Heart Vessels
DOI 10.1007/s00380-015-0712-y

ORIGINAL ARTICLE

Relationship between abdominal aortic and coronary artery calcification as detected by computed tomography in chronic kidney disease patients

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Received: 5 March 2015 / Accepted: 3 July 2015

Abstract The purpose of this study was to investigate the relationship between abdominal aortic calcification (AAC) and coronary artery calcification (CAC) in chronic kidney disease (CKD) patients. We evaluated 126 asymptomatic CKD patients (mean estimated glomerular filtration rate: 36.1 ± 14.1 mL/min/1.73 m^2, mean age 70.3 ± 10.1 years). A non-contrast computed tomography scan was used to determine the abdominal aortic calcification index (ACI) and CAC score, and this relationship was investigated. Among the subjects, AAC was present in 109 patients (86.5 %) as defined by ACI >0 and median ACI was 11.7 %. ACI increased in accordance with advances in CAC score grades (3.0, 5.2, 17.2, and 32.8 % for CAC score 0, 1–100, 101–400, and 401 or more, respectively, $p < 0.001$). Even after multivariate adjustment, ACI was independently associated with severe CAC score as defined by CAC score >400 [odds ratio 1.08, 95 % confidence interval (CI) 1.04–1.12, $p < 0.001$]. Receiver-operating curve analysis showed that the ACI optimal cut-off value predicting severe CAC score was 16.5 % (area under the curve = 0.79, 95 % CI 0.69–0.90, $p < 0.001$). The C statics for predicting CAC score was significantly increased by adding ACI values to the model including other risk factors (0.853 versus 0.737, $p = 0.023$). In conclusion, the ACI value of 16.5 % allows us to predict the presence of severe CAC in CKD patients, and that the addition of ACI to the model with traditional risk factors significantly improves the predictive ability of severe CAC score. These data reinforce the utility of ACI as a screening tool in clinical practice.

Keywords Abdominal aortic calcification index · Non-contrast CT scan · Chronic kidney disease · Coronary artery calcification

Introduction

Cardiovascular disease (CVD) is the leading cause of mortality and morbidity in patients with chronic kidney disease (CKD) [1, 2]. Moreover, these patients frequently experience cardiovascular (CV) events associated with accelerated atherosclerosis and vascular calcification before the initiation of hemodialysis [3–5]. Thus, risk stratification for CVD mortality is clinically important for improving survival in these patients. It is well known that one of the main factors for the heightened CV risk in this population, besides advanced age and a high proportion of diabetes and hypertension, is the presence of mineral bone disorders (MBD), indicated by abnormal levels of serum calcium, phosphorus and parathyroid hormone (PTH).

Non-contrast cardiac computed tomography (CT) scan for the assessment of coronary artery calcification (CAC) is highly sensitive for the detection of coronary artery disease as well as predictive of future CV events beyond traditional CV risk factors [6–9]. Abdominal aortic calcification (AAC) is common in CKD and its presence is also associated with increased risk of CV events in hemodialysis, peritoneal dialysis, and pre-dialysis CKD patients [10–12]. However, few studies have examined the association of

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Published online: 12 July 2015

CAC and AAC. The aim of the study was to evaluate the prevalence and the predictive value of AAC for the presence of severe CAC score in CKD patients.

Materials and methods

Subjects

We evaluated 126 asymptomatic CKD patients newly referred to the outpatient clinic at the Department of Nephrology of the Nagoya University Hospital from November 2009 to October 2011. To investigate the prevalence and degree of subclinical atherosclerosis in individuals, CAC and AAC were quantified by non-contrast CT scan and these relationships were investigated. Patient exclusion criteria were hemodialysis, prior history of percutaneous coronary intervention, and had undergone previous abdominal aortic artery repair or stenting. This study was approved by the local ethics committee and was conducted in accordance with the ethical principles stated by the Declaration of Helsinki (1975). Written informed consent was obtained from all patients.

