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ORIGINAL ARTICLES

The clinical significance of aortic calcification in chest radiography in community-dwelling, healthy adults: The PRESENT project

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Abstract

Background: Aortic calcification (AC), a predictor of generalized atherosclerosis, may precedes cerebral white matter lesions. Cerebral white matter changes (WMCs) are associated with cognitive decline and future dementia. The aim of study was to evaluate the usefulness of aortic calcification (AC) detection by chest radiograph for cueing early intervention in possible WMCs to prevent stroke and dementia in community-dwelling healthy people. *Methods*: We assessed the relationship between AC in chest radiography and vascular risk factors and severity of WMCs in 543 middle-aged and elderly individuals with no history of stroke or dementia. *Results*: The mean age of the subjects was 61.6 ± 7.4 years. Of these, AC was observed in 39 (7.2%) subjects. AC combined with grade 1 WMC (mild), 2 (moderate), and 3 (severe) were seen in 8 (25.8%), 7 (23.3%) subjects, and 3 (30.0%) subjects, respectively. After adjustment for age and vascular risk factors, diabetes (odds ratio [OR], 1.92, 95% confidence interval (CI) 1.01–3.65, $p<0.05$) and hypertension (OR, 1.86, 95% CI, 1.03-3.35, $p<0.05$), aortic knob width (OR, 1.07, 95% CI, 1.01–1.13, $p<0.05$) and aortic calcification (OR, 2.93, 95% CI, 1.36-6.33, $p<0.05$) were significantly associated with the severity of WMCs.
Conclusion: There is an association between the presence of AC in chest radiography and WMC. It may be useful in providing important information about development of WMCs for prevention of future vascular-related cognitive impairments or ischemic stroke.

Keywords: Aortic calcification; chest radiography; dementia; white matter changes

INTRODUCTION

Cerebral white matter changes (WMCs) are common imaging-defined cerebral vascular lesions in the periventricular space or subcortical areas.[1] MRI is more sensitive than CT and provides a more detailed observation of WMCs. Most studies on the prevalence of WMCs in population-based samples have been conducted with MRI. However, brain CT is still widely used due to its cost-effectiveness and its usefulness in detecting age-related lesions.[2] The presence of WMCs is significantly associated with cognitive decline and future dementia in the non-demented elderly.[2] WMCs are also known risk factors for future stroke[1,3], mood disturbances[4], gait disturbances[5], and urinary problems.[6] Given the possible substantial effect of WMCs on cognitive decline, dementia, and stroke, there has been much effort to elucidate the pathogenesis of WMCs.

To date, atherosclerosis is widely considered the most clinically relevant risk factor for the development of WMCs.[7,8] Atherosclerosis starts in the second decade of life, without the development of WMCs.[9] Thus, if atherosclerosis is a predictor of WMCs, intervention in the early stages of the disease could aid in the prevention of WMCs. Under this assumption, several studies have shown an association between aortic calcification (AC) and WMCs.[10–14] According to these studies, AC predicts the development of atherosclerosis

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at various sites, including the brain.[11,15-17] In addition, these studies have suggested that early intervention in cerebral atherosclerosis is needed in elderly people if AC is present. However, all previous studies used resource-intensive imaging modalities, including chest computed tomography (CT), digital subtraction angiography (DSA), and pulse wave velocity (PWV) measurement. These modalities are accurate and reliable for assessing the presence of AC.[10–14] However, access to intensive diagnostic tools can be limited due to insurance issues or regional inequalities. In addition, they are not readily available to primary care practitioners. Thus, there is a need for a simple and inexpensive modality to assist in the evaluation of AC for dementia prevention. Chest radiography meets the above-mentioned requirements, and is readily available.

With this in mind, we investigated in community-dwelling, healthy adults the usefulness of AC detection by chest radiography and the correlation of this data with the severity of WMCs.

