and pre-DM (P < 0.001 and P = 0.002, respectively). GFR ≤30 ml/min (RR 19.22), multivessel involvement (RR 7.59), hyperuricaemia (RR 3.95), use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blocker (RR 2.70) and DM (RR 2.34) were predictors of CIN. Length of hospital stay was 2.45 ± 1.45 day in DM, 2.27 ± 0.68 day in pre-DM and 1.97 ± 0.45 day in NFG (P < 0.001, DM vs NFG and P = 0.032, pre-DM vs NFG). The rate of major adverse cardiac events was 8.7% in DM, 5% in pre-DM and 2.1% in NFG (P = 0.042, DM vs NFG). Haemodialysis was required in 3.6% of DM and 0.7% in pre-DM (P = 0.036, DM vs NFG), and the total number of haemodialysis sessions during 3 months was higher in DM and pre-DM (P < 0.001). Serum glucose ≥124 mg/dl was the best cut-off point for prediction of CIN.

Conclusion. Our data support that patients with DM are at a higher risk of developing CIN, but patients with pre-DM are not at as high a risk for developing CIN as diabetes patients.

Keywords: contrast-induced nephropathy; coronary angiography; diabetes mellitus; pre-diabetes; renal insufficiency

Introduction

The term contrast-induced nephropathy (CIN) indicates an impairment of renal function (the elevation of serum creatinine by ≥0.5 mg/dl or ≥25%) occurring within 3 days following the intravascular administration of contrast media, not attributable to other causes [1,2]. CIN is independently associated with increased in-hospital and long-term mortality and increases the cost of medical care by at least extending the hospital stay [3,4]. The incidence of CIN can be increased to ~50% in patients at high risk for CIN [1,2,5]. A key step to minimize CIN is to identify patients at risk for CIN and initiating the appropriate prophylactic regimens. CIN most commonly occurs in patients with diabetes mellitus (DM), renal insufficiency, dehydration, congestive heart failure and advanced age. Diabetic nephropathy has been identified as a powerful and independent risk factor for CIN [2].

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oxide-dependent vasodilatation which plays a role in the pathogenesis of CIN [7–12]. We hypothesize that patients classified as having pre-DM would be at an increased risk of developing CIN due to the close relationship of the pathogenesis of pre-DM and CIN. In this study, we examined the effect of DM and pre-DM on the rates of CIN in patients with stages 3–4 chronic kidney disease (CKD) undergoing elective coronary angiography.

**Subjects and methods**

**Study population**

A prospective cohort study was performed in patients with baseline Cockcroft clearance between 15 and 60 ml/min (stages 3–4 CKD) who were referred to the First Cardiology Clinic at Ataturk Training and Research Hospital for non-emergent diagnostic coronary angiography between April 2005 and May 2006. A total of 429 patients met the inclusion criteria. Patients were divided into three groups: DM (n = 140), pre-DM (n = 144) and normal fasting glucose (NFG) (n = 145). The study complied with the Declaration of Helsinki and was approved by the local Ethics Committee. All patients gave written informed consent.

**Analytical methods**

A blood sample for measurement of serum creatinine, glucose, uric acid, lipids and haemoglobin was drawn in the morning before the angiography after an 8 h overnight fast and follow-up serum creatinine was measured 48 h after angiography. Serum glucose levels were determined by the glucose oxidase method and serum creatinine was determined by the Jaffe method. Baseline and follow-up glomerular filtration rate (GFR) were estimated using the Cockcroft–Gault formula: (140–age) x weight (kg)/serum creatinine (mg/dl) x 72 (×0.85 in females). The body mass index was calculated as the weight divided by the square of the height in metres.