Hypertension was defined as systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, or current antihypertensive medication use. According to the Japan Society of Hypertension 2009 guidelines, we measured clinic BP with a mercury sphygmomanometer. At each clinic visit, two consecutive values were performed with a 1-min interval after 5 min of rest in a sitting position; the average of the two values was adopted as the clinic BP [13]. Diabetes mellitus was defined as the use of any anti-hyperglycemic medication, a current diagnosis of diabetes, or having a fasting plasma glucose concentration of >126 mg/dL or a glycosylated hemoglobin concentration of >6.5 % (National Glycohemoglobin Standardization Program). Dyslipidemia was defined as serum low-density lipoprotein cholesterol concentration of >100 mg/dL, serum high-density lipoprotein cholesterol concentration of <40 mg/dL, and serum triglyceride concentration of >150 mg/dL. Current smokers were defined as those who declared active smoking. Past smokers were defined as those who declared not smoking in the past year. Never-smokers were defined as those who had never smoked before or during the study. Pack-years were calculated as the number of packs of cigarettes smoked per day multiplied by the number of years for which the patient had smoked.

Laboratory analysis

Blood samples were obtained from all patients after a 12-h overnight fast. The measurement of serum creatinine was performed every 3 months to obtain the estimated glomerular filtration rate (eGFR), and was measured using the isotope dilution mass spectrometry traceable enzymatic method, eGFR was calculated according to a new equation developed in Japan: eGFR (mL/min/1.73 m^2) = 194 × serum creatinine − 1.094 × age − 0.287 × 0.739 (in females) [14]. The eGFR levels were classified into four categories (eGFR 45–59, 30–44, 15–29, and <15 mL/min/1.73 m^2: G3a, G3b, G4, and G5, respectively) according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines [15]. Serum calcium levels were corrected for albumin using the following formula: corrected calcium = total calcium + (4.0 − albumin) × 0.8, if albumin <4.0 g/dL. Intact-PTH levels were measured by electrochemiluminescence immunoassay (Roche Diagnostics, Tokyo, Japan).

Abdominal CT

Patients were scanned in the supine position in the craniocaudal direction, using a 64-slice non-contrast CT scan (Siemens Medical Solutions, Forchheim, Germany), in which images were obtained with a 5-mm single slice thickness. Calcification was considered to be present if an area of ≥1 mm^2 displayed a density of ≥130 Hounsfield units. AAC score was calculated from the takeoff of the renal artery to the bifurcation of the aorta into the common iliac arteries. The cross section of the abdominal aorta on each slice was divided radially into 12 segments. The abdominal aortic calcification index (ACI) was calculated as follows: ACI = (total score for calcification in all slices)/12 × 1/(number of slices) × 100 (%) (Fig. 1) [16, 17]. Semi-quantitative measurement of AAC was conducted independently by two physicians who were blinded to the patient's clinical characteristics.

Multidetector coronary CT

Patients underwent CAC quantification using a multislice CT scanner (Siemens Medical Solutions, Forchheim, Germany) with a gantry rotation of 0.4 s, collimation of 2.5 mm (slice thickness), and reconstruction time of six frames/s. A calcium threshold of 130 or more Hounsfield units was used. The images were scored by a single radiologist blinded to the clinical and biochemical aspects of the patient. As described by Agatston et al. [18], the calcium score was determined by multiplying the area of each calcified lesion by a weighting factor corresponding to the peak pixel intensity for each lesion. The sum of each lesion of all coronary arteries was used for analysis. The CAC scores were classified into the following groups: 0, 1–100, 101–400, and 401 or more. Severe CAC was defined as CAC score >400 [19].

