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Renal tubular damage is associated with poor clinical outcome in patients with peripheral artery disease who underwent endovascular therapy

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ABSTRACT

Background: Kidney dysfunction is associated with adverse outcome in patients with peripheral artery disease (PAD). Renal tubulointerstitial damage (RTD) is another type of kidney dysfunction from glomerular damage. RTD is reported to be a risk for future cardiac event in patients with heart disease. However, it remains to be determined whether RTD is predictive of poor clinical outcome in patients with PAD.

Methods and results: RTD markers (urinary N-acetyl-β-D-glucosamidase; NAG and urinary β-2 microglobulin to creatinine ratio) and Glomerular damage markers (cystatin C-based estimated glomerular filtration rate, proteinuria, and microalbuminuria) were measured in 265 consecutive PAD patients who underwent endovascular therapy. Patients were prospectively followed for a median length of 804 days, with end points of major adverse cardiovascular and cerebrovascular events (MACCE). Overall, 73% of patients exhibited excess urinary NAG excretion, and values were higher in patients with critical limb ischemia. A multivariate Cox proportional hazard analysis revealed that NAG was an independent predictor of MACCE. When patients were divided according to NAG level, Kaplan–Meier analysis demonstrated that the third tertile was associated with the greatest risk for MACCE. The C index in NAG was the greatest among kidney dysfunction markers. Moreover, the net reclassification index was improved by the addition of NAG to basic predictors including glomerular damage markers.

Conclusion: RTD is common and associated with disease severity and clinical outcome in patients with PAD, indicating that it could be the additional clinical information to glomerular damage in patients with PAD.

1. Introduction

Peripheral artery disease (PAD) is an athero-occlusive disease of the lower limb arteries that increases morbidity. Despite advances in endovascular therapy, PAD remains an important medical issue with an increasing prevalence and high all-cause and cardiovascular mortality rate [1–4]. Therefore, it is increasingly important to consider during the early identification and risk stratification of PAD patients. Although reduced lower extremity performance was reported to be a prognostic marker for mortality, risk factors in patients with PAD have not yet been fully elucidated.

Kidney function is associated with PAD development [5]. Previous study found that glomerular damage, e.g. reduced glomerular filtration rate, proteinuria, and albuminuria, was related to PAD. Renal tubular damage (RTD) is another type of kidney dysfunction from glomerular damage. Renal tubule cells have diverse regulatory and endocrine functions and play pivotal roles in modulating acid–base balance, erythropoietin synthesis, and reabsorption of sodium, water, bicarbonate, and amino acid [6,7]. Some reports have indicated that severe RTD is related to future cardiovascular disease, as well as glomerular damage in subjects who live in a cadmium-polluted region [8,9]. Although cadmium exposure, which is a major cause of RTD, is reported to be associated with PAD development [10], it remains unclear whether RTD is associated with PAD. In the present study, we tested the hypothesis that RTD is common among PAD patients and can predict poor prognosis.

2. Methods

2.1. Study population

This was a prospective study of 265 de novo patients who were admitted to our hospital for PAD treatment. PAD was diagnosed by two physicians according to the ankle brachial index (ABI) and computed tomographic angiography. Endovascular therapy (EVT) was performed by an experienced cardiologist according to the Trans-Atlantic Inter-

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Society Consensus II (TASC II) guideline recommendation. An optimal medical therapy was independently administered based on symptom improvement by physicians who were blinded to the biochemical analysis results. The exclusion criteria of the present study were acute coronary syndrome within 3 months preceding admission and hemodialysis. Blood samples were obtained in the early morning before the first EVT. Demographic and clinical data including age, sex, and ABI were collected from patient medical records and interviews. Medications and ABI at discharge were recorded from hospital medical records.

2.2. Ethics statement

The institutional ethics committee of Yamagata University School of Medicine approved the study, and all participants provided written informed consent. The procedures were performed in accordance with the Helsinki Declaration.

2.3. Kidney function and biochemical assay

Urine and venous blood samples were obtained in the early morning before the first EVT session. Urinary N-acetyl-β-D-glucosamidase (NAG) levels, a marker of early RTD, were measured in single-spot urine specimens and corrected by urinary creatinine. The normal range of NAG was reported to be less than <5.8 U/g (log NAG, 1.76 U/g) [11]. High NAG was previously defined as NAG >14.2 U/g (log NAG >2.66 U/g) according to previous report [12].

Urinary β_2-microglobulin concentrations were determined by the latex agglutination method (BML, Inc., Tokyo, Japan). β_2-microglobulin levels were corrected for urinary creatinine (UBCR) [13]. We quantitatively measured urinary albumin by immunoturbidimetry in a single spot urine specimen collected. Urinary albumin levels were corrected for urinary creatinine in a single manner to urinary microalbumin-creatinine rate (UACR). We detected urinary protein with albumin-specific dipsticks at the same time. We defined proteinuria as positive dipstick test (1+ or more).

Serum cystatin C levels were determined by a sandwich enzyme-linked immunosorbent assay using two distinct anti-human cystatin C specific monoclonal antibodies (Human cystatin C, KRKA d.d., Novo Mesto, Slovenia) as previously reported [14,15]. Glomerular filtration rate (GFR) is the standard indicator of kidney function. Under steady-state conditions, it is estimated from serum creatinine (sCr) or cystatin C using the following equations: eGFRcr in males = $194 \times sCr^{-1.094} \times Age^{-0.287}$; eGFRcr in females = $(194 \times sCr^{-1.094} \times Age^{-0.287}) \times 0.739$; eGFRcys in males = $104 \times \text{cystatin C}^{-1.019} \times 0.996^{Age} - 8$; eGFRcys in females = $(104 \times \text{cystatin C}^{-1.019} \times 0.996^{Age} \times 0.929) - 8$ [16].