**Clinical definitions**

CIN was defined as an increase of ≥25% in serum creatinine over the baseline value within 48 h of coronary angiography. According to the American Diabetes Association Practice Guidelines, DM was defined as a fasting blood glucose concentration ≥126 mg/dl, or a clinical diagnosis of DM with dietary, oral or insulin treatment. Pre-DM was defined as having total cholesterol of ≥200 mg/dl or current use of cholesterol-lowering medication. Hyperuricaemia was defined as a serum uric acid ≥7 mg/dl in males and ≥6.5 mg/dl in females.

**Exclusion criteria**

Exclusion criteria included acute myocardial infarction, cardiogenic shock, sepsis, known acute renal failure, end-stage renal failure requiring dialysis, hyperglycaemia, administration of nephrotoxic agents (aminoglycosides, ciclosporin, tacrolimus, amphotericin B, cisplatin and non-steroidal anti-inflammatory drugs) within 3 days before the procedure, contrast load within the previous 6 days or the following 2 days, known allergy to contrast media or acetylcysteine and pregnancy. For patients with DM, metformin was stopped before the procedure and replaced by insulin or other oral anti-diabetics for 2 days after the coronary angiography to avoid lactic acidosis.

**Hypovolaemia**

Volume status was examined in all patients by the inferior vena cava (IVC) index. The diameter of IVC was measured by B-mode electron-scan in a supine position after 10 min of rest by the same radiologist. The diameter of the IVC was expressed as an index to the body surface area in mm/m² (IVC index). Hypovolaemia was defined as an IVC index of ≤8 mm/m².

**Coronary angiography**

Coronary angiography was performed with the use of low-osmolar, non-ionic contrast agent (iohexol, Omnipaque 300; Opakim, Istanbul, Turkey). Patients received normal saline at a rate of 2 ml/kg/h for 6 h before and 6 h after coronary angiography. N-acetylcysteine was given orally at a dose of 600 mg twice daily on the day before and the day of coronary angiography. Volume of contrast media was recorded for all patients during catheterization. Multivessel involvement was defined as the presence of two or more major coronary arteries with intraluminal diameter narrowing of at least 70%.

**Follow-up**

In-hospital and short-term clinical outcomes were recorded, including procedure-related complications, major adverse cardiac events, length of hospital stay, CIN requiring haemodialysis and the total number of haemodialysis sessions. Short-term clinical follow-up was performed by either telephone contact or office visit at 3 months.
Assuming a 15% incidence of CIN in the NFG group and 28% incidence in the pre-DM group, we found that a sample size of 290 (145 per group) patients would be required to detect a statistically significant difference with power of 80% ($\alpha = 0.05$). The primary study end-point was the development of CIN. Secondary end-points included changes in estimated GFR, length of hospital stay, development of major adverse cardiac events (MACE) and requiring haemodialysis after coronary angiography. 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 analysed using the $\chi^2$ test. Within-subject comparisons of continuous variables, i.e. before and after angiography, were carried out using a paired $t$-test. We performed logistic regression with the presence of CIN as the dependent variable and the following as potential covariates: presence of DM, pre-DM, hypertension, congestive heart failure, GFR $\leq$ 30 ml/min, age $\geq$ 70 years, hyperuricaemia, hypercholesterolaemia, angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) usage, metabolic syndrome, anaemia, female gender and multivessel coronary involvement. Variables that were statistically significant on univariate analysis were included in the final multivariate model to identify predictors of CIN. A two-sided 95% confidence interval (CI) was constructed around the point estimate of the relative risk (RR). All tests were two-sided, and a $P$ value of $<0.05$ was considered statistically significant. Receiver operating characteristic (ROC) curve analysis of serum glucose levels for the prediction of CIN and the positive predictive value and negative predictive value of glucose were performed with MedCalc software version 8.1.1.0 (Mariakerke, Belgium). Other analyses were performed with SPSS software version 13.0 for Windows (Chicago, IL, USA). Continuous data are reported as mean $\pm$ SD. Categorical data are presented as absolute values and percentages.