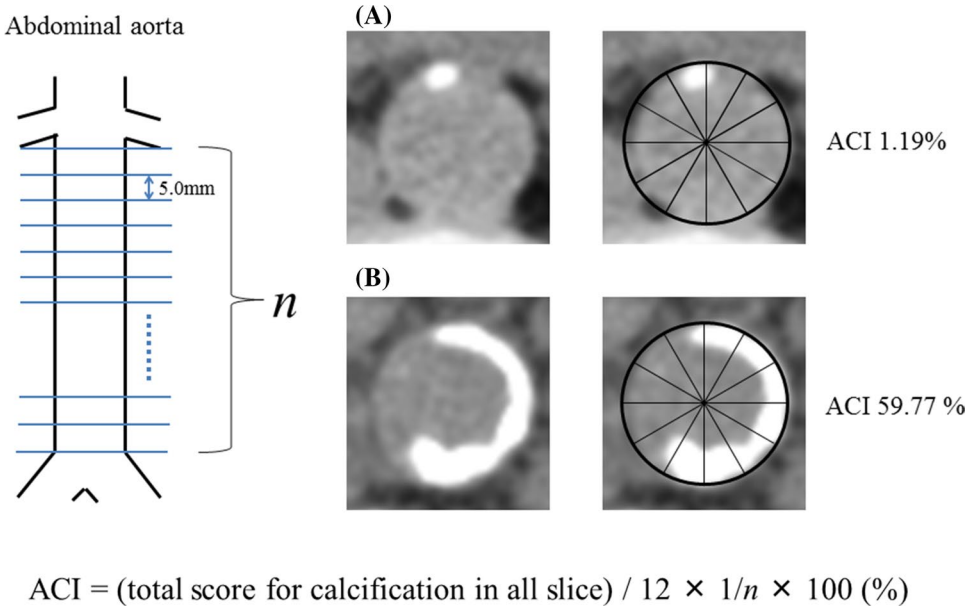

Fig. 1 Evaluation of abdominal aortic calcification index (ACI) on non-contrast computed tomography (CT) scan, and the representative CT images of ACI were presented. The percentage of ACI was 1.19 % in mild ACI patient (**a**), and the percentage of ACI was 59.77 % in severe ACI patient (**b**), respectively

$$\text{ACI} = (\text{total score for calcification in all slice}) / 12 \times 1/n \times 100\ (\%)$$

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) or median (interquartile range) if they were non-normally distributed. Categorical variables were expressed as percentages. Student's *t* test was used to statistically analyze normally distributed data (continuous variables), and the Chi-squared test or Fisher's exact test were used to statistically analyze categorical data. The relationship between ACI and CAC score was determined with Pearson's correlation. To identify independent predictors of severe CAC, multivariate logistic regression analysis, which included variables with $p < 0.10$, was performed for each parameter used as the dependent variable. The cut-off value of ACI was determined by a receiver-operating curve to maximize the power of ACI in predicting the presence of severe CAC. To compare the predictive value of severe CAC score between the models adjusted for established risk factors (age, sex, smoking index, systolic blood pressure, diabetes, and eGFR) with and without ACI, we performed the C statics model. The statistical significance of differences was compared using the methods of DeLong et al. [20]. A two-sided p value of <0.05 was considered to indicate statistical significance. SPSS version 18.0 for Windows (SPSS, Inc., Chicago, IL, USA) was used to perform all statistical analyses.

Results

A total of 126 patients were enrolled in the present study. The mean age was 70.3 ± 10.1 years, 72.2 % of the subjects were males, 42.0 % had diabetes and 84.1 % had hypertension. The mean eGFR level was 36.1 ± 14.1 mL/min/1.73 m^2, and the proportion of patients according to eGFR levels: 31.0, 35.7, 25.4, and 7.9 % for the eGFR categories G3a, G3b, G4, and G5, respectively). Among the subjects, AAC was present in 109 patients (86.5 %), as defined by ACI >0, and the median ACI was 11.7 %. The median CAC score was 59.1, and the proportion of patients according to CAC score grades: 23.8, 34.9, 21.5, and 19.8 % for CAC score 0, 1–100, 101–400, and 401 or more, respectively).

