Abdominal aortic calcification is associated with morbidity of cardiovascular disease and Fib-4 index in type 2 diabetes: a retrospective cross-sectional study

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Abstract

Background: Little is known about the association between abdominal aortic calcification (AAC) and the risk of cardiovascular disease (CVD) among patients with diabetes. This study evaluated the cross-sectional association between AAC and CVD morbidity in patients with type 2 diabetes.

Methods: This retrospective cross-sectional study enrolled 285 inpatients with type 2 diabetes. The lateral view of an abdominal X-ray image obtained while each subject was in a standing position was examined, and the AAC score and AAC length, corresponding to the area of calcific deposits in the anterior and posterior aortic wall for the L1-4 and L1-5 regions, respectively, were measured. The associations between the AAC scores and lengths and the presence of coronary artery disease (CAD), cerebral infarction (CI), and peripheral artery disease (PAD) were then assessed. The correlation between the AAC grades and other clinical factors were also evaluated.

Results: The degree of AAC was significantly correlated with a higher prevalence of CAD and CI but not PAD after adjustments for cardiovascular risk factors. The AAC score was inversely correlated with BMI, and both the AAC score and the AAC length were correlated with the Fib-4 index; these correlations persisted after adjustments for cardiovascular risk factors and BMI, although AAC was not associated with ultrasonography-diagnosed fatty liver.

Conclusion: AAC is associated with CAD and CI morbidity in patients with type 2 diabetes. AAC grading also predicts the Fib-4 index, a hepatic fibrosis marker, suggesting a novel potential predictor of liver disease that is independent of cardiovascular risk factors and obesity.

Background

Type 2 diabetes accelerates atherosclerosis and increases cardiovascular disease (CVD) morbidity including coronary artery disease (CAD), cerebral infarction (CI), and peripheral artery disease (PAD) [1-3]. The clinical assessment of cardiovascular risk in individual patients with type 2 diabetes is required for proper management. However, little is known about the significance of each clinical indicator in estimating disease progression.

Abdominal aortic calcification (AAC) is a known marker of systemic atherosclerosis burden. AAC can be evaluated non-invasively using X-ray imaging or computed tomography scanning. The grade of AAC has been shown to be an independent predictor of CVD mortality and mobility in previous reports [4-6]. The presence or extent of AAC is also reportedly associated with diabetes [7, 8]. Independent associations of advanced AAC with higher prevalences of PAD, CAD, and all combined cardiovascular diseases have also been demonstrated in patients with type 2 diabetes [9]. On the other hand, the risk of AAC is reportedly lower among Hispanic and African Americans, but not among Chinese-Americans, compared with the risk in Caucasians [10]. These ethnic differences in the significance of AAC cannot be explained by differences in classical CVD risk factors [10]. The prevalence of coronary calcification also reportedly

differs between Caucasians and Chinese, despite similar prevalences of AAC in these two ethnic groups [11].

Multiple studies have suggested that smoking, hypertension, dyslipidemia, and obesity are possible causes of the development of AAC [12]. Several cross-sectional studies and a prospective cohort trial involving patients with diabetes have shown a positive correlation between smoking and AAC [2, 13-17]. The associations between AAC and hypertension, systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure have all been investigated. Of these measures, hypertension over 140/90 mmHg was significantly correlated with AAC in numerous trials including those examining diabetes patients [14-17]. Whether SBP and pulse pressure are correlated with AAC remains controversial, while DBP is not correlated with AAC. As for lipid composition, AAC was positively correlated with non-HDL-C, TC, and the TC/HDL-C ratio and negatively correlated with HDL-C in studies that did not include patients with type 2 diabetes [17, 18]. However, one study involving patients with type 2 diabetes did not show a correlation between lipid profiles and AAC [2]. Thus, whether dyslipidemia is a risk factor in the progress of AAC in patients with type 2 diabetes remains controversial. Obesity has also been shown to be associated with AAC. Visceral fat, % trunk mass, and visceral fat mass measured using dual-energy X-ray absorptiometry (DXA) were reportedly correlated with AAC in a positive manner in women [19], though many reports have failed to show a correlation between BMI and AAC [2, 14-16, 20, 21]. However, few studies have investigated the clinical significance of AAC in patients with type 2 diabetes.

In the present study, we investigated the association between AAC and CVD and explored factors related to AAC progression in Japanese patients with type 2 diabetes.

Research Design And Methods

Study design and patients

This study was a retrospective cross-sectional study (ISRCTN 13124221). The primary outcome was to clarify the nature of the relationship between the grade of AAC and the presence of cardiovascular disease, such as CAD, CI, and PAD. The secondary outcome was to determine which factors are related to AAC in Japanese patients with type 2 diabetes. The subjects included Japanese type 2 diabetes patients who had been hospitalized at Yokohama City University Hospital between January 1, 2016, and March 31, 2018. All patients aged 20 years or older who had undergone a standing lateral abdominal radiography examination between 2 months before and 2 months after admission were eligible for inclusion in this study. We excluded patients with severe hepatic disorders, psychiatric disorders, cancers, severe ketosis, diabetic coma or precoma, severe infections, severe traumatic injuries, pancreatic exocrine diseases, hepatic cirrhosis, endocrine diseases, and postoperative patients.

