Impact of Albuminuria on the Incidence of Periprocedural Myocardial Injury in Patients Undergoing Elective Coronary Stent Implantation

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Albuminuria has traditionally been associated with an elevated risk of cardiovascular events. However, few studies have examined the potential relation between albuminuria and periprocedural risk in percutaneous coronary intervention (PCI). The aim of this study was to evaluate the impact of albuminuria on the incidence of periprocedural myocardial injury (PMI) in patients who underwent PCI. The study included 252 consecutive patients who underwent PCI. The incidence of PMI was significantly higher in patients with albuminuria than in those with normoalbuminuria (31.9% vs 43.3%, respectively, p = 0.014). Even after adjustment for confounders, the presence of albuminuria predicted PMI (odds ratio 2.07, 95% confidence interval 1.08 to 3.97, p = 0.029). Furthermore, patients with albuminuria and preserved estimated glomerular filtration rate had a 4.2-fold higher risk for PMI than did patients with normoalbuminuria and preserved estimated glomerular filtration rate. In conclusion, albuminuria was a strong predictor of PMI in patients who underwent PCI. **(Am J Cardiol 2014;114:42−46)**

Many studies have suggested that microalbuminuria is strongly associated with an increased risk of cardiovascular disease.[1,2] However, the mechanisms underlying the relation are still unclear but are thought to reflect vascular endothelial vascular damage.[3,4] Postprocedural cardiac biomarker elevation is now widely known as periprocedural myocardial injury (PMI).[5] In addition, PMI is widely accepted to be related to subsequent mortality and other poor clinical outcomes.[6] Recently, we reported a correlation between chronic kidney disease and the incidence of PMI.[7] However, few studies have evaluated the relation between albuminuria and the periprocedural risk of percutaneous coronary intervention (PCI). Therefore, the aim of this study was to evaluate the impact of albuminuria on the incidence of PMI in patients who underwent PCI.

Methods

This observational study included total 252 patients who treated successfully with PCI at Nagoya University Hospital from September 2011 to June 2013. All patients had stable angina pectoris and documented myocardial ischemia. The exclusion criteria included congestive heart failure, and/or history of chronic hemodialysis treatment, elevated preprocedural cardiac biomarkers, and needed for rotational atherectomy. Written informed consent was obtained from all patients before their procedures, and the study protocols were approved by the institutional ethics committee.

After an overnight fast of 12 hours, blood samples were obtained from all patients. Urinary albumin excretion was expressed as the albumin-to-creatinine concentration ratio (ACR), evaluated in a random morning urine specimen. Immunoturbidometry (TIA-ALBG; Serotec, Chitose, Japan) was used to determine the urinary albumin concentration, and a modified Jaffe method was used to measure the urinary creatinine concentration. Albuminuria was defined as a urinary ACR (UACR) of ≥30 μg/mg: microalbuminuria, as a UACR of 30 to 300 μg/mg, and macroalbuminuria, as a UACR of >300 μg/mg. UACR of <30 μg/mg was defined as normoalbuminuria.[8] Cardiac enzymes were measured just before and at 24 hours after the procedure. An electrochemiluminescence immunoassay (Roche Diagnostics, Tokyo, Japan) was used to measure high-sensitivity troponin T. In this method, the upper normal limit of the reference range was defined as 0.014 ng/ml for high-sensitivity troponin T. In this study, PMI was defined as an increase in high-sensitivity troponin T >5 times (0.070 ng/ml) the upper normal limit at 24 hours after PCI.[9]

All patients had received dual antiplatelet therapy with aspirin (100 to 162 mg/day) and thienopyridine derivatives before PCI. In addition, any statins had been administered for ≥1 month before PCI. Coronary stents were implanted with or without predilation. Procedural success was defined as a reduction of stenosis to <30% residual narrowing without flow-limiting dissection or occlusion of the large side branch (>1 mm) or no-flow/slow-reflow phenomenon during a procedure. The operator, who was blinded to our patients' characteristics and treatments, selected the position

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Table 1
Baseline characteristics