Statistical analysis

**Patient population and baseline characteristics**

Twenty-three patients were screened out because of volume depletion or technically unsatisfactory ultrasound. Three patients in the DM group, four patients in the pre-DM group and one patient in the NFG group did not complete the second kidney function tests and were therefore dropped from the study (Figure 1). Of these eight patients, none were readmitted to the hospital during the immediate post-procedural period for any reason. Ultimately the study was carried out with 421 patients: 194 males and 227 females and a mean age of 59.36 $\pm$ 8.09 years. The baseline characteristics of the study patients are shown in Table 1. Patients with DM and pre-DM had significantly higher serum glucose levels ($P < 0.001$). Diabetic patients had significantly greater incidence of metabolic syndrome ($P = 0.007$) and patients with NFG had a slightly higher incidence of $\beta$-blocker usage ($P = 0.048$, NFG vs DM). Thirty-five (26%) patients of the DM group were insulin-dependent.

**Markers of renal function and incidence of CIN**

Prior to angiography, the three groups had comparable serum creatinine and GFR. The GFR range was 19.5–60 ml/min and the mean GFR was 49.2 ml/min for all study patients. The majority of patients (91%) were in CKD stage 3. A total of 125 patients (91%) in DM, 128 patients (92%) in pre-DM and 133 patients (92%) in NFG had stage 3 CKD ($P = $ NS). Twelve patients (9%) in DM, 12 patients in Pre-DM (9%) and 11 patients (8%) in NFG had stage 4 CKD ($P = $ NS). Post-procedural serum creatinine was significantly higher in the DM group ($P < 0.001$; DM vs NFG).
Contrast volume (ml) 106.83
Body mass index (kg/m²) 27.35
Female gender 69 (50%) 76 (53%) 82 (56%)
Hypertension 49 (36%) 46 (33%) 40 (27%)
ACE inhibitor usage 45 (33%) 32 (23%) 42 (29%)
Multivessel disease 56 (38%)*** 38 (27%) 28 (21%)
Ca-channel blocker usage 25 (18%) 35 (25%) 29 (20%)
Diuretic usage 37 (27%) 37 (26%) 34 (24%)
Serum glucose (mg/dl) 137.7
LVEF (%) 54.3
Congestive heart failureb 17 (12%) 16 (11%) 22 (15%)
bNew York Heart Association functional classification III/IV.

Values are expressed as mean±SD or number (%) of patients. DM, diabetes mellitus; NFG, normal fasting glucose; ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; LVEF, left ventricular ejection fraction; IVC, inferior vena cava.

and P = 0.002; DM vs pre-DM). After coronary angiography, the GFR was significantly lower in the DM group (P < 0.001; DM vs NFG and P = 0.001; DM vs pre-DM). Following angiography, the decrease in GFR (P < 0.001) and increase in serum creatinine (P < 0.001) concentration were significantly higher in the DM and pre-DM groups than NFG group. Following angiography, serum creatinine increased (P < 0.001) and GFR decreased (P < 0.001) significantly in each group (Table 2). CIN occurred in 12.4% (52 of 421) of the overall study population, in 20% of the diabetic patients, 11.4% of the pre-diabetic patients and 5.5% of the NFG subjects (P = 0.001; DM vs NFG, Figure 2). Twenty (71%) of the 28 patients who developed CIN in the DM group were insulin-dependent (P < 0.001).

In-hospital complications and 3-month follow-up results
Procedure-related complications were similar in the three groups. None of the patients required intra-aortic balloon pump or cardiopulmonary resuscitation, none of the patients developed major bleeding, cardiac arrest, cardiogenic shock or ventricular fibrillation during coronary angiography. Two patients in the DM group, two patients in the pre-DM group and one patient in the NFG group developed prolonged hypotension during coronary angiography. Length of hospital stay was 2.45±1.45 day in DM, 2.27±0.68 day in pre-DM and 1.97±0.45 day in NFG (P < 0.001; DM vs NFG and P = 0.032; pre-DM vs NFG). MACE in 3 months (8.7% in DM, 5% in pre-DM and 2.1% in NFG), multivessel coronary involvement, and CIN requiring haemodialysis were significantly higher in DM patients (P = 0.042; DM vs NFG, P = 0.006; DM vs NFG and P = 0.036; DM vs NFG, respectively). The need for CIN requiring haemodialysis in the whole group was 1.4% (6 of 521 patients). Six of the 52 patients (11%) who developed CIN required haemodialysis.