Evaluation criteria

Information on the history of CAD and CI, the duration of diabetes, and the history of smoking, alcohol drinking, and anti-diabetic agents were collected from interviews at the time of hospital admission. All the subjects underwent physical examinations at admission. They also had blood drawn while in a fasted state (8:00 AM) to assess their general health and cardiovascular risk factors and at 2 hours after breakfast (10:30 AM) to assess their postprandial plasma glucose and plasma c-peptide reaction (CPR) levels. The corrected Ca level was calculated as Ca + (4 - albumin) in patients with hypoalbuminemia. The standard blood glucose deviations were calculated using values measured with a glucometer at 8:00, 10:30, 12:00, 14:30, 18:00 and 20:30 on the second hospital day. The urinary albumin excretion rate (AER) was measured using 24-h urine samples. Peripheral neuropathy was defined based on two symptoms: a diminished deep tendon reflex, and a loss of vibration sense or nerve conduction velocity. PAD was defined as an ABI of <0.9. Autonomic neuropathy was defined by a reduction in the coefficient of variation of R-R interval (CVRR) in the electrocardiogram below the reference values for each age. Fatty liver was diagnosed using ultrasonography, if the examination had been performed within 6 months before or after admission.

Quantification of abdominal aortic calcification

AAC was evaluated using two methods, AAC score and AAC length, based on the results of standing lateral abdominal radiography examinations performed between 2 months before and 2 months after hospital admission. The AAC score is a validated grading system [22] in which the extent of calcific deposits per vertebral segments L1-4 are graded on a scale of 0 to 3 for both the anterior and posterior wall of the aorta. The sum of these eight scores results in the AAC score, ranging from 0 to 24 points. The AAC length is the total length of calcific deposits along the anterior and posterior aortic wall in the segments between L1 and L5. In this study, we corrected the value using the ratio to the total spine length of L1-5 (approximated by the continuous distance connecting the upper end of L1, the midpoint between L3 and L4, the midpoint between L4 and L5, and the lower end of L5). The scoring and measurement of abdominal aortic calcification were performed by an observer who did not know the patients' background data.

Statistical methods

The results were expressed as the mean ± SD or the medians and the 25th to 75th percentiles. Statistical significance was analyzed using the Spearman correlation coefficient for correlations between parameters and the Mann-Whitney U-test for comparisons between two groups. A multiple regression linear analysis was performed to evaluate the independent associations of the AAC levels with the presence of CAD, CI, and PAD and to identify independent determinants of the extent of AAC. Correlations, β-values and differences between two groups were considered significant if the p value was <0.05. Data processing and the statistical analysis were performed using SPSS 16.0 software.

Results

The background characteristics of the subjects are shown in Table 1. We compared the AAC score and the AAC length between groups with and those without a history of CAD, CI, or PAD. Representative images of the AAC scores and AAC lengths are shown in Fig. 1 (see details in Research design and methods). The AAC scores and the AAC lengths in the group with CAD and the group with CI were significantly higher than those in the corresponding groups without these diseases (Fig. 2). The AAC score and the AAC length in the group with PAD were higher than those in the group without PAD, but the difference in AAC length did not reach statistical significance (Fig. 2). We evaluated whether the AAC score and the AAC length were independently associated with CAD, CI, and PAD using multiple regression linear analyses after adjustments for known arteriosclerotic risk factors (age, duration of diabetes, BMI, SBP, DBP, alcohol intake, smoking, HbA1c, 2-hour postprandial plasma glucose, eGFR, LDL-C, HDL-C, TG, hsCRP) (Table 2). Both the AAC score and the AAC length showed independent associations with both the CAD history and the CI history, while only the AAC length was independently associated with PAD.

Next, we investigated the association of AAC levels with various parameters (Table 3). The AAC score and the AAC length were positively correlated with age, duration of diabetes, Fib4-index, sCr, HDL-C, corrected Ca, baPWV, and peripheral neuropathy and were inversely correlated with BMI, DBP, HbA1c, 2-hour postprandial CPR, ALT, eGFR, LDL-C, and hsCRP. Negative correlations with fasting CPR, γ-GTP, and triglyceride were significant for the AAC score, while the trends did not reach significance for AAC length. Age, duration of diabetes, BMI, Fib4-index and baPWV showed relatively strong associations with the AAC score and the AAC length. Of note, known cardiovascular risk factors including BMI, DBP, LDL-C, HDL-C, and hsCRP were inversely correlated with AAC.