Serum hemoglobin (Hb), serum albumin (Alb), and high sensitivity C-reactive protein (hsCRP) were also measured at the same time.

Table 1
Clinical characteristics of 265 patients with peripheral artery disease.

Variables	All patients n = 265
Age (years old)	75 ± 9
Male/female	216/49
Hypertension, n (%)	216 (82%)
Diabetes mellitus, n (%)	119 (45%)
Previous IHD, n (%)	82 (31%)
Previous cerebrovascular disease	49 (19%)
Fontaine II/III/IV	200/31/34
Revascularized artery segments	
Iliac artery, n (%)	177 (67%)
Femoropopliteal artery, n (%)	153 (58%)
Tibial or peroneal artery, n (%)	39 (15%)
Stent, n (%)	240 (91%)
Pre ABI	0.59 ± 0.16
Post ABI	0.89 ± 0.18
Kidney function	
Creatinine (mg/dL)	0.88 ± 0.32
eGFRcr (ml/1.73/m^2)	71 ± 30
Cystatin C (mg/dL)	1.19 ± 0.38
eGFRcys (mL/1.73/m2)	62 ± 20
Log UACR (mg/g)	1.32 ± 0.70
Proteinuria, n (%)	49 (18%)
Log UBCR (μg/g)	2.39 ± 0.58
Log NAG (U/g)	2.20 ± 0.66
Biochemical data	
Alb (mg/dL)	3.8 ± 0.5
Hb (mg/dL)	12.7 ± 1.7
Log hsCRP (pg/mL)	4.73 ± 1.36
Medication	
Aspirin, n (%)	182 (69%)
Clopidogrel, n (%)	169 (64%)
Other antiplatelet drug, n (%)	149 (56%)
ACEIs and/or ARBs, n (%)	162 (61%)
Calcium channel blockers, n (%)	145 (55%)
Statin, n (%)	145 (55%)

Data are expressed as mean ± SD, number (percentage).
ABI, ankle brachial index; ACEIs, angiotensin-converting enzyme inhibitors; Alb, serum albumin; ARBs, angiotensin II receptor blockers; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; hsCRP, high sensitivity C-reactive protein; IHD, ischemic heart disease; MACCE, major adverse cardiovascular and cerebrovascular event; NAG, N-acetyl-β-D-glucosamidase; UACR, urinary microalbumin-creatinine ratio; UBCR, urinary β_2-microglobulin-creatinine ratio.

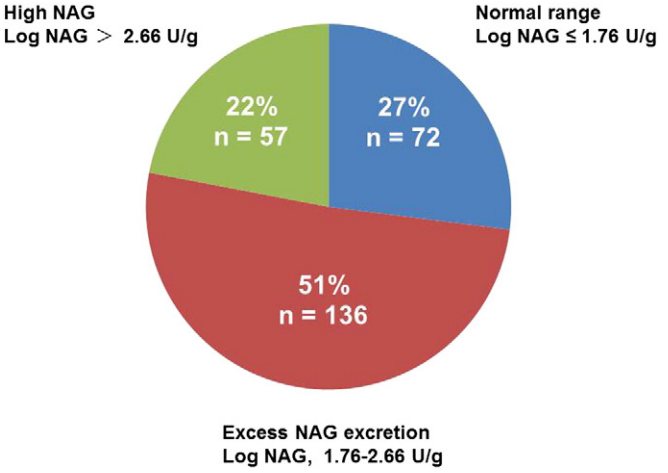

Fig. 1. Distribution of normal (log NAG <1.76 U/g), excess excretion (log NAG, 1.76–2.66 U/g), and high NAG (log NAG >2.66 U/g) in patients with PAD. NAG, N-acetyl-β-D-glucosamidase; PAD, peripheral artery disease.

2.4. Measurement

Hypertension (HT) was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or antihypertensive medication use. Diabetes mellitus (DM) was defined as glycosylated hemoglobin A1c ≥6.5% (National Glyco hemoglobin Standardization Program), or anti-diabetic medication use.

2.5. Endpoint and follow-up

All subjects were prospectively followed for a median period of 804 days (interquartile range, 365–1388 days). Patients were followed by telephone or medical record twice a year until 1500 days. The endpoints were all-cause death, rehospitalization due to cardiovascular and cerebrovascular disease (such as stroke, ischemic heart disease, heart failure(IHD), and aortic abdominal aneurysm), and the development of critical limb ischemia (CLI) and amputation.

2.6. Statistical analysis

Because NAG, UACR, UBCR and hsCRP were not normally distributed, we used log-transformed NAG and hsCRP for all analyses. All values are expressed as the mean ±

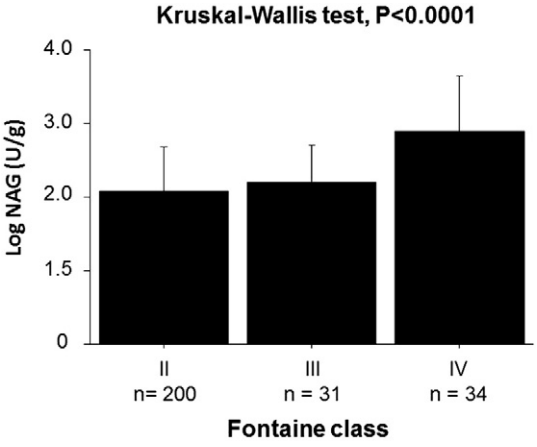

Fig. 2. The association between Fontaine class and NAG level. NAG, N-acetyl-β-D-glucosamidase.