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Predictors of abdominal aortic calcification progression in patients with chronic kidney disease without hemodialysis

Dai Yamamoto [a], Susumu Suzuki [a, *], Hideki Ishii [a], Kenshi Hirayama [a], Kazuhiro Harada [a], Toshijiro Aoki [a], Yohei Shibata [a], Yosuke Negishi [a], Yosuke Tatami [a], Takuya Sumi [a], Takeo Ichii [a], Kazuhiro Kawashima [a], Ayako Kunimura [a], Toshiki Kawamiya [a], Ryota Morimoto [a, b], Yoshinari Yasuda [b], Toyoaki Murohara [a]

[a] Department of Cardiology, Nagoya University Graduate School of Medicine, Nagoya, Japan
[b] Department of CKD Initiatives Internal Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan

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ABSTRACT

Background and aims: Abdominal aortic calcification (AAC) is an important predictor of cardiovascular mortality in patients with chronic kidney disease (CKD). However, little is known regarding AAC progression in these patients. This study aimed to identify risk factors associated with AAC progression in patients with CKD without hemodialysis.

Methods: We recruited 141 asymptomatic patients with CKD without hemodialysis [median estimated glomerular filtration rate (eGFR), 40.3 mL/min/1.73 m^2] and evaluated the progression of the abdominal aortic calcification index (ACI) over 3 years. To identify risk factors contributing to the rate of ACI progression, the associations between baseline clinical characteristics and annual change in ACI for each CKD category were analyzed. The annual change of ACI (ΔACI/year) was calculated as follows: (second ACI − first ACI)/duration between the two evaluations.

Results: Median ΔACI/year values significantly increased in advanced CKD stages (0.73%, 0.87%, and 2.24%/year for CKD stages G1-2, G3, and G4-5, respectively; p for trend = 0.041). The only independent risk factor for AAC progression in mild to moderate CKD (G1-3, eGFR ≥ 30 mL/min/1.73 m^2) was pulse pressure level (β = 0.258, p = 0.012). In contrast, parathyroid hormone (PTH) level was significantly correlated with ΔACI/year (β = 0.426, p = 0.007) among patients with advanced CKD (G4-5, eGFR < 30 mL/min/1.73 m^2).

Conclusions: This study suggests that the AAC progression rate was significantly accelerated in patients with advanced CKD. In addition, measuring PTH is useful to evaluate both bone turnover and AAC progression in patients with advanced CKD.

1. Introduction

Chronic kidney disease (CKD) is widely accepted as an independent risk factor for unfavorable health outcomes that include cardiovascular disease [1–3]. Moreover, patients with CKD frequently experience cardiovascular events associated with accelerated athero- and arteriosclerosis prior to the development of end-stage kidney disease [4,5]. Thus, risk stratification for preventing cardiovascular events is clinically important to improve CKD prognosis.

The mechanisms underlying the high risk for cardiovascular mortality in populations with CKD remain to be elucidated. However, vascular calcification, a major component of CKD–mineral and bone disorder (CKD–MBD), is known as an important risk factor that influences cardiovascular outcomes in these patients [6,7]. Thus, recent guidelines recommend the evaluation of vascular calcification, including abdominal aortic calcification (AAC), along with mineral/bone abnormalities in patients with early stage CKD [8].

However, little is known regarding the progression of vascular calcification in patients with CKD without hemodialysis. Therefore,

* Corresponding author. Department of Cardiology, Nagoya University Graduate School of Medicine, 65, Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan.
E-mail addresses: susumusuzuki@med.nagoya-u.ac.jp, sususu0531@yahoo.co.jp (S. Suzuki).

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this study aimed to identify risk factors associated with AAC progression in each CKD category.

2. Materials and methods

2.1. Subjects

Between 2008 and 2010, a total of 141 asymptomatic patients with CKD without hemodialysis were recruited from the outpatient clinic of the Department of Nephrology, Nagoya University Hospital. CKD was defined as an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2, the presence of proteinuria, or renal disease as a complication at study entry [9]. Patients with active autoimmune disease, active malignancy, or a history of abdominal aortic artery repair and stenting were excluded. The study protocol was approved by the ethics committee of the Nagoya University Hospital and conducted according to the ethical principles described in the Declaration of Helsinki. Written informed consent was obtained from all patients.

2.2. Measurement of abdominal aortic calcification index (ACI) and ΔACI/year

Each patient underwent non-contrast computed tomography (CT) at the first examination to investigate renal morphology and the degree of subclinical vascular calcification. After 3 yrs of standard medical treatment, we conducted a second examination to evaluate the progression of vascular calcification. All patients were scanned in the supine position at a 5 mm slice thickness using a 64-slice non-contrast CT scan (Siemens Medical Solutions, Forchheim, Germany). Calcification was considered to be present if an area of ≥1 mm^2 displayed a density of ≥130 Hounsfield units. The AAC score was calculated from the site where the renal artery arises to the bifurcation of the aorta into common iliac arteries. The cross-section of the abdominal aorta on each slice was radially divided into 12 sectors. ACI was calculated as follows: ACI = (total score of calcification on all slices)/12 × 1/(number of slices) × 100% [10,11]. The ΔACI/year was calculated to assess annual changes in ACI, as follows: ΔACI/year = (second ACI − first ACI)/duration between the two evaluations (years). Semi-quantitative measurement of AAC was independently conducted by two physicians who were blinded to the patient's clinical characteristics. The cutoff point for rapid ACI progression was defined as ΔACI/year 3.0%, which was the 75th percentile for the ΔACI/year in this study population.