Variable	Periprocedural Myocardial Injury		p Value
	No (n = 174)	Yes (n = 78)	
Men	144 (81%)	58 (74%)	0.13
Age (years)	68.6 ± 9.2	73.2 ± 8.7	<0.001
Body mass index (kg/m^2)	23.9 ± 3.3	24.1 ± 4.4	0.71
Hypertension	126 (71%)	62 (80%)	0.27
Diabetes mellitus	69 (39%)	27 (35%)	0.49
Current smoker	48 (27%)	17 (22%)	0.36
Previous myocardial infarction	32 (18%)	13 (17%)	0.86
Previous coronary angioplasty	69 (39%)	29 (37%)	0.78
Estimated glomerular filtration rate (ml/min/1.73 m^2)	70.3 ± 18.9	61.5 ± 22.7	0.002
Albumin-to-creatinine concentration ratio (μg/mg)	9 (4–19)	17 (6–61)	0.005
Low-density lipoprotein (mg/dl)	91.8 ± 25.4	92.6 ± 27.8	0.83
High-density lipoprotein (mg/dl)	43.3 ± 11.4	45.7 ± 11.7	0.12
Triglycerides (mg/dl)	113 (82–155)	112 (78–161)	0.68
Fasting glucose (mg/dl)	111.5 ± 29.3	110.3 ± 33.4	0.77
Hemoglobin A1c (%)	6.3 ± 0.9	6.2 ± 0.9	0.75
High-sensitive C-reactive protein (mg/dl)	0.071 (0.035–0.177)	0.079 (0.029–0.186)	0.82
Brain natriuretic peptide (pg/dl)	30.1 (13.4–81.1)	45.9 (15.1–128.7)	0.16
Medications			
Angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers	95 (53%)	45 (58%)	0.68
Ca-channel blocker	74 (42%)	34 (44%)	0.89
β blocker	56 (32%)	27 (35%)	0.77
Diuretics	28 (16%)	16 (21%)	0.47
Antidiabetic drugs	55 (31%)	21 (27%)	0.46

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

Table 2
Lesion and procedural characteristics

Variable	Periprocedural Myocardial Injury		p Value
	No (n = 174)	Yes (n = 78)	
Coronary lesion location			0.018
Left anterior descending	90 (52%)	25 (32%)	
Left circumflex	40 (23%)	24 (31%)	
Right coronary	43 (25%)	29 (37%)	
Bypass graft	1 (1%)	0	
AHA/ACC type B_2 or C	73 (42%)	40 (51%)	0.17
Multivessel coronary disease	83 (48%)	37 (47%)	0.97
Intravascular ultrasound findings			
External elastic membrane volume (mm^3)	224.0 ± 167.5	216.9 ± 154.6	0.82
Lumen volume (mm^3)	84.0 ± 129.3	71.6 ± 53.9	0.57
Plaque volume (mm^3)	151.5 ± 117.8	145.3 ± 103.8	0.77
Procedure			
Number of stents	1.2 ± 0.5	1.4 ± 0.6	0.012
Drug-eluting stent use	65 (37%)	35 (45%)	0.27
Direct stenting	63 (36%)	26 (33%)	0.67
Total stent length (mm)	20.3 ± 10.4	24.3 ± 12.9	0.011
Maximum pressure inflation (atm)	16.3 ± 4.4	17.2 ± 5.3	0.15
Total inflation time (seconds)	100 (69–160)	132 (74–215)	0.10

Data are presented as mean ± SD, or median (interquartile range), or n (%).
AHA/ACC = American Heart Association/American College of Cardiology.

and length of the angioplasty and stent implantation according to angiography and conventional intravascular ultrasound findings.

Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or current antihypertensive medication use. Diabetes mellitus was defined as the use of any antihyperglycemic medication or a current diagnosis of diabetes or having a fasting plasma glucose concentration >126 mg/dl or a glycosylated hemoglobin concentration ≥6.5% (National Glycohemoglobin Standardization Program). Smoking habit was defined as having a current habit or having discontinued cigarette use

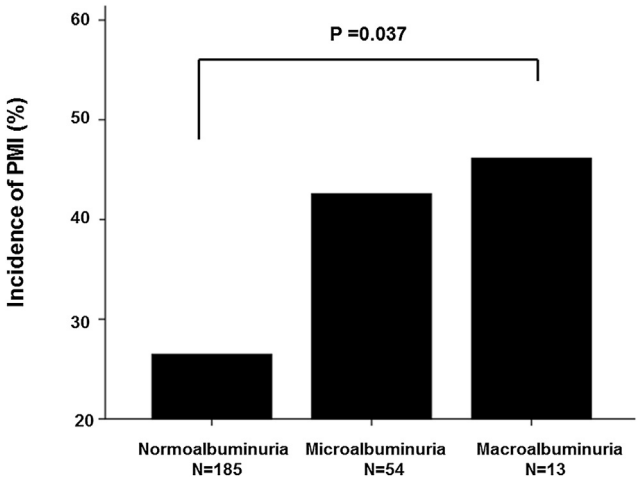
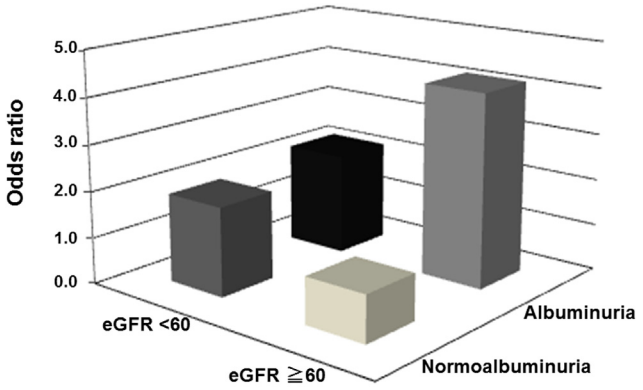