Haemodialysis was required in five patients (3.6%) in the DM group, and one of these patients required permanent haemodialysis. One patient (0.7%) in the pre-DM group required temporary haemodialysis and, none of the patients developed CIN requiring dialysis in the NFG group. The total number of haemodialysis sessions during the follow-up period was 50 in the DM and five in the pre-DM group (P < 0.001). Although the incidences of MACE, multivessel coronary involvement and CIN requiring haemodialysis were higher in the pre-DM group when compared with the NFG group, they were not statistically significant (Table 3).

Univariate and multivariate variables associated with CIN
We used univariate analysis to study 13 different possible risk factors for developing CIN. Univariate variables associated with CIN were GFR ≤30 ml/min, multivessel coronary involvement, hyperuricaemia, use of ACE inhibitors or ARB, DM, metabolic syndrome and age ≥70 years. Pre-DM was not associated with CIN (RR 1.14, 95% CI 0.61–2.13, P = 0.68). Multivariate analysis showed that the significant predictors of CIN were GFR ≤30 ml/min (P < 0.001), multivessel coronary involvement (P < 0.001),
Table 2. Post-angiographic changes in glomerular filtration rate and serum creatinine in the study patients

<table>
<thead>
<tr>
<th></th>
<th>DM (n = 137)</th>
<th>Pre-DM (n = 140)</th>
<th>NFG (n = 144)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR (ml/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>49.13 ± 8.01</td>
<td>49.61 ± 7.94</td>
<td>48.84 ± 9.42</td>
</tr>
<tr>
<td>Post-procedure</td>
<td>40.22 ± 6.77</td>
<td>44.10 ± 10.06</td>
<td>45.24 ± 8.96</td>
</tr>
<tr>
<td>Absolute change</td>
<td>−8.91 ± 1.56</td>
<td>−5.51 ± 6.27</td>
<td>−3.60 ± 1.67</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.51 ± 0.25</td>
<td>1.46 ± 0.19</td>
<td>1.49 ± 0.39</td>
</tr>
<tr>
<td>Post-procedure</td>
<td>1.84 ± 0.32</td>
<td>1.68 ± 0.38</td>
<td>1.61 ± 0.40</td>
</tr>
<tr>
<td>Absolute change</td>
<td>0.33 ± 0.08</td>
<td>0.22 ± 0.32</td>
<td>0.11 ± 0.06</td>
</tr>
</tbody>
</table>

One-way ANOVA was used for the comparisons among the study groups and paired t-test for the comparisons within groups.

Serum creatinine increased (P < 0.001) and GFR decreased (P < 0.001) significantly in each group after coronary angiography. *P < 0.001 DM vs NFG **P < 0.001 and ***P < 0.01 DM vs pre-DM.

Table 3. In-hospital and short-term clinical outcomes in study patients

<table>
<thead>
<tr>
<th></th>
<th>DM (n = 137)</th>
<th>Pre-DM (n = 140)</th>
<th>NFG (n = 144)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of hospital stay (day)</td>
<td>2.45 ± 1.45*</td>
<td>2.27 ± 0.68***</td>
<td>1.97 ± 0.45</td>
</tr>
<tr>
<td>Procedure-related complications</td>
<td>4 (2.9%)</td>
<td>3 (2.1%)</td>
<td>2 (1.4%)</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>56 (38%)*</td>
<td>38 (27%)</td>
<td>28 (21%)</td>
</tr>
<tr>
<td>Major adverse cardiac event in 3 months</td>
<td>12 (8.7%)*</td>
<td>7 (5%)</td>
<td>3 (2.1%)</td>
</tr>
<tr>
<td>CIN requiring haemodialysis</td>
<td>5 (3.6%)*</td>
<td>1 (0.7%)</td>
<td>0</td>
</tr>
<tr>
<td>Total haemodialysis sessions in 3 months</td>
<td>50***</td>
<td>5*</td>
<td>0</td>
</tr>
</tbody>
</table>