Table 1 shows the baseline clinical characteristics of the study patients divided into three groups, in accordance with tertiles of ACI. With increasing tertiles of ACI, age and habitual smoking were significantly higher. Systolic blood pressure level and prevalence of hypertension tended to be higher with increasing tertiles of ACI. However, other variables, such as body mass index, eGFR levels, and prevalence of diabetes mellitus, were comparable among the three groups. ACI showed a significant positive correlation with CAC score in this study population ($r = 0.516$, $p < 0.001$) (Fig. 2a). As shown in Fig. 2b, ACI increased in accordance with advances in the CAC score grades (3.0, 5.2, 17.2, and 32.8 % for CAC score 0, 1 to 100, 101 to 400, and 401 or more, respectively, $p < 0.001$). Even after multivariate adjustment, ACI was independently associated with severe CAC score (odds ratio 1.08, 95 % CI 1.04–1.12, $p < 0.001$). In addition, presence of diabetes mellitus and body mass index were independently associated with severe CAC score (Table 2). Receiver-operating characteristic curve analysis showed that the ACI optimal cut-off value predicting severe CAC score was 16.5 % (area under the

Table 1 Baseline patient characteristics stratified by tertile of abdominal aortic calcification index

	Tertile 1 (0–3.70) $n = 42$	Tertile 2 (3.95–21.93) $n = 42$	Tertile 3 (23.25–76.56) $n = 42$	p
Male gender, *n* (%)	30 (71 %)	31 (74 %)	30 (71 %)	0.96
Age, years	66.0 ± 10.7	70.3 ± 8.7	74.8 ± 8.8	<0.001
Body mass index, kg/m^2	23.7 ± 4.2	23.0 ± 3.0	23.3 ± 3.3	0.70
Hypertension, *n* (%)	31 (71 %)	36 (86 %)	39 (93 %)	0.067
Duration of hypertension, years	11.3 ± 7.3	12.9 ± 9.1	16.0 ± 13.7	0.41
Diabetes (type 2), *n* (%)	16 (38 %)	16 (38 %)	21 (50 %)	0.49
Duration of diabetes, years	13.2 ± 9.6	13.7 ± 9.0	13.5 ± 5.8	0.99
Dyslipidemia, *n* (%)	24 (57 %)	30 (71 %)	29 (69 %)	0.36
Smoking status				0.007
Never, *n* (%)	29 (69 %)	21 (50 %)	13 (31 %)	
Past, *n* (%)	12 (29 %)	19 (45 %)	22 (52 %)	
Current, *n* (%)	1 (2 %)	2 (5 %)	7 (17 %)	
Pack-year history	0 (0–7)	1 (0–44)	25 (0–43)	<0.001
Systolic blood pressure, mmHg	132.3 ± 15.3	135.4 ± 20.6	141.3 ± 21.1	0.091
Diastolic blood pressure, mmHg	81.7 ± 9.6	80.8 ± 10.7	79.7 ± 11.0	0.68
eGFR (mL/min/1.73 m^2)	37.8 ± 14.2	36.9 ± 14.9	33.6 ± 13.3	0.35
Chronic kidney disease etiology				
Hypertension, *n* (%)	20 (48 %)	23 (55 %)	27 (64 %)	0.10
Diabetes, *n* (%)	9 (21 %)	9 (21 %)	12 (29 %)	
Others, *n* (%)	13 (31 %)	10 (24 %)	3 (7 %)	
Hemoglobin, g/dL	12.6 ± 2.0	12.5 ± 2.0	12.0 ± 1.8	0.25
Serum albumin, g/dL	3.9 ± 0.6	3.9 ± 0.5	3.9 ± 0.4	0.90
LDL-C, mg/dL	107.5 ± 33.2	100.7 ± 30.9	104.1 ± 33.3	0.63
HDL-C, mg/dL	50.4 ± 14.5	47.0 ± 15.7	49.9 ± 16.9	0.57
Triglycerides, mg/dL	169.9 ± 142.5	145.5 ± 74.0	146.4 ± 85.6	0.60
Hemoglobin A1c, %	6.1 ± 1.4	5.8 ± 0.8	5.8 ± 0.6	0.40
Serum corrected calcium, mg/dL	9.3 ± 0.4	9.2 ± 0.5	9.4 ± 0.5	0.28
Serum phosphorus, mg/dL	3.5 ± 0.6	3.5 ± 0.8	3.5 ± 0.5	0.79
Calcium × phosphorus product, mg^2/dL^2	32.9 ± 5.2	32.0 ± 7.3	33.5 ± 4.9	0.51
Serum intact PTH, pg/mL	65.2 ± 45.6	83.3 ± 63.8	77.9 ± 55.9	0.30
Coronary artery calcification score	6.5 (0–81.1)	41.0 (1.4–175.1)	338.6 (128.7–897.5)	<0.001
Medications				
ACE-I or ARB, *n* (%)	27 (64 %)	31 (74 %)	31 (74 %)	0.57
Ca channel blocker, *n* (%)	21 (50 %)	25 (60 %)	31 (74 %)	0.085
Beta-blocker, *n* (%)	1 (2 %)	7 (17 %)	11 (26 %)	0.009
Statins, *n* (%)	13 (31 %)	23 (55 %)	23 (55 %)	0.043
Vitamin D (Active form), *n* (%)	3 (7 %)	1 (2 %)	3 (7 %)	0.70
Calcium carbonate, *n* (%)	0 (0 %)	3 (7 %)	1 (2 %)	0.32
Warfarin, *n* (%)	3 (7 %)	3 (7 %)	3 (7 %)	1.00