Next, we further analyzed the correlation between BMI and the AAC score or AAC length using a multiple linear regression analysis after adjustments for potential arteriosclerosis risk factors (age, duration of diabetes, BMI, SBP, DBP, alcohol intake, smoking, HbA1c, 2-hour postprandial plasma glucose, eGFR, LDL-C, HDL-C, TG and hsCRP). In the final model, postprandial CPR, corrected Ca, peripheral neuropathy, and the Fib4-index were entered as independent variables (Table 4). The significance of an association between a lower BMI and an increased AAC score was maintained, although that with the AAC length disappeared after adjustments for gender and age.

The Fib4-index was another notable factor associated with AAC levels, as shown in Table 3. We next investigated the further associations of the Fib4-index with the AAC score and the AAC length using multiple linear regression analyses after adjustments for age, duration of diabetes, BMI, SBP, DBP, alcohol intake, history of smoking, HbA1c, 2-hour postprandial plasma glucose, eGFR, LDL-C, HDL-C, TG, hsCRP, postprandial CPR, corrected Ca, and peripheral neuropathy (Table 5). The Fib4-index remained positively associated with both the AAC score and the AAC length in a significant manner. Type 2 diabetes patients frequently have non-alcoholic fatty liver disease (NAFLD), which includes non-progressive non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH) with progressive inflammation and liver fibrosis. The Fib-4 index is a scoring system used to predict liver fibrosis in patients with NAFLD. We next

extracted patients who had undergone an abdominal ultrasonography examination within 6 months before and after hospitalization and assessed the relationship between fatty liver and the AAC score and AAC length. The AAC score and the AAC length were not significantly different between patients with and those without fatty liver (Fig. 3A). An analysis of the AAC score and the AAC length for each Fib-4 index level (<1.3 predicts no fibrosis, >2.67 predicts fibrosis) in the group with and the group without fatty liver showed a more evident trend toward an increasing AAC score and AAC length in patients with a high Fib-4 index in the group without fatty liver (Fig. 3B). Similar trends were observed in an analysis using the Forns index, which is another liver fibrosis scoring system (Fig. 3C). A multiple regression analysis after adjustment for the presence or absence of fatty liver showed that the correlation of the Fib-4 index with the AAC score and the AAC length was independent of the presence of fatty liver (β=0.280, p=0.027, N=65).

Multiple linear regression analyses demonstrated that the correlations of HDL-C and hsCRP were diminished after adjustment for age and that the correlations of DBP, LDL-C, corrected Ca, and peripheral neuropathy were diminished after adjustments for age, gender, and duration of diabetes. The correlation of postprandial CPR remained significant after adjustments for these three variables and was diminished after additional adjustments for BMI (data not shown).

Discussion

The results of the present cross-sectional study demonstrated that the progression of AAC was correlated with the prevalences of CAD, CI, and PAD. The correlations of AAC with CAD and CI were independent of established cardiovascular risk factors, though the independency of the correlation between AAC and PAD was not shown. A previous cross-sectional study of subjects enrolled in the Veterans Affairs Diabetes Trial (VADT) showed a significant association between the AAC grade and not only the prevalences of CAD and CI, but also with the prevalence of PAD in a manner that was independent of lifestyle behavior and cardiovascular risk factors, even though the prevalence of PAD was less relevant to AAC than that of CAD [9]. The patient characteristics, including age, duration of diabetes, and HbA1c level, in the VADT were similar to those reported in the present study, while the prevalences of CAD and PAD in the VADT were 27% and 13%, respectively, which were higher than those in the present study (CAD, 16.7% and PAD, 6.3%) [9]. Therefore, the relatively small number of patients with PAD included in this study may be responsible for the failure to detect a significant association. Our primary outcome indicated that AAC could be a predictor of CAD and CI independent of standard cardiovascular risk factors in patients with type 2 diabetes.

In the linear regression analysis, BMI was negatively correlated with both the AAC score and the AAC length, and these correlations were the strongest next to age and diabetes duration. Although the correlations decreased after adjustments for gender and age, the correlation between the BMI and the AAC score remained significant after adjustments for standard cardiovascular risk factors. A decreasing postprandial CPR was correlated with an increasing AAC score and AAC length, and this correlation was diminished after adjustment for BMI. The decreasing postprandial CPR could reflect a decreasing residual

pancreatic beta cell function to secrete insulin in response to glucose. Metabolic syndrome is often characterized by obesity and hyperinsulinemia. The negative associations of AAC with BMI and postprandial CPR indicated that AAC was not uniquely caused by atherosclerosis arising from metabolic syndrome. Since insulin users accounted for 30% of the subjects in this study, further study is required to confirm the association between AAC and a reduction in insulin secretion.

In this study, an increasing Fib-4 index was correlated with the progression of AAC independent of cardiovascular risk factors. The Fib-4 index is a predictor of liver fibrosis. The AAC score and the AAC length were not altered by the presence of ultrasonography-diagnosed fatty liver, and these parameters were associated with the Fib-4 index independently of the presence of fatty liver. The ultrasonic findings of steatosis gradually disappear according to the progression of fibrosis in patients with NAFLD. Indeed, the AAC score and the AAC length tended to be elevated in a group of patients with a Fib-4 index >2.67 but without fatty liver, although the sample number was too small to assess the significance of this observation.