METHODS

The Prevention of Stroke and Dementia (PRESENT) project is an ongoing regional government project initiated in Korea in July 2007 for the prevention of stroke and dementia through public education, public relations, early medical check-ups, and research. As part of the PRESENT project, adult participants (aged 50–75 years) without stroke or dementia were recruited by random sampling or voluntarily. Data collection took place in two steps, and extended over two years from January 2009 to December 2010. Systematic random sampling, with administrative support from the regional government, was performed in 2009. From the baseline cohort (n = 119,359), aged between 50 and 75 years, we contacted every 100th person using a registered list received officially from the regional government office. If a potential participant could not be contacted, refused to participate, or had moved, we contacted the next person on the list. Telephone interviews for study participation were conducted by trained research nurses, and 682 persons were contacted using this process. Of these, we excluded those deemed to have dementia, stroke, severe liver or kidney disease, or to be incapable of performing activities of daily living. In total, 621 persons participated in this study and provided informed consent. Subsequently, a further 78 persons were excluded because of improper chest radiographic images showing tracheal deviation or mediastinal shifting, or because of a previous history of aortic disease. Finally, total 543 healthy subjects aged between 50 and 75 years were included for this study (Figure 1).

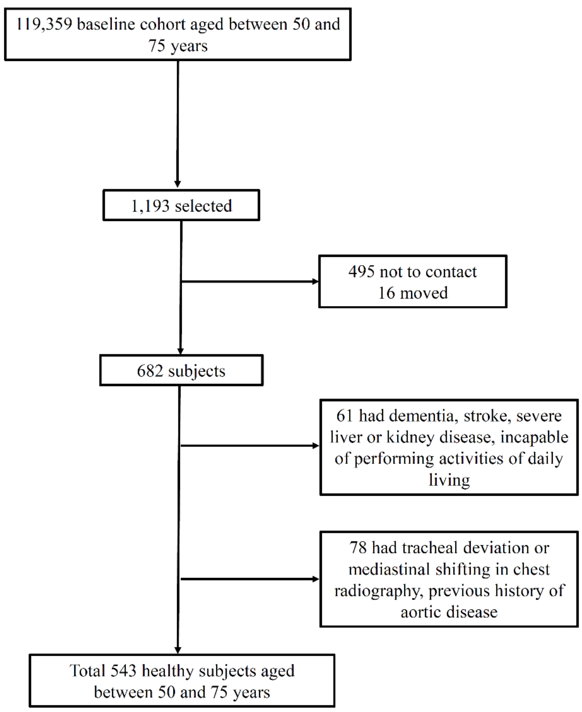

Figure 1. Flow sheet for study patients' selection

We investigated the medical history of patients in relation to their risk factors for dementia, including hypertension, diabetes mellitus, personal history of smoking, and previous cardio-cerebrovascular event such as stroke or myocardial infarction. According to the hypertension management guidelines from the Korean Society for Hypertension, hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90mmHg, or current use of antihypertensive medications. Diabetes was defined according to the treatment guidelines for diabetes of the Korean Diabetes Association. Venous blood samples were collected after at least 12 h of overnight fasting, and the serum concentrations of glucose, total cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL-C), high-sensitivity C-reactive protein (hs-CRP), and total homocysteine were measured. Abdominal waist circumference (AWC) was measured at the midpoint between the margin of the lower rib and the iliac crest.

Chest radiography in the posteroanterior view was obtained from all participants. Radiologists blinded to clinical information checked for the presence of AC (Figure 2, thick arrow). In addition, the width of the aortic knob on the ascending aorta was measured along a horizontal line extending from the left edge of the trachea to the left lateral wall of the aortic knob (Figure 2, two-headed arrow). Brain CT was performed on all participants, and the results obtained were independently evaluated by two expert and highly experienced neurologists blinded to the clinical condition and laboratory assessment of the participants. Based on the white-matter rating scales published by Blennow *et al.*,[18] one of the widely used efficient visual rating scales, we assessed the extent of WMCs. The use of Blennow scale has been widely accepted for assessment of WMC and its effectiveness has been proven and reported earlier.[2,18] These were graded as follows: 0 = no decrease in the attenuation of white matter; 1 = decreased attenuation of white matter at the margins of the frontal and occipital horns of the lateral ventricle; 2 = decreased attenuation of white matter extending entirely around the lateral ventricle; 3 = marked decrease in the attenuation of white matter (Figure 3).