Major adverse cardiac events include death, reinfarct, stroke, cardiogenic shock and cardiac arrest. Procedure-related complications include major bleeding requiring blood transfusion, requiring intra-aortic balloon pump, cardiogenic shock, cardiac arrest, requiring cardiopulmonary resuscitation, ventricular tachycardia or ventricular fibrillation and prolonged hypotension during coronary angiography. *P < 0.001, **P < 0.01 and ***P < 0.05 DM vs NFG.

hyperuricaemia (P = 0.001), use of ACE inhibitors or ARB (P = 0.011) and DM (P = 0.036) (Table 4).

Receiver operating characteristic (ROC) curve analysis and predictive values

Using the ROC curve analysis we found that a serum glucose ≥124 mg/dl was the best cut-off point for prediction of CIN with a sensitivity of 53.8% and a specificity of 73.4%, P = 0.0042. Area under the curve was 0.625 (Figure 3). With a CIN prevalence of 20%, we found that the positive predictive value of serum glucose ≥124 mg/dl was 33.5% and the negative predictive value of serum glucose ≥124 mg/dl was 86.4%.

Discussion

The main novel findings of this study are that we found an 11.4% incidence of CIN in pre-DM patients with stages 3–4 CKD; this study is the first to report the incidence of CIN in pre-DM patients. Second, pre-DM increases the incidence of CIN 2.1-fold in comparison to patients with NFG but pre-DM is not as strong as DM as a risk of developing CIN. Third, the decrease in the GFR and the increase in the serum creatinine are significantly higher in pre-DM and DM after coronary angiography. Fourth, the length of hospital stay is significantly longer in DM and pre-DM after coronary angiography. Fifth, the number of patients who required haemodialysis secondary to CIN is significantly higher in DM and the total number of haemodialysis sessions during 3 months is significantly higher in DM and pre-DM. Sixth, major adverse cardiac events are significantly higher in DM after coronary angiography. Seventh, high incidence of multivessel coronary involvement and high incidence of metabolic syndrome in DM may explain the high risk of CIN in diabetics. Eighth, serum glucose level ≥124 mg/dl is a cut-off point for developing CIN.

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 [2,13]. 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 are 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 [2]. In our study, we found that in patients with the same degree of pre-existing renal disease, diabetic patients have a significantly higher incidence of CIN than patients with NFG. Some studies have suggested that DM is associated with an increased risk of CIN, even when serum creatinine is normal. In a study, it was found that the incidence of CIN was rather low (2%) in patients with neither DM nor azotaemia, significantly higher (16%) in individuals with DM but preserved renal function, and much higher (38%) in patients who had both DM and azotemia [14]. In another study, the incidence of CIN was found to be 2% in patients without DM and 3.7% in patients with DM with a baseline creatinine concentration of $\leq 1.1$ mg/dl ($P = 0.005$) [5]. Other research has failed to detect this connection [15]. Additionally, insulin-dependent diabetics are likely at higher risk of developing CIN than non-insulin-dependent diabetics [2], as in the present study. Currently, it is not known whether pre-DM is a potential risk factor for CIN. To our knowledge, our study is the first to study the pre-diabetic state as a risk for CIN.

