Prevalent Rate of Nonalbuminuric Renal Insufficiency and Its Association with Cardiovascular Disease Event in Korean Type 2 Diabetes

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Background: Nonalbuminuric renal insufficiency is a unique category of diabetic kidney diseases. The objectives of the study were to evaluate prevalent rate of nonalbuminuric renal insufficiency and to investigate its relationship with previous cardiovascular disease (CVD) event in Korean patients with type 2 diabetes mellitus (T2DM).

Methods: Laboratory and clinical data of 1,067 subjects with T2DM were obtained and reviewed. Study subjects were allocated into four subgroups according to the CKD classification. Major CVD events were included with coronary, cerebrovascular, and peripheral vascular events.

Results: Nonalbuminuric stage ≥3 CKD group, when compared with albuminuric stage ≥3 CKD group, had shorter diabetic duration, lower concentrations of glycated hemoglobin, high density lipoprotein cholesterol, and high-sensitivity C-reactive protein, lower prevalent rates of retinopathy and previous CVD, and higher rate of treatment with angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers. Nonalbuminuric stage ≥3 CKD group showed a greater association with prior CVD events than no CKD group; however, albuminuric stage ≥3 CKD group made addition to increase prevalence of prior CVD events significantly when CKD categories were applied as covariates. Association of prior CVD events, when compared with normal estimated glomerular filtration rate (eGFR) and nonalbuminuria categories, became significant for declined eGFR, which was higher for eGFR of <30 mL/min/1.73 m², and albuminuria.

Conclusion: The results show that subjects with nonalbuminuric stage ≥3 CKD is significantly interrelated with occurrence of prior CVD events than those with normal eGFR with or without albuminuria. Comparing with normal eGFR and nonalbuminuria categories, the combination of increased degree of albuminuria and declined eGFR is becoming significant for the association of prior CVD events.

Keywords: Nonalbuminuric renal insufficiency; Diabetes mellitus; Cardiovascular diseases
INTRODUCTION

In the current global epidemic, the high incidence of diabetes is dramatically related to an enlarged emerging of cardiovascular diseases (CVD) [1] and end-stage renal disease [2]. Preceding studies showed that both declined estimated glomerular filtration rate (eGFR) and increased degree of albuminuria presuppose CVD events in nondiabetics and subjects with type 2 diabetes mellitus (T2DM) [3-5]. Lately, Soveri et al. [6] showed that it may be possible to detect a rise in the risk of CVD development and cardiovascular death in those with eGFR of <90 mL/min/1.73 m². On the average, 30% of diabetic patients will develop chronic renal disease [7], and nonalbuminuric form of renal insufficiency is also found [8,9]. The two large-scale clinical trials have analyzed and shown the self-determining influences of both increased degree of albuminuria and decreased renal function on the development of CVD and cardiovascular death [10,11]. A worsening of kidney function may not always be go together with high excretion rate of urinary albumin [12,13]. Therefore, nonalbuminuric renal insufficiency is a distinctive form of renal diseases in T2DM. But, its clinical progression and pathophysiology are still not conclusive. The recent study using meta-analysis showed that albuminuria and declined eGFR (<60 mL/min/1.73 m²) have both been confirmed—without any evidence of interaction—as independent predictors of cardiovascular death [14]. According to some studies in patients with T2DM, albuminuria predicts cardiovascular death better than declined eGFR [14,15]. Italian multicenter studies showed that nonalbuminuric renal insufficiency, compared with albuminuric renal insufficiency is significantly related to any CVD events in T2DM [16,17]. Still it is unclear whether nonalbuminuric form of renal insufficiency is linked with developing CVD, especially in Korean patients.

The purposes of the study were to evaluate prevalent rate of nonalbuminuric renal insufficiency in Korean diabetic patients and to investigate association of previous CVD events with nonalbuminuric renal insufficiency compared with albuminuric renal insufficiency or no CKD in the study subjects.