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

eGFR estimated glomerular filtration rate, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *PTH* parathyroid hormone, *ACE-I* angiotensin-converting enzyme inhibitors, *ARB* angiotension receptor blocker

curve = 0.79, 95 % CI 0.69–0.90, $p < 0.001$, sensitivity 0.88, specificity 0.71). The C statics for predicting CAC score was significantly increased by adding ACI values to the model including other risk factors (0.853 versus 0.737, $p = 0.023$). The correlation of ACI measured by two physicians who conducted non-contrast CT scan measurements independently was $r = 0.990$ ($p < 0.001$) (Fig. 3).

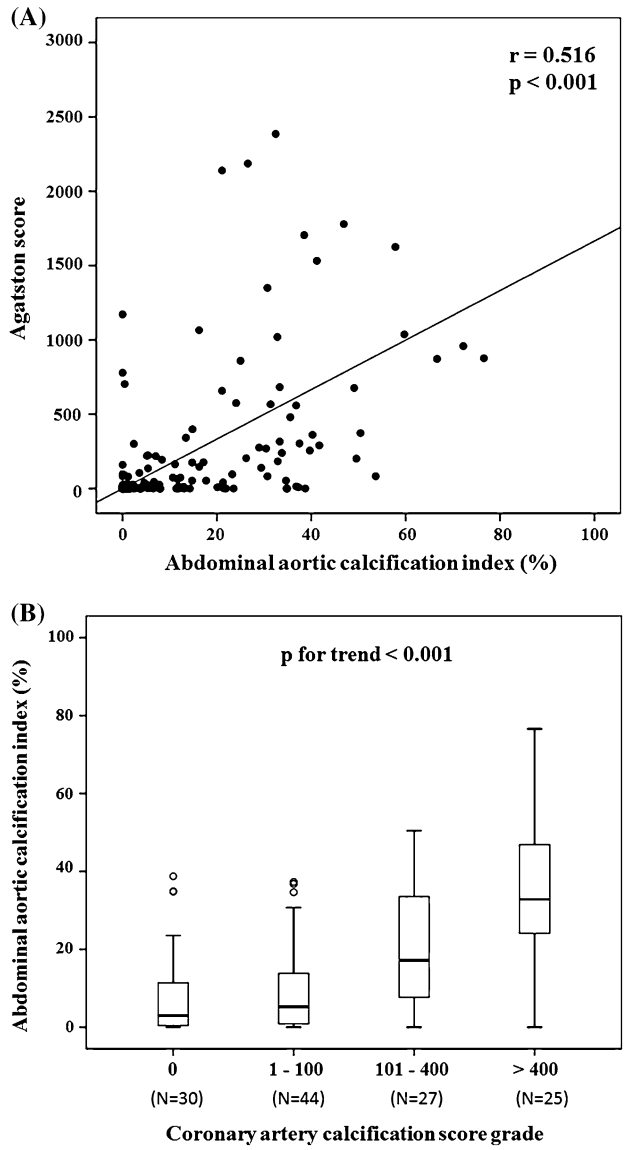

Fig. 2 Association between abdominal aortic calcification index (ACI) and coronary artery calcification (CAC) score. **a** ACI showed a significant positive correlation with CAC score in this study population ($r = 0.516$, $p < 0.001$). **b** ACI increased in accordance with advances in the CAC score grades (3.0, 5.2, 17.2, and 32.8 % for CAC score 0, 1–100, 101–400, and 401 or more, respectively, p for trend <0.001)

Discussion

The present study found that ACI is strongly associated with CAC score in CKD patients. Furthermore, a value of ACI of 16.5 % allowed us to predict the presence of severe CAC in these patients.

It is widely accepted that AAC is common in CKD and its presence is also associated with increased risk of CV events in hemodialysis, peritoneal dialysis, and pre-dialysis patients [10–12]. Thus, the Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommended the evaluation of AAC in patients with CKD stages 3–5 [21]. The presence of AAC (ACI >0) in our subjects was 87 %, consistent with the rate of 90 % reported in pre-dialysis CKD patients [22], and far exceeding the rates of 33–70 % found in the general elderly population [23, 24]. Furthermore, AAC was present in 82 % of the patients with G3 categories (eGFR 45–59 mL/min/1.73 m^2) in the present study; it is considered that AAC was already present at an earlier CKD stage. These results suggest that assessments of AAC are needed to identify patients with more advancement of atherosclerosis and to initiate appropriate preventive measures earlier.