The prevalence of NAFLD as defined using CT or ultrasonography imaging is reportedly correlated with cardiovascular events independent of classical cardiovascular risk factors. An association between the histological diagnosis of NASH and cardiovascular events has also been reported [23], as well as an association between the histological stage of liver fibrosis and mortality from cardiovascular events [24]. Our results suggest that the Fib-4 index might be involved in the link between AAC and the risk of cardiovascular events.

The association between NAFLD and AAC may differ between ethnic groups. In a Multi-Ethnic Study of Atherosclerosis (MESA), NAFLD was significantly associated with the prevalence of AAC in African Americans but was not significantly associated with the prevalences in Caucasians, Asians, or Hispanics [25]. A cohort study of African Americans also showed that NAFLD was independently correlated with AAC [26]. No independent correlation was observed between NAFLD and AAC in a cohort study where the majority of subjects were Caucasians [27]. In the Coronary Artery Risk Development in Young Adults (CARDIA) study, which included 50% Caucasians and 50% African Americans, NAFLD was not independently correlated with AAC [28]. In this previous study, the association decreased after adjustments for obesity, suggesting that obesity may mediate the association between NAFLD and AAC [28]. Our results indicated that NASH, but not NAFLD, may be associated with AAC independently of the risk factors for cardiovascular disease in Japanese patients with type 2 diabetes. Notably, the correlation between the increase in the Fib4-index and the progress of AAC was not affected by adjustments for obesity. This observation is consistent with the finding that the association between the Fib4-index and AAC was independent of the presence of fatty liver. Because this study did not exclude participants with a history of excessive alcoholic consumption, NAFLD and alcoholic steatosis were not distinguished. To clarify the relationship between NAFLD, BMI and AAC in Japanese non-diabetic and type 2 diabetics, further research with sufficient sample numbers and the classification of NAFLD using imaging studies will be necessary.

The limitations of this study are its retrospective cross-sectional design and a possible selection bias, since patients who had not undergone a standing lateral abdominal radiography were not included. In addition, the study subjects were comprised of Japanese type 2 diabetic inpatients, who had relatively high HbA1c levels.

Conclusion

In summary, this study suggested that the extent of AAC is associated with CAD and CI independently of cardiovascular risk factors in Japanese patients with type 2 diabetes. AAC was associated with a lower BMI and postprandial CPR, suggesting a mechanism that differs from that based on insulin resistance caused by metabolic syndrome. Furthermore, AAC might be an independent predictor of liver fibrosis. To confirm this, further research involving liver biopsy or non-invasive diagnostic imaging of liver fibrosis is required.

Abbreviations

AAC: abdominal aortic calcification

AER: urinary albumin excretion rate

CAD: coronary artery disease

CI: cerebral infarction

CPR: c-peptide reaction

CVD: cardiovascular disease

CVRR: coefficient of variation of R-R interval

DBP: diastolic blood pressure

DXA: dual-energy X-ray absorptiometry

NAFL: non-alcoholic fatty liver

NAFLD: non-alcoholic fatty liver disease

NASH: non-alcoholic steatohepatitis

PAD: peripheral artery disease

SBP: systolic blood pressure

Declarations

Ethics approval and consent to participate

This study was approved by the Clinical Ethics Committee of Yokohama City University, Yokohama, Japan (B180900053). Informed consent was not sought due to a retrospective study design.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

J.S. contributed to the study concept and design. Y.To., and J.S. analyzed the data, wrote the manuscript, contributed to the discussion, and reviewed and edited the manuscript. Y.To., D.M., M.A., K.K., and S.K. contributed to gathering the data. M.K., T.O., and R.I. contributed to the discussion. Y.Te. wrote the manuscript, reviewed and edited the manuscript, and contributed to the discussion. J.S., and Y.Te. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Tables

Table 1. Background factors of the subjects

Number of subjects (M/F)	285 (168/117)
Age (years)	64.6±13.3
Duration of diabetes (years)	14.6±11.5
BMI (kg/m^2)	26.5±6.0
Systolic BP (mmHg)	131.7±18.5
Diastolic BP (mmHg)	77.7±14.0
HbA1c (NGSP/IFCC) (%/mmol/mol)	9.5±1.9/80±20.8
eGFR (mL/min/1.73 m^2)	68.1±25.5
LDL-C (mg/dL)	109.2±30.5
HDL-C (mg/dL)	50.5±15.2
Triglyceride (mg/dL)	173.1±30.5
Alcohol intake (%)	44.6
History of smoking (%)	42.1
Peripheral neuropathy (%)	18.4
Retinopathy (NDR/SDR/PPDR and PDR) (%)	70.1/17.9/12.0
Nephropathy stage (1/2/3/4) (%)	65.6/19.3/8.4/6.7
Coronary artery disease (%)	14.7
Cerebral infarction (%)	15.4
Peripheral artery disease (%)	18.4
Insulin treatment (%)	31.2

Values are the mean ± SD.