Data are presented as means ± SD values for continuous variables, and as number and percentage for categorical variables. Inter- and intra-observer agreement correlations were determined using Cohen's weighted kappa

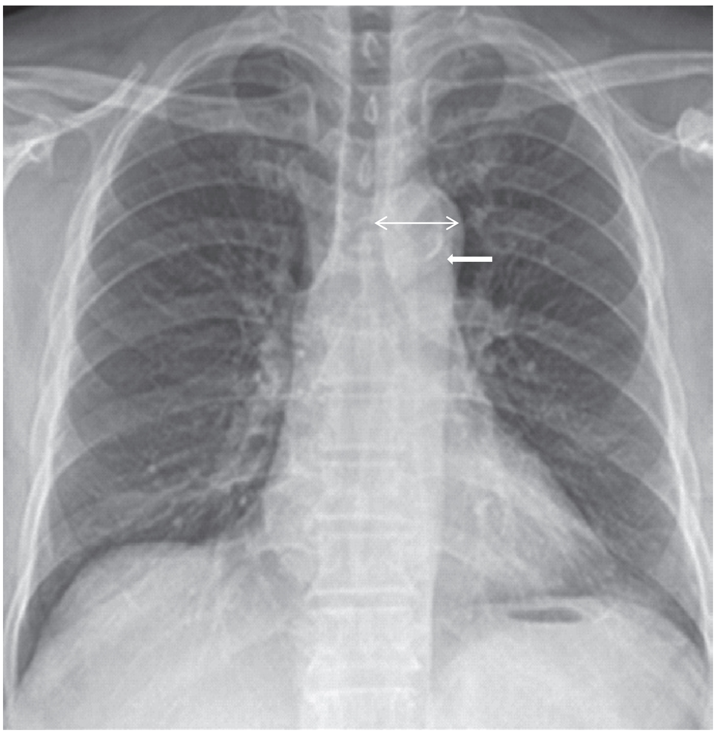

Figure 2. Aortic knob calcification (thick arrow) in chest posteroanterior view and the line segment (two-headed arrow) that was measured to obtain aortic knob width.

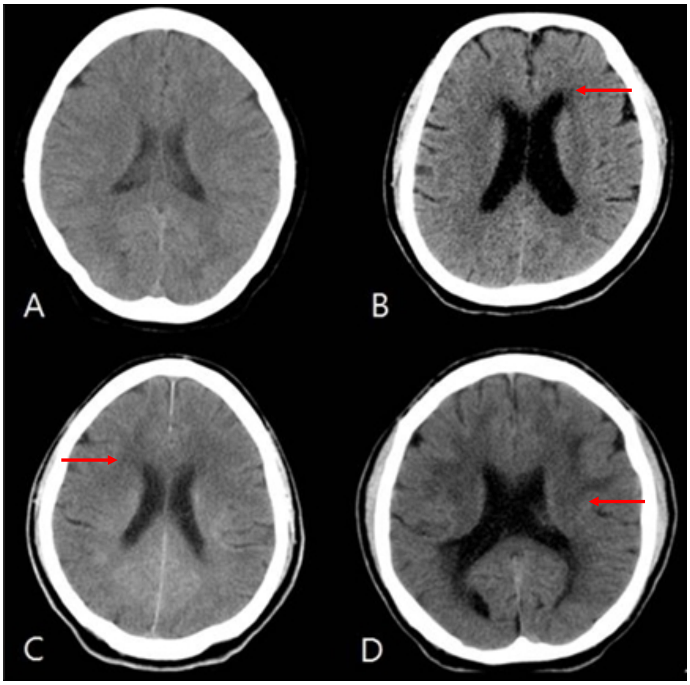

Figure 3. Scoring of cerebral white matter changes on brain computed tomographs. A through D, examples of progressively greater that were given score of 0, 1, 2, and 3, respectively. Zero indicates on changes. Changes are shown by arrows.