METHODS

Study subjects

The data were obtained for 1,067 patients with T2DM (561 men, 506 women) at the baseline visit attending the Diabetes Center at Pusan National University Yangsan Hospital for management of diabetes, between January 2011 and December 2013. We excluded patients under 18 or over 80 years of age, patients with receiving renal replacement therapy, patients with systemic conditions that may affect vascular glomerulonephritis or vasculitis, patients with other reasons of renal dysfunction, and patients with malignancy. The study was received the ethical approval from the Ethical Review Board of the Clinical Research Institute at Pusan National University Yangsan Hospital.

Clinical information and biochemical data analysis

We retrospectively reviewed the records to evaluate patients’ sex, age, body mass index, smoking status, diabetic duration, blood pressure, and previously documented history of major CVD events, including coronary diseases (myocardial infarction and/or coronary artery revascularization), cerebrovascular diseases (cerebral infarction and/or carotid artery revascularization), and peripheral artery diseases (peripheral artery occlusive disease and/or lower limb revascularization). Occurrence of retinopathy was determined by an ophthalmoscope examination by an expert ophthalmologist. Medication histories regarding antihypertensive drugs, including renin-angiotensin system (RAS) inhibitors, and lipid-lowering drugs were also reviewed. We measured the concentrations of blood urea nitrogen, creatinine, total cholesterol, triglyceride, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), and high-sensitivity C-reactive protein (hsCRP) using an autoanalyzer and an enzymatic colorimetric method (Hitachi 7600, Hitachi Ltd., Tokyo, Japan). Glycated hemoglobin (HbA1c) was measured using high performance liquid chromatography (Bio-Rad Laboratories, Hercules, CA, USA).

We calculated eGFR with the Modification of Diet in Renal Disease (MDRD) study equation \[\text{eGFR} = 175 \times \left(\frac{\text{SCr}}{\text{max}}\right)^{-1.154} \times \text{age}^{-0.203} \times (\text{if female})^{-1.212} \times (\text{if black})\] [18], and renal insufficiency was defined as eGFR <60 mL/min/1.73 m² (i.e., stage ≥3 CKD) according to the guidelines from the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) [19]. Moreover, we also measured eGFR using Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation \[\text{eGFR} = 141 \times \min\left(S_\text{cr}/\kappa, 1\right)^\alpha \times \max\left(S_\text{cr}/\kappa, 1\right)^{-1.209} \times 0.993^\kappa \times 1.018 \times (\text{if female}) \times 1.159 \times (\text{if black}),\] where: \(S_\text{cr}\) is serum creatinine in mg/dL, \(\kappa\) is 0.7 (females) and 0.9 (males), \(\alpha\) is –0.329 (females) and –0.411 (males), minimum of \(S_\text{cr}/\kappa\) or 1, and maximum of \(S_\text{cr}/\kappa\) or 1, which was recently developed to provide a lower estimate of CKD prevalence than the MDRD study formula [20].

Urinary albumin levels were calculated using Roche/Hitachi MODULAR analyzers (Roche Diagnostic GmbH, Mannheim,
Germany) and urine creatinine concentrations were measured by the Jaffe method (Hitachi 7170, Hitachi, Tokyo, Japan). Albumin excretion rate was recalculated from the albumin-creatinine ratio (ACR) in the single spot urine samples using an adaptation formula developed in patients with type 1 diabetes mellitus (T1DM) [19]. Study subjects were then allotted to the subsequent groups according to the NKF KDOQI [19]: group 1 is no CKD (eGFR $\geq 60$ mL/min/1.73 m$^2$ and ACR $<30$ mg/g), group 2 is stages 1 to 2 CKD (eGFR $\geq 60$ mL/min/1.73 m$^2$ and ACR $\geq 30$ mg/g), group 3 is nonalbuminuric stage $\geq 3$ CKD (eGFR $<60$ mL/min/1.73 m$^2$ and ACR $<30$ mg/g), and group 4 is albuminuric stage $\geq 3$ CKD (eGFR $<60$ mL/min/1.73 m$^2$ and ACR $\geq 30$ mg/g).

**Statistical analyses**

Data were described as the mean±SD and median, or as the percentages and number of cases. The Kruskal-Wallis one-way analysis of variance for continuous variables or Pearson chi-square test for categorical variables were applied.