Table 2. Multiple linear regression analysis using AAC score and AAC length for the determination of CAD, CI and PAD

	CAD		CI		PAD	
	β	*p* value	β	*p* value	β	*p* value
AAC score	0.284	<0.001	0.315	<0.001	0.131	0.104
AAC length	0.221	<0.01	0.217	<0.01	0.178	<0.05

β: standardized regression coefficients.
The model was adjusted for age, duration of diabetes, BMI, systolic BP, diastolic BP, alcohol intake (0: No, 1: Yes), History of smoking (0: No, 1: Yes), HbA1c, postprandial PG, eGFR, LDL-C, HDL-C, TG, and hsCRP.

Table 3. Correlations between AAC Score or AAC length and various other parameters

	AAC score		AAC length	
	r	*p* value	r	*p* value
Age (years)	0.548	<0.001	0.542	<0.001
Gender	-0.023	0.695	-0.011	0.848
Duration of diabetes (years)	0.339	<0.001	0.294	<0.001
BMI (kg/m^2)	-0.361	<0.001	-0.281	<0.001
Waist circumference (cm)	-0.315	<0.001	-0.274	<0.001
Systolic BP (mmHg)	-0.002	0.974	0.010	0.861
Diastolic BP (mmHg)	-0.241	<0.001	-0.228	<0.001
Pulse pressure (mmHg)	0.225	<0.001	0.233	<0.001
Alcohol intake (%)	0.066	0.265	0.119	0.044
History of smoking (%)	0.028	0.635	0.080	0.177
HbA1c (NGSP value) (%)	-0.172	0.006	-0.136	0.032
Fasting PG (mg/dL)	-0.006	0.920	0.023	0.704
Postprandial PG (mg/dL)	-0.006	0.921	0.010	0.869
Fasting CPR (ng/mL)	-0.105	0.078	-0.080	0.178
Postprandial CPR (ng/mL)	-0.211	<0.001	-0.194	0.001
SD-blood glucose	0.060	0.315	0.084	0.159
AST (mg/dL)	-0.065	0.274	-0.049	0.410
ALT (mg/dL)	-0.219	<0.001	-0.190	0.001
Fib4-index	0.343	<0.001	0.342	<0.001
γ-GTP (mg/dL)	-0.126	0.033	-0.051	0.391
sCr (mg/dL)	0.187	0.002	0.172	0.004
eGFR (mL/min/1.73 m^2)	-0.306	<0.001	-0.282	<0.001
AER (mg/gCr)	0.009	0.882	0.013	0.834
LDL-C (mg/dL)	-0.246	<0.001	-0.224	<0.001
HDL-C (mg/dL)	0.148	0.012	0.132	0.026
Triglyceride (mg/dL)	-0.163	0.006	-0.103	0.082
Corrected Ca (mg/dL)	0.182	0.002	0.140	0.018
P (mg/dL)	0.011	0.851	0.028	0.640
hsCRP (mg/dL)	-0.203	0.001	-0.146	0.014
baPWV (R)	0.365	<0.001	0.351	<0.001
baPWV (L)	0.355	<0.001	0.337	<0.001
Peripheral neuropathy	0.208	<0.001	0.254	<0.001
Autonomic neuropathy	0.065	0.298	0.062	0.322
Retinopathy	0.109	0.084	0.079	0.212
Nephropathy	0.091	0.124	0.108	0.069

Gender (0: male, 1: female), Alcohol intake (0: No, 1: Yes), History of smoking (0: No, 1: Yes), Peripheral neuropathy (0: No, 1: Yes), Autonomic neuropathy (0: No, 1: Yes), Retinopathy (NDR: 0, SDR: 1, (P)PDR: 2), Nephropathy (Stage 1: 1, Stage 2: 2, Stage3: 3, Stage4: 4).

Table 4. Multiple linear regression analysis using BMI for the determination of AAC score and AAC length

	AAC score		AAC length	
	β	*p*	β	*p*
unadjusted	-0.361	<0.001	-0.281	<0.001
Model 1	-0.151	0.009	-0.089	0.135
Model 2	-0.157	0.014	-0.086	0.186
Model 3	-0.171	0.010	-0.084	0.210
Model 4	-0.168	0.023	-0.105	0.162
Model 5	-0.188	0.008	-0.102	0.162

β: standardized regression coefficients of BMI. Model 1 was adjusted for gender and age. Model 2 was adjusted for factors in Model 1 + duration of diabetes, systolic BP, diastolic BP, alcoholic intake and history of smoking. Model 3 was adjusted for factors in Model 2 + LDL-C, HDL-C and TG. Model 4 was adjusted for factors in Model 3 + HbA1c, postprandial PG, eGFR and hsCRP. Model 5 was adjusted for factors in Model 4 + postprandial CPR, corrected Ca, peripheral neuropathy and Fib4-index.