2.3. Baseline laboratory data

After an overnight fast of 12 h, blood samples were collected from all patients. eGFR was calculated using the equation for Japanese subjects recommended by the Japanese Society of Nephrology, as follows: eGFR (mL/min/1.73 m^2) = 194 × SCr − 1.094 × age − 0.287 (×0.739, if female) [12]. eGFRs were classified according to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative guidelines (eGFR ≥ 90, 60–89, 45–59, 30–44, 15–29, and <15 mL/min/1.73 m^2 for stages G1, G2, G3a, G3b, G4, and G5, respectively) [13]. Urinary protein excretion was determined as the urinary protein (mg) to creatinine (g) ratio in the morning spot urine. The protein-to-creatinine ratio was classified into three categories (<0.15, 0.15–0.5, and >0.5 g/gCr: A1, A2, and A3, respectively). Serum calcium levels were corrected for albumin using the following formula: corrected calcium = total calcium + (4.0 − albumin) × 0.8, if albumin was <4.0 g/dL. Hypertension was defined as systolic blood pressure (BP) of ≥140 mmHg, diastolic BP of ≥90 mmHg, and/or receiving treatment for hypertension. According to the 2009 guidelines of the Japan Society of Hypertension, BP was measured using a mercury sphygmomanometer. At each visit, two consecutive measurements were performed with a 1 min interval after 5 min of rest in the sitting position, and the average of the two values was adopted as the final BP [14]. Diabetes mellitus (DM) was defined as the use of any anti-hyperglycemic medication, a current diagnosis of diabetes, a fasting plasma glucose concentration of >126 mg/dL, and/or a glycosylated hemoglobin concentration of ≥6.5%, according to the guidelines of the National Glycohemoglobin Standardization Program. Current smokers were defined as those who declared themselves to be active smokers during the examinations.

2.4. Statistical analyses

Continuous variables are expressed as the mean ± standard deviation or median (interquartile range) if non-normally distributed, while categorical variables are expressed as percentages. One-way ANOVA was used to statistically analyze normally distributed data (continuous variables), while the Kruskal–Wallis test was used for data with non-normal distribution. The Chi-square or Fisher's exact test was used to statistically analyze categorical data. The association between ΔACI/year and each clinical parameter was determined using the Spearman's correlation coefficient. To obtain an independent predictor for AAC progression, multivariate stepwise regression analysis was performed for each parameter as a dependent variable. A two-sided p value of <0.05 was considered statistically significant. All statistical analyses were performed using the SPSS software, version 18.0 for Windows (IBM-SPSS, Inc., Chicago, IL, USA).

3. Results

A total of 141 patients with a mean age of 69.5 ± 10.0 years, median eGFR of 40.3 mL/min/1.73 m^2 were recruited for this study. Among the subjects, 38.3% had DM and 86.5% had hypertension. Baseline clinical characteristics of study subjects with rapid and non-rapid ACI progression are shown in Table 1. There were significant differences in age, blood pressure, hemoglobin, serum albumin, serum creatinine, intact parathyroid hormone (PTH), C-reactive protein (CRP) levels, and in the prevalence of hypertension between the 2 groups. However, other variables, such as lipid profiles, and prevalence of habitual smoking were comparable among the 2 groups. Moreover, Supplementary Table 1 shows the clinical characteristics among the eGFR grades.

Representative CTs of cases with or without rapid ACI progression between the first and second examinations are shown in Fig. 1. The inter- and intra-observer variabilities of ACI were well correlated ($r = 0.97$, $p < 0.001$ and $r = 0.96$, $p < 0.001$, respectively). Overall, the median first ACI value was 16.7%. With respect to eGFRs, baseline ACI values tended to increase with CKD progression (13.5%, 13.2%, and 25.4% for stages G1-2, G3, and G4-5, respectively; p for trend = 0.27).

The mean interval period between the first and second examinations was 3.7 years, and the median ΔACI/year value was 1.08%. As shown in Fig. 2, the median ΔACI/year values significantly increased with the CKD stage (0.73%, 0.87%, and 2.24% per year for CKD stages G1-2, G3, and G4-5, respectively; $p = 0.041$). The results of univariate linear regression analyses for ΔACI/year for each CKD category are shown in Table 2. Overall, pulse BP levels, eGFR levels, intact PTH levels (log-transformed), and CRP levels (log-transformed) were positively correlated with ΔACI/year ($r = 0.213$, $p = 0.011$; $r = -0.171$, $p = 0.043$; $r = 0.194$, $p = 0.021$; and $r = 0.188$, $p = 0.025$, respectively).

The results of multivariate stepwise analysis after adjusting for