Pre-DM is a relatively new clinical diagnosis. Pre-DM is a condition in which fasting serum glucose levels are higher than normal but not high enough to diagnose DM [6]. About 40% of US adults aged 40–74 years are living with pre-DM, and most remain unaware of their condition. Each year between 4% and 9% of the people with pre-DM go on to develop type 2 DM [16,17]. Several epidemiological studies have shown that pre-DM is associated with DM, CKD, atherosclerosis, cardiovascular events, metabolic syndrome, stroke, hypertension, proteinuria and dyslipidaemia [7–11,18,19]. The risk of developing CKD is associated with pre-DM. In a study among 6453 adults without DM, the prevalence of CKD increased from 1.2% with NFG to 4% with pre-DM [18,19]. Several mechanisms have been suggested as etiological factors for CIN, most of which are associated with DM and pre-DM. The proposed mechanisms of CIN are medullary hypoxia due to decreased renal blood flow secondary to renal artery vasoconstriction and direct tubular toxicity by contrast media. Increased endothelin-1, angiotensin II and decreased nitric oxide levels, which are produced by healthy endothelium, are some of the potential mediators leading to intrarenal vasoconstriction in CIN [1,12]. Impaired endothelial function, increased

### Table 4. Risk factors for contrast-induced nephropathy by logistic regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th></th>
<th></th>
<th>Multivariate analysis</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
<td>$P$-value</td>
<td>RR</td>
<td>95% CI</td>
<td>$P$-value</td>
</tr>
<tr>
<td>GFR $\leq$30 ml/min</td>
<td>12.7</td>
<td>5.97–27.02</td>
<td>$&lt;0.001$</td>
<td>19.22</td>
<td>6.74–54.80</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Multivessel involvement</td>
<td>8.93</td>
<td>4.62–17.25</td>
<td>$&lt;0.001$</td>
<td>7.59</td>
<td>3.41–16.89</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Hyperuricaemia</td>
<td>4.12</td>
<td>2.23–7.59</td>
<td>$&lt;0.001$</td>
<td>3.95</td>
<td>1.82–8.56</td>
<td>0.001</td>
</tr>
<tr>
<td>Use of ACEI or ARB</td>
<td>2.25</td>
<td>1.24–4.09</td>
<td>0.007</td>
<td>2.70</td>
<td>1.25–5.81</td>
<td>0.011</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3.82</td>
<td>2.09–6.97</td>
<td>$&lt;0.001$</td>
<td>2.34</td>
<td>1.05–5.17</td>
<td>0.036</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>2.19</td>
<td>1.22–3.94</td>
<td>0.008</td>
<td>1.79</td>
<td>0.84–3.81</td>
<td>0.126</td>
</tr>
<tr>
<td>Age $\geq$70 years</td>
<td>2.28</td>
<td>1.13–4.59</td>
<td>0.02</td>
<td>1.41</td>
<td>0.57–3.50</td>
<td>0.449</td>
</tr>
<tr>
<td>Anaemia</td>
<td>1.66</td>
<td>0.90–3.05</td>
<td>0.104</td>
<td></td>
<td></td>
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<tr>
<td>Hypercholesterolaemia</td>
<td>2.16</td>
<td>0.27–16.71</td>
<td>0.46</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-diabetes</td>
<td>1.14</td>
<td>0.61–2.13</td>
<td>0.68</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.06</td>
<td>0.56–1.98</td>
<td>0.86</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td>1.00</td>
<td>0.56–1.79</td>
<td>0.99</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CHF$^a$</td>
<td>1.04</td>
<td>0.44–2.43</td>
<td>0.92</td>
<td></td>
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</tr>
</tbody>
</table>

RR, relative risk; CI, confidence interval; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; GFR, estimated glomerular filtration rate; $^a$New York Heart Association functional classification III/IV.
endothelin-1 and angiotensin II levels, and altered nitric oxide-dependent renal vasodilatation are important findings of DM and pre-DM [7–12,20,21]. Also, increased reactive oxygen species and oxidative stress are other findings in CIN and these findings can be seen in the DM and pre-DM state [8,20]. Furthermore, both diabetics and pre-diabetics are more likely to develop additional CIN risk factors such as pre-existing renal failure, hypercholesterolaemia, hypertension and metabolic syndrome [7,10,11,18,19]. We hypothesized that pre-DM may be a potential risk for CIN according to the close relationship of the pathogenesis of CIN and pre-DM. Opposite to our hypothesis, we have not found that pre-DM is a risk for CIN in logistic regression analysis. In the present study, we found that in addition to DM, GFR $\leq 30$ ml/min, multivessel coronary involvement, hyperuricaemia, and use of ACE inhibitors or ARB were indicators of CIN risk.