statistic for the WMC rating scale (k = 0.7). The data between groups were analyzed using one-way analysis of variance for continuous variable and chi-square test for categorical variable. Ordinal logistic regression analyses were used to evaluate the relative risk and clinical factors for WMCs. Test for proportional odds assumption of ordinal logistic regression was done (Fig.4).

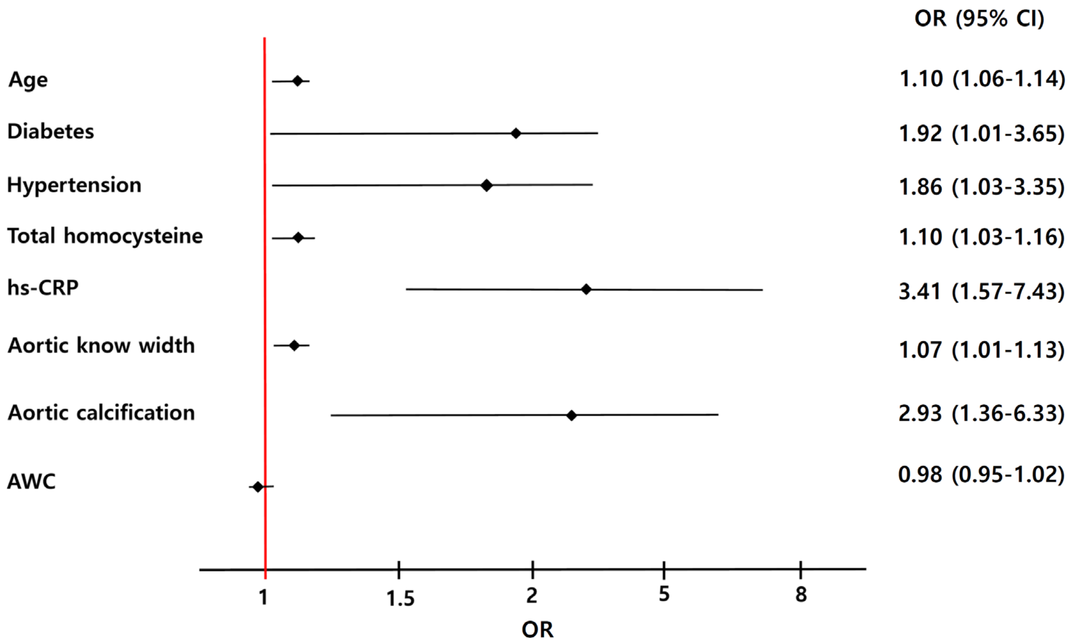

Figure 4. Ordinal logistic regression of predictors for white matter change. OR, odds ratio; CI, confidence interval; hs-CRP, high sensitivity C-reactive protein; AWC, abdominal waist circumference

All differences were considered statistically significant if $p< 0.05$. All statistical analyses were performed using the free statistical software R-project version 3.2.3 (https://www.R-project.org). The study protocol was approved by the Wonkwang University Institutional Review Board (IRB No. 2016-11-BM-071). Informed consent was submitted by all subjects when they were enrolled.

