Brachial intima-media thickness is associated with coronary artery atherosclerosis in patients with diabetes mellitus

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Brief title: Brachial IMT and coronary artery calcification

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Abstract

Background: Coronary artery calcification (CAC) as measured by computed tomography is a strong predictor of coronary artery disease. The brachial intima-media thickness (IMT) was recently reported to be associated with cardiovascular risk factors. This study investigated the association of brachial IMT with CAC, which is a marker of coronary artery atherosclerosis, in patients with diabetes.

Methods: We enrolled 292 patients with diabetes (mean age, 65 ± 12 years; 59% men) who underwent both endothelial function testing and computed tomography for risk assessment of coronary artery disease. Flow-mediated dilation (FMD) and IMT in the brachial artery were measured with a specialized machine.

Results: FMD was lower and brachial IMT was thicker in patients with than without CAC. The CAC score was significantly correlated with both brachial IMT and FMD, while the multivariate logistic analysis demonstrated that brachial IMT (>0.32 mm) but not FMD (<5.1%) was significantly associated with the presence of CAC (odds ratio, 2.03; 95% confidence interval, 1.10–3.77; $p = 0.02$). The receiver operating characteristic curve analysis showed that the area under the curve for discriminating patients with CAC was 0.66 for IMT ($p < 0.01$) and 0.59 for FMD ($p = 0.02$). When patients were classified into four groups based on brachial IMT and FMD, the CAC score was higher in patients with thicker brachial IMT and lower FMD than in patients of the other groups ($p < 0.001$).

Conclusion: Measurement of brachial IMT could be useful for the risk assessment of patients with diabetes.

Key words: Endothelial function, flow-mediated dilatation, intima-media thickness, coronary artery calcification

Introduction

Diabetes mellitus is associated with a substantial risk of cardiovascular disease [1]. Endothelial dysfunction is an early event in the pathological process of atherosclerosis [2]. Several studies have shown that brachial flow-mediated dilatation (FMD) is associated with cardiovascular events [3, 4, 5, 6, 7, 8, 9, 10]. The brachial intima-media thickness (IMT), which can be measured simultaneously with FMD, was recently reported to be associated with coronary risk factors [11].

Coronary artery calcification (CAC) as measured by computed tomography (CT) is a useful marker of subclinical coronary atherosclerosis and a predictor of future cardiovascular events [12, 13, 14]. Previous population-based studies established an association between higher CAC scores and a higher incidence of cardiovascular events [15, 16]. A recent study also showed that patients with a CAC score of 0 had a lower cardiovascular disease risk than patients with CAC [17]. Thus, CAC is a useful measure for cardiovascular risk assessment.

Although the carotid IMT is associated with cardiovascular events, the clinical relevance of the brachial IMT remains unclear. This study was performed to investigate the association between brachial IMT and CAC, a marker of coronary atherosclerosis, in patients with diabetes.

Methods

Study population

Patients with diabetes who had no prior cardiovascular disease and who underwent both multidetector row CT for measurement of the CAC score and endothelial function testing within a period of 1 week at Okayama University Hospital were prospectively enrolled from May 2011 to October 2016. A flow diagram is shown in Figure 1. In total, 292 consecutive patients with diabetes were analyzed.

CT protocol

For CAC imaging, a 64-slice non-enhanced CT scan was obtained with a diagnostic CT scanner (Somatom Definition Flash; Siemens Medical Solutions, Erlangen, Germany) as described previously [18]. The detector collimation was 64 × 0.6 mm, equaling a slice acquisition of 128 × 0.6 mm using the flying focal spot technique; the table pitch was adapted to the heart rate (0.17–0.38); the rotation time was 275 ms; the tube current–time product was 360 mA; and the tube voltage was 120 kVp. CAC was quantified using calcium-scoring software (Virtual Place Formula; AZE Inc., Tokyo, Japan), and measurements were performed by a qualified CT technologist using the standard Agatston calcium-scoring algorithm [19]. The CAC score was defined by the Agatston score. The intra- and inter-observer correlation coefficients for CAC measurement were 0.99 and 0.98, respectively.

Measurement of brachial IMT

Longitudinal ultrasonographic images of the brachial artery were obtained at the end of diastole from each of 10 cardiac cycles before FMD measurement with a linear, phased-array, high-frequency (10-MHz) transducer using a specialized ultrasound unit (Unex Company Ltd., Nagoya, Japan) as previously described [11]. Measurement of IMT was automatically performed on A-mode images of the far wall of the brachial artery. The mean value of 21 points over a 3-mm length of IMT in the 10-mm longitudinal image was automatically calculated. The average of the mean values obtained from 10 cardiac cycles was defined as the brachial IMT.

Measurement of FMD

FMD was measured according to the published guidelines for ultrasound assessment of FMD of the brachial artery [20]. Using a 10-MHz linear-array transducer probe (Unex Company Ltd.), longitudinal images of the brachial artery at baseline were recorded with a stereotactic arm, and the artery diameter was measured after the patient had rested in the supine position for ≥5 min. The artery diameter was measured from clear anterior (media-adventitia) and posterior (intima-media) interfaces, which were determined manually. Suprasystolic compression (50 mmHg higher than systolic blood pressure) was performed at the right forearm for 5 min, and the artery diameter was measured continuously from 30 s before to ≥2 min after cuff release. All FMD measurements were performed by a single technician blinded to the drug allocation, and the intra- and inter-observer correlation coefficients were high (>0.9).