Table 5. Multiple linear regression analysis of Fib4-index for the determination of AAC score and AAC length

	AAC score		AAC length	
	β	*p*	β	*p*
unadjusted	0.343	<0.001	0.342	<0.001
Model 1	0.264	<0.001	0.253	<0.001
Model 2	0.271	<0.001	0.260	<0.001
Model 3	0.256	<0.001	0.256	<0.001
Model 4	0.331	<0.001	0.335	<0.001
Model 5	0.329	<0.001	0.331	<0.001

β: standardized regression coefficients of Fib4-index. Model 1 was adjusted for gender and age. Model 2 was adjusted for factors in Model 1 + duration of diabetes, BMI, systolic BP, diastolic BP, alcoholic intake and history of smoking. Model 3 was adjusted for factors in Model 2 + LDL-C, HDL-C and TG. Model 4 was adjusted for factors in Model 3 + HbA1c, postprandial PG, eGFR and CRP. Model 5 was adjusted for factors in Model 4 + postprandial CPR, corrected Ca and peripheral neuropathy.

Figures

Fig.1

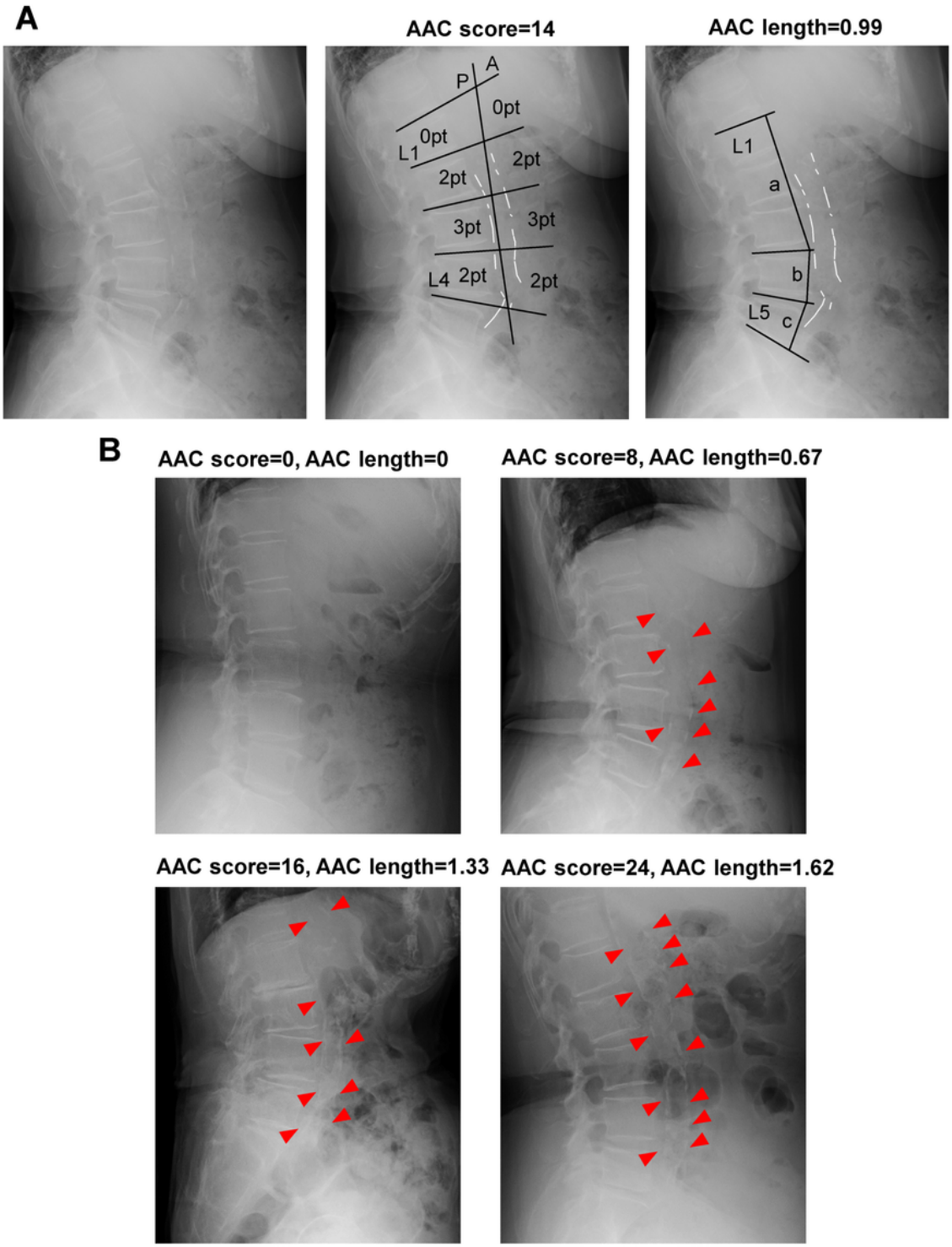

Figure 1

Grading of abdominal aortic calcification. (A) The middle panel shows an example of the AAC score calculation. The anterior and posterior aortic walls are divided into eight segments, corresponding to the L1-4 vertebral areas. Aortic calcification is scored as 0 (no calcification), 1 (1/3 or less of the aortic wall in that segment is calcified), 2 (1/3 to 2/3 of the aortic area is calcified), or 3 (more than 2/3 of the aortic area is calcified). The total score ranges from 0 to 24. The left panel shows an example of the AAC length