Figure 1. Association of albuminuria with the incidence of PMI in patients with normoalbuminuria, microalbuminuria, and macroalbuminuria (26.5%, 42.6%, 46.2%, respectively, p = 0.037).



	Events (%)	HR, 95%CI	P-value
Normoalbuminuria and eGFR ≧ 60	29/135 (21.5)	ref	
Albuminuria and eGFR ≧ 60	15/30 (50.0)	4.17 (1.59-10.9)	0.004
Normoalbuminuria and eGFR <60	20/50 (40.0)	1.92 (0.81-4.56)	0.14
Albuminuria and eGFR <60	14/37 (37.8)	2.19 (0.83-5.79)	0.11

Figure 2. Combined effects of albuminuria and eGFR levels on the risk of PMI. The estimates are adjusted for multiple risk factors for PMI, such as baseline covariates, lesions, and procedural characteristics.

Table 3
Multivariate logistic regression analysis to identify predictors of periprocedural myocardial injury

	Odds Ratio	95% CI	p Value
Albuminuria	2.07	1.08−3.97	0.029
Age (years)	1.07	1.03−1.11	<0.001
Total stent length	1.04	1.01−1.06	0.011
High-density lipoprotein	1.03	1.00−1.06	0.027

CI = confidence interval.

≤6 months before PCI. The estimated glomerular filtration rate (eGFR) was calculated according to the new Japanese equation: eGFR (ml/min/1.73 m^2) = 194 × serum creatinine − 1.094 × age − 0.287 × 0.739 (in women).[10] Preserved eGFR was defined as ≥60 ml/min/1.73 m^2, and low eGFR was defined as <60 ml/min/1.73 m^2.

Continuous variables are expressed as mean ± SD or median (interquartile range) if they were non-normally distributed. Categorical variables are expressed as percentages. Student *t* test was used to compare continuous variables, and chi-square or Fisher exact test was used to compare categorical variables. To identify independent predictors of PMI, multivariate logistic regression analysis was performed for each parameter used as the dependent variable. A 2-sided p value of <0.05 was considered to indicate statistical significance. SPSS version 18.0 for Windows (SPSS, Inc., Chicago, Illinois) was used to perform all statistical analyses.

Results

Angiographical residual stenosis or large side-branch occlusion was not observed in any patient. In addition, no deaths or critical events occurred during the PCI procedure. Albuminuria was detected in 67 patients (26.6%): 54 (21.4%) had microalbuminuria and 13 (5.2%) had macroalbuminuria. Furthermore, 30 patients (18.2%) with preserved eGFR had albuminuria: 27 (16.4%) had microalbuminuria and 3 (1.8%) had macroalbuminuria.

The clinical characteristics of the patients with and without PMI are listed in Table 1. Lesion and procedural characteristics are listed in Table 2. The incidence of PMI was significantly higher in the patients with albuminuria than in those without (31.9% vs 43.3%; p = 0.014). An apparent dose-response relation between the severity of albuminuria and the incidence of PMI was determined. The incidence of PMI increased significantly from 26.5% in the patients with normoalbuminuria to 42.6% in those with microalbuminuria to 46.2% in those with macroalbuminuria (p for trend = 0.037; Figure 1).

Table 3 lists the results of multiple logistic regression analysis of the relation among the incidences of PMI with multiple risk factors. The presence of albuminuria was an independent predictor of PMI after adjusting for all other variables (p = 0.029), as were age (p <0.001), total stent length (p = 0.011), and high-density lipoprotein cholesterol levels (p = 0.027). We also estimated the combined effects of baseline ACR and eGFR levels on the risk of PMI (Figure 2). After adjusting for multiple risk factors for PMI, the odds ratios (95% confidence interval) of PMI were 4.17 (1.56 to 11.0), 1.92 (0.81 to 4.56), and 2.19 (0.83 to 5.80) for those with albuminuria and preserved eGFR, normoalbuminuria and low eGFR, and albuminuria and low eGFR, respectively.