To detect the factors related to previous CVD events, logistic regression analyses were done. Individual values, deciles, or categories of eGFR and albuminuria or CKD types, such as nonalbuminuric stage $\geq 3$ CKD, albuminuric stage $\geq 3$ CKD, or stages 1 to 2 CKD and no CKD as a reference category, as covariates were together with age, sex, smoking, duration of diabetes, HbA1c, levels of triglycerides, HDL-C, LDL-C, and hsCRP, lipid-lowering treatment, antihypertensive medication, and retinopathy. The analyzed results were described as the odds ratios with their 95% confidence interval. A $P<0.05$ was considered statistically significant. Statistical analyses were executed using SPSS version 21.0 (IBM Co., Armonk, NY, USA).

**RESULTS**

We enrolled 1,067 study subjects (561 males [52.5%] and 506 females [47.5%]). The mean enrolled patients’ age was $59.5\pm 15.9$ year. Median diabetic duration was 6.2 years, and mean value of eGFR calculated by the CKD-EPI formula was greater than by the MDRD study formula in the study subjects (66.9 mL/min/1.73 m$^2$ vs. 64.9 mL/min/1.73 m$^2$, correspondingly). Study subjects were allotted to one of the following eGFR classes: class 1 ($\geq 90$), class 2 (60 to 89), class 3 (30 to 59), and class 4 ($<30$). When calculated by the MDRD study equation, prevalent rates of classes 1, 2, 3, and 4 were 37.2%, 23.9%, 24.3%, and 14.5%, respectively. The prevalent rates of classes 1, 2, 3, and 4 were 38.1%, 25.8%, 24.4%, and 11.7%, respectively, when measured by the CKD-EPI formula. Prevalent rates of non-, micro-, and macroalbuminuria were 39.3%, 42.5%, and 18.2%, respectively (Fig. 1). The occurrences of previous CVD events and retinopathy significantly increased according to eGFR classes and degree of albuminuria (Fig. 2). Of the 414 patients with declined eGFR, 98 subjects were nonalbuminuric and 316 subjects were albuminuric. Among those with declined eGFR, 310 subjects did not have any history of CVD events and 384 subjects presented without albuminuria and previous CVD.

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**Fig. 1.** Prevalence of non-, micro-, and macroalbuminuria according to classes of estimated glomerular filtration rate (eGFR) by the Modification of Diet in Renal Disease (MDRD) study and the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formulas.
events, whereas any CVD history were presented in 20 subjects with stages 1 to 2 CKD, 105 subjects having both albuminuria and previous CVD events. Amongst those with declined eGFR, 153 subjects showed retinopathy and the other 261 subjects lacked retinopathy. Additionally, 383 subjects had neither albuminuria nor retinopathy, and only 149 subjects had both albuminuria and retinopathy (Table 1).

Nonalbuminuric stage ≥ 3 CKD group had shorter diabetic duration, lower concentrations of HbA1c, HDL-C, and hsCRP, lower prevalent rates of retinopathy and previous CVD, and higher rate of treatment with angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ACEIs/ARBs), than albuminuric stage ≥ 3 CKD group (Table 1). Likewise, when comparing no CKD group, nonalbuminuric stage ≥ 3 CKD group was more nonsmokers and had lower concentration of HDL-C, higher rates of treatment with ACEIs/ARBs and statin, and higher rates of previous CVD events and retinopathy (Table 1).

Subjects with nonalbuminuria and subnormal eGFR categories (60 to 89 mL/min/1.73 m²), when comparing with normal renal function (≥ 90 mL/min/1.73 m²), were not significantly related with previous CVD events. However, its relevance was significantly increasing for those with declined renal function (< 60 mL/min/1.73 m²), which was greater for eGFR of < 30 mL/min/1.73 m², and albuminuria (Table 2).