In the present study at baseline, not surprisingly, we found a significantly higher incidence of metabolic syndrome in DM patients. Furthermore, the incidence of metabolic syndrome was higher in pre-DM but it was not statistically significant. According to the literature, 53–86% of the DM patients, 28–71% of the pre-DM patients and 7–25% of the NFG patients had metabolic syndrome. Our metabolic syndrome incidences in DM and pre-DM patients were lower than the US and German populations, but the incidences were close to the Japanese [17,22,23]. In literature, we have not found any CIN study that gave the baseline incidences of metabolic syndrome of the patients, except in our previous study. In a prospective cohort study of 219 non-diabetic elderly patients with reduced kidney function, we reported that metabolic syndrome was a risk indicator of CIN ($P = 0.026$). CIN occurred in 14% of the metabolic syndrome group and 3.6% of the non-metabolic syndrome group (RR 3.93, $P = 0.007$) [24]. Although, in the present study, metabolic syndrome was shown to be a risk factor for CIN only in univariate analysis. Maybe the different characteristics of the study patients played a role in this different consequence. In the present study, use of ACE inhibitors or ARB and hyperuricaemia were the other CIN indicators. The available data on the use of ACE inhibitors, and the associated risks for CIN are sparse and conflicting. Some studies concluded that ACE inhibitors were effective in the prevention of CIN, while some concluded that it was a risk for CIN [25–27]. ACE inhibitor usage may have been a proxy for more severe CKD and may not actually reflect a real biological effect on CIN. In a recent study of 230 patients with renal insufficiency and $\geq 65$ years of age, we found that chronic ACE inhibitor administration was a risk for developing CIN (OR $= 3.37$, $P = 0.028$). CIN occurred 15.6% in the ACE inhibitor group and 5.8% in the control group ($P = 0.015$). Also, compatible with the literature, hyperuricaemia was a risk for CIN in the present study [28]. In our study, we found that if a CKD patient’s serum glucose level is $< 124$ mg/dl, the patient has a 86.4% chance of not developing CIN after coronary angiography. We may decrease the patient’s serum glucose level to 124 mg/dl before coronary angiography. The level of 124 mg/dl is 2 mg/dl lower than the cut-off point of the current definition of DM [6].

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 CKD the incidence of CIN has ranged from 10% to 80%, and CIN can occur in 10–50% of the patients with stages 3–4 CKD without diabetes [2,3,5,29]. Our reported CIN rates were slightly lower than those reported in the literature. Dialysis might be required in 0.15–12% in those who developed CIN [3,4]. Our rate of haemodialysis in patients who developed CIN (11%) is well within this range.

How can we adapt the findings of the present study to the clinical practice? According to our results, DM and pre-DM act as CIN risk multipliers in patients with CKD. It seems reasonable that in pre-DM and DM patients with CKD, in short-term we can normalize the glucose levels before coronary angiography and in the long-term with lifestyle adjustments such as weight loss and increased physical activity we may delay DM in pre-DM and may return glucose levels to normal, and thus, we may decrease the incidence of CIN.

In conclusion, serum glucose measurement is an easily available and inexpensive marker. Therefore, detecting the pre-DM and DM condition before coronary angiography seems to be a useful guide to assess the risk for the development of CIN.
Conflict of interest statement. None declared.

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Received for publication: 20.8.06
Accepted in revised form: 3.10.06

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