Discussion

We found that the presence of albuminuria was strongly associated with the incidence of PMI (Type 4a MI).[9] The findings emphasize that patients with early-stage chronic kidney disease should be considered to be a high risk for PMI. From the viewpoint of risk stratification in the PCI procedure, our findings might be of considerable significance because albuminuria is a powerful predictor of PCI-related myocardial

infarction. These data reinforce the utility of albuminuria as a biomarker in clinical practice.

Previous data on the prevalence of microalbuminuria have been reported in several clinical populations. In large cohort studies, the prevalence of microalbuminuria was ≤27% in patients with diabetes[11] and ≤23% in patients with hypertension.[12] Microalbuminuria has also been detected in 5.1% of the general population without diabetes and hypertension.[13] In the present study, 21.4% of patients had microalbuminuria. Albuminuria was detected in 16.7% of patients with preserved eGFR. Furthermore, because we excluded all patients with acute coronary syndrome, it is possible that the prevalence of albuminuria was greater in the patients with ischemic heart disease.

Many cross-sectional and prospective studies have reported the value of albuminuria for identification of patients at high risk of stroke and several acute cardiovascular events, including myocardial infarction,[14,15] and a positive correlation between the degree of albuminuria and the severity of the event was usually documented.[16] Several studies have shown an association between microalbuminuria and coronary atherosclerosis.[17,18] Hong et al[19] reported that, in diabetic patients, vulnerable coronary plaques were significantly greater in the patients with microalbuminuria than in those with normoalbuminuria. In the present study, patients with albuminuria had a significantly greater incidence of PMI, which was independent of traditional risk factors. Thus, our data suggests that the presence of albuminuria in coronary artery disease patients is an indicator for more advanced and vulnerable states of coronary plaques.

Recent studies have emphasized that patients with both elevated albuminuria and reduced eGFR were at the highest risk for cardiovascular outcomes in a general population.[20] Similar results have also been reported from several community-based studies.[11,21] These findings support the idea that albuminuria is a predictor of adverse cardiovascular events independent of eGFR; this suggests that there are distinct mechanisms underlying the cardiovascular risks associated with albuminuria and reduced eGFR.[22,23] Current proposals have focused on evaluating the incorporation of albuminuria in the staging system for chronic kidney disease to identify patients at high risk.[24] However, in the present study, the risk of PMI was higher in the patients with albuminuria and eGFR ≥60 ml/min/1.73 m^2 than in those with albuminuria and eGFR <60 ml/min/1.73 m^2, which indicated a possible reduction in statistical power because of the small number of patients with macroalbuminuria in our study. These results suggest that assessments of both albuminuria and eGFR levels are needed to improve our ability to identify patients at high risk of PMI and to institute appropriate preventive measures.

The mechanisms underlying the relation between microalbuminuria and cardiovascular disease are still unclear but are thought to reflect increased endothelial vascular damage,[3,4] which cause atherosclerosis and lead to clinical cardiovascular disease. Furthermore, albuminuria has been associated with several other risk factors that might themselves be linked with atherosclerosis, including diabetes, hypertension, and obesity.[25] However, even after adjustment for these factors, our data showed that the presence of albuminuria remained strongly associated with PMI.

Recently, several studies reported that the remission/regression of microalbuminuria occurred frequently and was associated with control of multiple atherosclerotic risk factors.[26] In addition, the relation between remission/reduction in microalbuminuria and reduction in cardiovascular events has been reported in diabetes and essential hypertension.[27,28] If remission/reduction of albuminuria cannot be achieved, more intensive medical treatment for achieving better cardiovascular outcomes and delaying progression of atherosclerosis should be considered.

The present study had several limitations. First, this was a single-center study involving a relatively small number of patients. Second, albuminuria measurement was based on a single spot urine sample; therefore, we did not look at serial changes in the amount of urine albumin. However, a previous study reported that an early morning UACR of ≥30 μg/mg was associated with an albumin excretion rate ≥30 mg/min, with high sensitivity and specificity.[29] Third, relatively few participants had macroalbuminuria and/or an eGFR <30 ml/min/1.73 m^2, which limited the ability to assess the impact of these factors in more advanced nephropathy. Fourth, we obtained no information on the duration of diabetes mellitus or status of blood glucose levels.

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