According to the logistic regression analyses, there were positive correlations of male sex, diabetic duration, current smok-
We found that nonalbuminuric stage ≥3 CKD group had lower prevalent rates of retinopathy and previous CVD than albuminuric stage ≥3 CKD group. In addition, albuminuric stage ≥3 CKD group showed a stronger association with retinopathy than those with the normal eGFR with or without albuminuria. We also showed that nonalbuminuric stage ≥3 CKD group was significantly related with the incidence of any CVD events than no CKD. There is a consistency between the higher CVD prevalent rate observed in albuminuric stage ≥3 CKD group and the additional cardiovascular risk associated with combination of declined eGFR and increased degree of albuminuria [14]. Therefore, nonalbuminuric form of renal insufficiency is the clinically
distinctive entity of renal diseases in T2DM, and it should be considered in the management of these patients. There is a weak association between previous CVD events and patients with albuminuria alone because patients with increased degree of albuminuria and normal/subnormal eGFR were assigned to the early stage of CKD than patients with declined eGFR, without regard to albuminuria. But on the other, when compared with nonalbuminuric stage $\geq 3$ CKD group, the additively higher cardiovascular burden associated with the integration of declined eGFR and albuminuria bears out that patients with albuminuric stage $\geq 3$ CKD should be considered at higher cardiovascular risk, which is in line with previous studies [8,10]. Microalbuminuria is a first sign of renal dysfunction based on the clinical progression of diabetic kidney diseases [21]. Thus, in diabetic patients, it is important to measure and monitor excretion of urine albumin, as a predictive clinical marker of chronic renal complications, for preventing overt diabetic nephropathy [22,23]. Measuring excretion of albumin in 24 hours collected urine sample is the standard method [24], although a substitute way is measuring excretion of albumin and creatinine in single spot urine sample [25,26]. Ratio of albumin and creatinine excretion was accepted as a reliable screening method for selecting study population in many trials [25,27]. However, the early loss of renal function may occur even in the condition without albuminuria in some T1DM with a long duration, and this is more of a common occurrence than in T2DM. The mechanism of this is not clear; however, possible factors of nonalbuminuric form of renal insufficiency are renal nephron loss according to aging, interstitial fibrosis, cholesterol emboli, and atherosclerotic changes in renal vasculature [28]. To interpret the growing prevalent rate of nonalbuminuric renal insufficiency, the impact of recent treatment trends should be also considered. For example, during the last two decades, there has been an intense rise in hypertension and/or renal insufficiency treated with RAS inhibitors in patients with T2DM [8]. The role of RAS blocking agents have distinct effects on degrees of both GFR and albuminuria [10,23]. In our study subjects, 72% of patients were used with such a treatment; and a greater proportion has been described previously [8]. Moreover, the rising prevalent rate of nonalbuminuric renal insufficiency may reveal alterations in the fundamental renal pathology with macrovascular lesions prevailing against microvascular lesions [24]. Such an alteration may also be attributed to the recent changes in treatment modality, especially to the intensive management of blood pressure, glucose, and lipids, which has been achieved in diabetic patients established on results of previous trials [25,27].

Matsushita et al. [28] has proposed that CKD-EPI formula was able to more accurately detect patients in respect to risk of cardiovascular events and death compared to MDRD study.
pathophysiologic mechanism for the connection between declined renal function with albuminuria and cardiovascular death [25,33]. Therefore, albuminuric renal insufficiency, as a prevalent feature of renal macrovascular lesions, would be more commonly related with cardiovascular events.

The limitations of the study are as follows. First, the cross-sectional design and small number of study population limit the inferences of the observed causal relations between relevant factors of nonalbuminuric renal insufficiency and occurrence of any CVD events. Second, this study was conducted at a single-center hospital. Therefore, the making generalization from our results to the entire the Korean patients with T2DM is weak. Third, the assessment of degree of albuminuria was done with only one spot urine sample. A single urine specimen might not exactly estimate albuminuria compared with 24 hours urine collection.

In conclusion, we confirm that nonalbuminuric stage ≥3 CKD group is significantly interrelated with occurrence of prior CVD events than group with normal eGFR with or without albuminuria. Comparing with normal eGFR and nonalbuminuria categories, the combination of increased degree of albuminuria and declined eGFR is becoming significant for the association of prior CVD events. Additional large prospective studies will be required in order to clear up the relevant causes for the development of any CVD events in nonalbuminuric renal insufficiency in patients with T2DM.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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