In previous studies analyzing calcification of the coronary arteries, an Agatston score of >400 has been considered as severe and to predict worse CV outcomes independently of other CV risk factors [19]. However, there has not been any study aimed at establishing the optimal cutoff value of AAC that would predict CV mortality. In the present study, we showed a strong relationship between ACI and CAC score, where the optimal cutoff value of ACI for the prediction of severe coronary calcification was 16.5 %. From the viewpoint of risk stratification in CKD patients, assessment of AAC might be of considerable significance.

Recently, the severity of vascular calcification has been thought to be associated not only with the imbalance of calcium, phosphorus, and PTH but also with abnormalities of various calcium-regulatory factors in pre-dialysis CKD patients [25]. For example, it has been reported that fibroblast growth factor 23 (FGF23), which is elevated during the early stages of CKD, and serum Klotho, which is decreased in patients with CKD, are both associated with vascular calcification [26, 27]. Several epidemiologic studies have reported a significant positive relationship between higher FGF23 levels and the risk of developing CVD [28, 29]. In addition, recent studies have found that low serum Klotho concentrations were associated with the presence and severity of CVD independently of established CV risk factors [30–32]. In the present study, both serum calcium and phosphorus levels were not independent risk factors for severe CAC, although the serum intact-PTH level showed tendencies for associations in univariate analysis. Unfortunately, because we did not have the opportunity to measure biomarkers such as FGF23 and Klotho, which are related to vascular calcification in earlier CKD stages, the association between the severity of the vascular calcification and these biomarkers could not be determined in the present study. Further investigation is, therefore, needed.

There are some limitations to the present study. First, it was an observational analysis conducted in a single center and included a relatively small sample. Second, the

Table 2 Multiple logistic regression analysis for prediction of severe coronary artery calcification