RESULTS

In total, 543 persons participated in this study. Table 1 shows the demographic characteristics of the participants with univariate analysis of the severity of WMCs with each variable in this study. The mean age of included participants was 61.6 ± 7.4 years. The greater the age of the participant, the more severe was the degree of WMCs ($p<0.05$). In addition, diabetes, hypertension, total homocysteine, and hs-CRP level were significantly associated with the severity of WMCs ($p<0.05$). In total, 39 participants (7.2%) showed the presence of AC (mean age 67.4 ± 6.8 years, $p<0.01$). AC combined with grade 1 WMCs (mild), grade 2 (moderate), and grade 3 (severe) was seen in 8 (25.8%), 7 (23.3%), and 3 (30.0%) participants, respectively. Participants who have AC combined WMCs was older than those without WMCs, however age differences were not significant owing to small number.

Figure 4 shows ordinal logistic regression with the severity of WMCs as dependent variable and age, diabetes, hypertension, total homocysteine, hs-CRP level, AC, aortic knob width, and AWC as independent variables. All variables satisfied the proportional odds assumption in ordinal logistic regression. AC (odds ratio [OR], 2.93; 95% confidence interval [CI], 1.36–6.33; $p<0.05$), and aortic knob width (OR, 1.07; CI, 1.01–1.13; $p<0.05$) were significantly associated with the severity of WMCs. In addition, diabetes (OR, 1.92; CI, 1.01–3.65; $p<0.05$), hypertension (OR, 1.86; CI, 1.03–3.35; $p<0.05$), total homocysteine level (OR, 1.10; CI, 1.03–1.16; $p<0.05$), and hs-CRP (OR, 3.41; CI, 1.57–7.43; $p<0.05$) were associated with the severity of WMCs.

Table 1: Clinical characteristics of the study group by extent of white matter changes

	White matter changes				
	Normal (n = 472)	Mild (n = 31)	Moderate (n = 30)	Severe (n = 10)	p value
Age (years; mean ± SD)	60.7 ± 6.9	66.9 ± 7.8	67.5 ± 8.0	69.5 ± 8.6	<0.05
Male (n, %)	203 (43.0)	14 (45.2)	12 (40.0)	3 (37.5)	0.97
Diabetes (n, %)	73 (15.5)	9 (29.0)	11 (36.7)	2 (25.0)	<0.05
Hypertension (n, %)	161 (34.1)	18 (58.1)	21 (70.0)	5 (62.5)	<0.05
Atrial fibrillation (n, %)	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0.93
Smoking (n, %)	83 (27.9)	5 (25.0)	4 (22.2)	1 (16.7)	0.88
Total homocysteine (mg/dL)	11.3 ± 3.9	13.1 ± 4.0	13.8 ± 4.0	12.2 ± 2.3	<0.05
Total cholesterol (mg/dL)	217.2 ± 4.5	208.5 ± 44.8	218.1 ± 61.7	211.1 ± 48.3	0.63
HDL cholesterol (mg/dL)	60.1 ± 13.6	58.7 ± 15.6	59.7 ± 13.6	57.0 ± 12.3	0.53
Triglyceride (mg/dL)	150.6 ± 98.0	151.5 ± 76.9	172.4 ± 98.9	173.9 ± 81.7	0.21
hs-CRP (mg/dL)	0.1 ± 0.2	0.2 ± 0.3	0.3 ± 0.5	0.2 ± 0.2	<0.05
AWC (cm)	84.9 ± 8.6	87.5 ± 8.1	86.3 ± 8.2	86.5 ± 5.8	0.15
Aortic knob width (mm)	33.8 ± 4.3	36.5 ± 5.4	36.2 ± 4.7	37.2 ± 5.9	<0.05
Aortic calcification (n, %)	21 (4.4)	8 (25.8)	7 (23.3)	3 (30.0)	<0.05

HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; AWC, abdominal waist circumference