calculation. The AAC length is calculated using the ratio of the total length of calcific deposits along the anterior and posterior aortic wall in the segments between L1 and L5 to the total spine length of L1-5 (approximated by a+b+c, where a is the distance from the upper end of L1 to the midpoint between L3 and L4, b is the distance from the midpoint between L3 and L4 to the midpoint between L4 and L5, and c is the distance from the midpoint between L4 and L5 to the lower end of L5). (B) Examples of AAC images. The arrowheads point to calcification deposits. Upper left panel: AAC score=0, AAC length=0. Upper right panel: AAC score=8, AAC length=0.67. Lower left panel: AAC score=16, AAC length=1.33. Lower right: AAC score=24, AAC length=1.62.

Fig.2

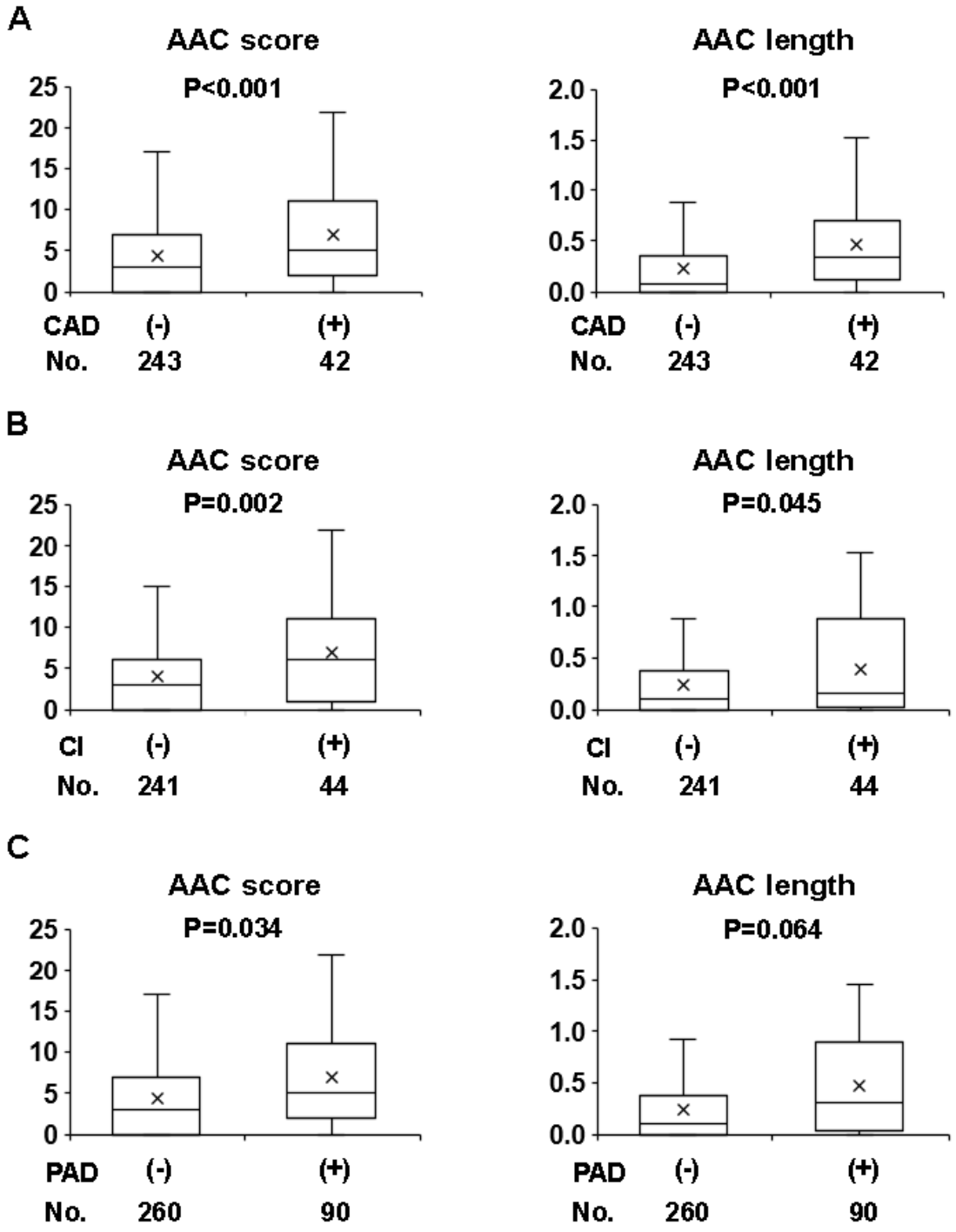

Figure 2

AAC score and AAC length in patients with and without CAD, CI or PAD. (A) AAC score (left panel) and AAC length (right panel) in patients with or without CAD. (B) AAC score (left panel) and AAC length (right panel) in patients with or without CI. (C) AAC score (left panel) and AAC length (right panel) in patients with or without PAD. The box plots represent the medians and the 25th to 75th percentiles, and the crosses represent the means. P values were estimated using the Mann Whitney U test.