Variables	Simple regression			Multiple regression		
	OR	95 % CI	*p*	OR	95 % CI	*p*
Male gender	0.62	0.24–1.56	0.31			
Age, years	1.05	1.00–1.10	0.049	1.01	0.95–1.08	0.67
Systolic blood pressure, mmHg	1.02	1.00–1.05	0.034	1.01	0.98–1.04	0.56
Diabetes	2.49	1.02–6.09	0.046	4.36	1.13–16.9	0.033
Body mass index, kg/m^2	0.86	0.74–0.99	0.034	0.82	0.67–0.99	0.037
Smoking index	0.99	0.98–1.02	0.83			
HDL-C, mg/dL	1.01	0.99–1.03	0.44			
LDL-C, mg/dL	1.00	0.99–1.01	0.84			
eGFR, mLl/min/1.73 m^2	0.99	0.97–1.03	0.85			
Hemoglobin, g/dL	0.86	0.68–1.08	0.19	1.08	0.75–1.55	0.69
Serum corrected calcium, mg/dL	0.78	0.29–2.08	0.62			
Serum phosphorus, mg/dL	1.19	0.94–2.37	0.63			
Calcium × phosphorus product, mg^2/dL^2	1.02	0.94–1.09	0.69			
Calcium carbonate use	1.36	0.14–13.7	0.79			
Intact-PTH > 65 pg/mL	1.99	0.79–4.99	0.14	0.68	0.17–2.70	0.58
Abdominal aortic calcification index, %	1.07	1.04–1.11	<0.001	1.08	1.04–1.12	<0.001

Multivariate model includes all variables at baseline with $p < 0.20$ by univariate analysis

HDL-C high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *eGFR* estimated glomerular filtration rate, *PTH* parathyroid hormone

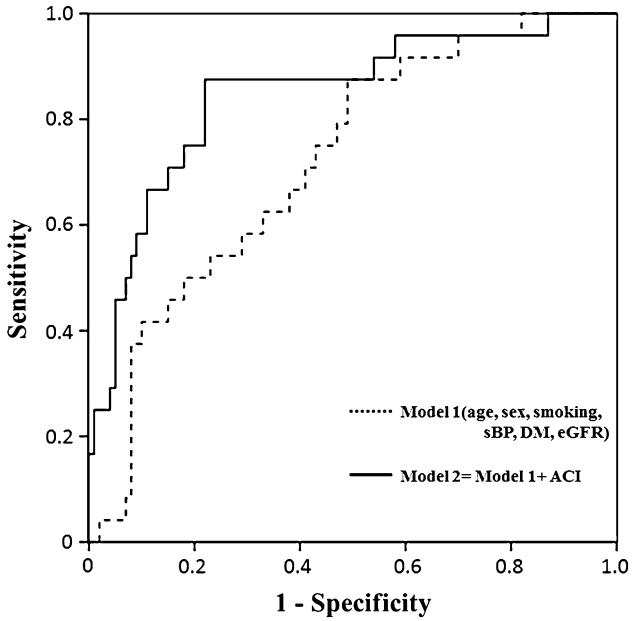

Fig. 3 The C index for predicting the severe coronary artery calcification (CAC) score was higher in a baseline model (age, sex, smoking index, systolic blood pressure, diabetes, and estimated glomerular filtration rate) with abdominal aortic calcification index (ACI) than in a baseline model alone (0.853 versus 0.737, $p = 0.023$)

evaluation using multi-slice CT did not allow the assessment of early-stage, minute calcification. Also, this method did not allow the distinction between intimal and medial vascular calcification. Third, we did not compare the semi-quantitative methods using non-contrast CT scan with the previous qualitative methods, such as plain X-ray films. As for the diagnostic accuracy, CT scan is better than X-ray films. However, we must also consider the radiation exposure and cost. Fourth, other possible factors that may be associated with vascular calcification in CKD patients, for example serum FGF23 and Klotho, were not measured in the present study. Finally, since we had conducted only medical records survey, we could not obtain complete information on the duration of diabetes mellitus and hypertension. Such study limitations need to be carefully considered.

In conclusion, severe AAC is strongly associated with severe CAC in CKD patients. The evaluation of AAC by semi-quantitative methods using non-contrast CT scan is simple and non-invasive, and the ACI can be of value in the risk stratification of patients with CKD. The ACI value of 16.5 % allows us to predict the presence of severe CAC in these patients, and that the addition of ACI to the model with traditional risk factors significantly improves the predictive ability of severe CAC score. These data reinforce the utility of ACI as a useful screening tool in clinical practice.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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