DISCUSSION

This study indicated that the presence of AC confirmed on chest radiography could provide useful information about the possible development of WMCs in community-dwelling, healthy people. WMCs are known to be an important predictor of cognitive decline and future dementia.[2] In addition, cerebral small-vessel diseases, including WMCs, make up 30.7% of all causes of ischemic stroke in South Korea and up to 54.1% in Japan.[19,20] The presence of WMCs also increases the risk of intracerebral hemorrhage following acute-phase stroke treatments such as intravenous tissue plasminogen activator or intra-arterial thrombolysis.[21] Moreover, the presence of WMC predicts poor functional outcomes after stroke in the acute and chronic phases.[22] To date, definite treatment options for WMCs do not exist. However, it is accepted that early detection of WMCs at the asymptomatic stage is advantageous.[1,7,23] Although MRI is more sensitive than CT and provides a more detailed observation of WMCs, Brain CT is still widely and easily used due to its cost-effectiveness and its usefulness in detecting age-relatedlesions.[2]

AC develops ahead of WMCs[9], and early detection of AC might enable early intervention in WMCs, leading to prevention of future stroke and dementia. For assessing the presence of AC, chest CT, DSA, and PWV have proven effective.[10–14] Lately, ultrasonographic methods such as transesophageal echocardiography (TEE) and intravascular ultrasonography (IVUS) have also been introduced into practice.[24,25] However, due to high cost and limited accessibility in rural areas, these modalities cannot be used in common clinical settings or as screening tools for AC. On the other hand, the chest radiography used in our study is a relatively inexpensive, non-invasive procedure. Chest radiography is routinely used in emergency rooms and outpatient departments worldwide. In addition, its reliability for assessing AC has been validated in several studies.[26,27] Based on our results, we propose that the use of chest radiography as a screening tool to determine the presence of AC might play an important role in the early detection of WMCs and contribute to early intervention for the prevention of future vascular-related cognitive impairments or ischemic stroke. Furthermore, studies on the relation between AC and WMCs are still scanty, and we suggest that our study provides basic data on which future advances may be built.

Our study produced another significant finding. Increased aortic knob width was here significantly associated with WMC, and a mild degree of WMC appeared above 36 mm (median value) of aortic knob width. Aortic knob width is a known indicator of atherosclerosis.[28] Aortic knob width in chest radiography has been proposed as a reliable calibrator for thoracic aorta volume in comparisons with aortic measurements by echocardiography.[29] Dilation of aortic knob width is associated with left ventricular diastolic dysfunction, unstable angina, and severe coronary artery disease.[28,30,31] Rayner *et al*. suggested that an aortic knob width of more than 36mm should be considered target organ damage by atherosclerosis.[29] Thus, we suggest that assessing aortic knob width in the presence of AC may have an important role in early intervention for cognitive decline. However, further research is needed.

Our study has several limitations. First, we collected previous cardio-cerebrovascular history by interview, without checking previous hospital or medical records in study participants. Although we excluded those with abnormal CT findings, such as previous hemorrhage or stroke, it is possible that we included participants who did not remember previous minor stroke or transient ischemic accidents or who ignored them. Second, we used chest radiography for determining only the presence/absence of AC at the aortic knob; thus, the degree of AC could not be evaluated. Moreover, chest radiography cannot assess atheromatous plaque in the absence of calcification of the aortic knob, or calcification in the thoracic or abdominal aorta, known consequences of atherosclerosis. Third, we could not confirm the presence of AC using other modalities such as chest CT, DSA, TEE, or IVUS. Currently, there is no gold standard for assessing the presence of AC. Moreover, the accuracy and reproducibility of chest radiography was not tested. Thus, further study with other modalities for confirming the presence of AC is necessary for validating chest radiography as a screening method for AC.

In conclusion, the presence of AC in simple and routine chest radiography may be useful in providing important information about the early intervention of WMCs. It is important for the prevention of future vascular-related cognitive impairments or ischemic stroke.

DISCLOSURE

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collection, data analysis, data interpretation, report writing, or in the decision to submit the article for publication.

Conflicts of interest: None.

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