Fig.3

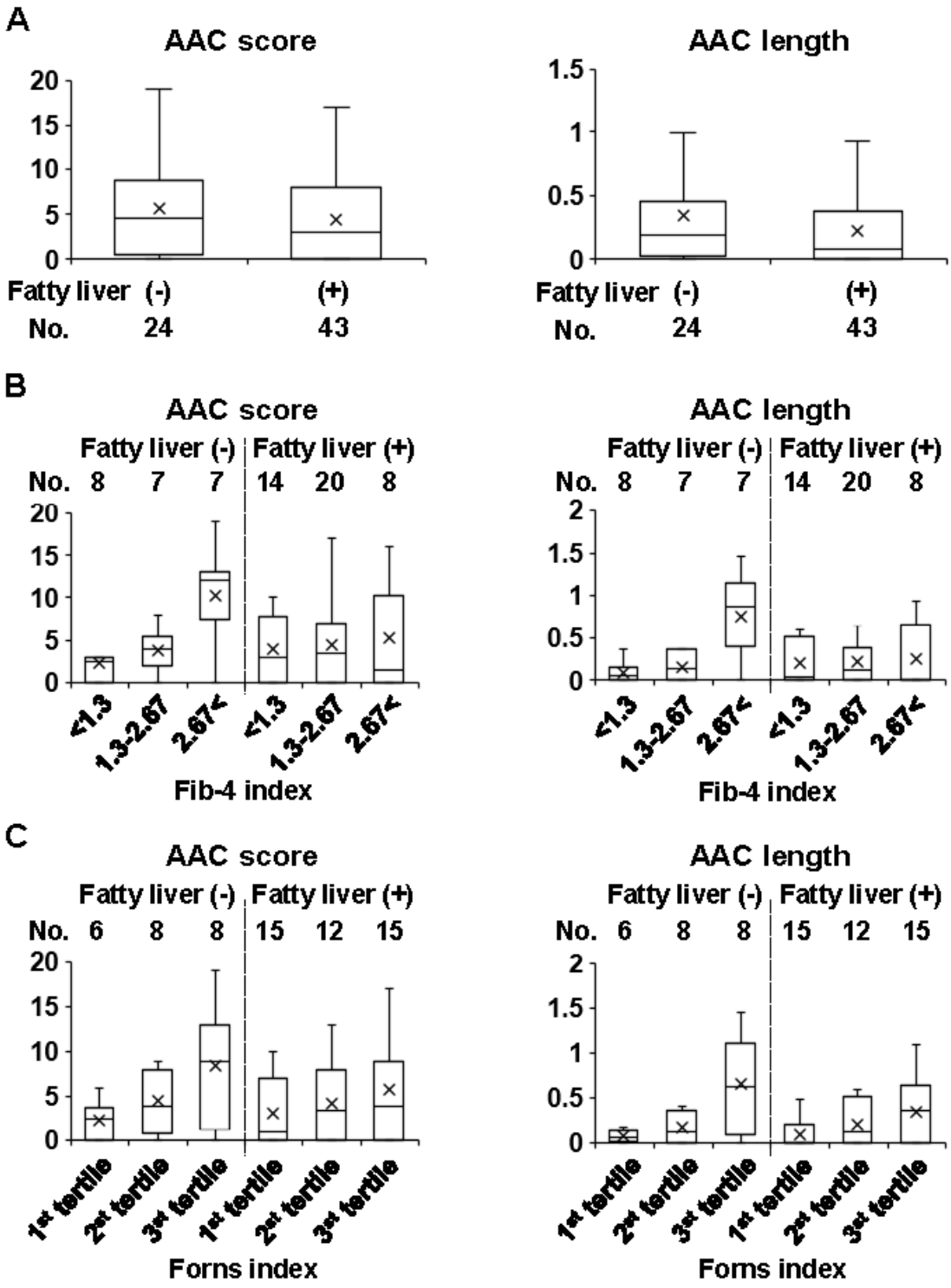

Figure 3

AAC score and AAC length in patients with and without fatty liver diagnosed using ultrasonography (A) AAC score (left panel) and AAC length (right panel) in patients with or without fatty liver. (B) AAC score (left panel) and AAC length (right panel) within three levels of Fib-4 index among patients with or without fatty liver. (C) AAC score (left panel) and AAC length (right panel) within tertiles of Forns index among patients with or without fatty liver.