Measurement of carotid IMT

An ultrasound unit (Aloka-α7; Aloka Co., Tokyo, Japan) equipped with a linear, phased-array, high-frequency (13-MHz) transducer was used to scan the common carotid artery. The carotid IMT was used to measure the distance between the luminal border of the intima and the outer border of the media of the carotid artery far wall, as previously described [11]. The mean IMT of the common carotid artery was measured in a 10-mm-long segment located 5 mm proximal to the carotid artery bulb.

Statistical analysis

Data are expressed as mean and standard deviation. A paired or unpaired Student's t test was used for intergroup comparisons. The relationship between continuous variables was investigated by means of Pearson's correlation coefficient. Predictors of CAC were assessed using univariate logistic regression analysis as well as multivariate logistic regression analysis using age, sex, coronary risk factors, FMD, and brachial IMT. A p value of <0.05 was considered statistically significant. All statistical analyses were performed using a personal computer equipped with IBM SPSS software, version 21.0 (SPSS Inc., Chicago, IL, USA).

Results

The accuracy and reproducibility of the brachial IMT measurement method were first evaluated in 100 patients in this cohort. As shown in Figure 2, a good correlation was observed between the brachial IMT measured with the software and the brachial IMT measured manually. The intra- and inter-observer correlation coefficients for the brachial IMT measured with the software were 0.960 ($p < 0.001$, difference = 0.001, Bland–Altman limits of agreement = −0.038 to 0.038) and 0.951 ($p < 0.001$, difference = 0.006, Bland–Altman limits of agreement = −0.035 to 0.047), respectively.

The clinical characteristics of the 292 enrolled patients are shown in Table 1. Of all 292 patients, 211 (72%) had CAC. Patients with CAC were older and more often had hypertension than those without CAC. The mean brachial IMT and FMD were 0.33 ± 0.07 mm and 5.3% ± 1.9%, respectively. Patients with CAC had significantly lower FMD and thicker brachial IMT than patients without CAC ($p = 0.006$ and $p < 0.001$, respectively). The association of clinical variables with brachial IMT and FMD are shown in Table 2. Brachial IMT was significantly associated with FMD, age, systolic blood pressure, and the CAC score. FMD was significantly associated with age, systolic blood pressure, the hemoglobin A1c level, and the CAC score. The carotid IMT was measured in 128 patients in this study. The mean carotid IMT was 0.91 ± 0.33 mm. The carotid IMT was significantly correlated with the brachial IMT ($r = 0.178$, $p = 0.045$). Patients with CAC had a significantly higher carotid IMT than patients without CAC (0.98 ± 0.35 vs. 0.76 ± 0.20 mm, respectively; $p < 0.001$). The carotid IMT was significantly associated with FMD ($r = -0.246$, $p = 0.005$), age ($r = 0.402$, $p < 0.0001$), and the CAC score ($r = 0.348$, $p < 0.0001$). Table 3 shows the association between the presence of CAC and clinical variables, FMD, and brachial IMT. The univariate logistic analysis demonstrated that an age of >60 years, male sex, the presence of hypertension, and brachial IMT greater than the median value of 0.32 mm were significantly associated with the presence of CAC. After adjustment for age, sex, current smoking status, hypertension, dyslipidemia, and diabetes mellitus, the multivariate logistic analysis showed that brachial IMT of >0.32 mm was significantly associated with the presence of CAC (odds ratio, 2.034; 95% confidence interval, 1.098–3.770; $p = 0.024$).

Figure 3 shows the receiver operating characteristic curve analysis of brachial IMT and FMD for discriminating patients with CAC. The sensitivity and specificity of brachial IMT at the cut-off value of 0.31 mm were 74% and 57%, respectively (area under the curve, 0.67; $p < 0.001$). The sensitivity and specificity of FMD at the cut-off value of 6.5% were 76% and 46%, respectively (area under the curve, 0.62; $p < 0.001$). Next, to assess the clinical value of the combination of brachial IMT and FMD, the patients were classified into four groups based on the above cut-off values of brachial IMT and FMD (Table 4). Patients with thicker brachial IMT and lower FMD had higher CAC scores than patients in the other groups ($p < 0.001$).

Discussion

This is the first report of a significant relationship between brachial IMT and the CAC score, a marker of coronary atherosclerosis, in patients with diabetes. The patients with CAC had significantly lower FMD and thicker brachial IMT than patients without CAC. Multivariate logistic analysis revealed that brachial FMD was a significant determinant of CAC, independent of other confounding factors. The combination of brachial IMT and FMD may be useful for risk assessment of patients with diabetes.

In this study, brachial IMT was shown to be positively associated with age and systolic blood pressure and negatively associated with FMD. These findings confirmed previous data in a general population that brachial IMT was correlated with carotid IMT [11]. In addition, a case-control study showed that brachial IMT was independently associated with the presence of coronary artery disease [21]. Our study demonstrated that brachial IMT was correlated with the CAC score, which reflects the coronary atherosclerotic burden. Thus, brachial IMT could be a marker of atherosclerosis in patients with diabetes mellitus.

The present study demonstrated that CAC was significantly associated with brachial IMT, but not FMD. CAC generally appears at the advanced stage of atherosclerosis [18]. Brachial IMT may reflect the change in vascular structure [11], while FMD indicates endothelial function, which changes relatively early in atherosclerosis. This is one possible explanation for the difference in the association of brachial IMT and FMD with CAC. In addition, several studies showed that carotid IMT was correlated with the degree of CAC [22, 23], which is in line with our finding.

Our finding that the CAC score in patients with thicker brachial IMT and lower FMD was higher than that in patients of other groups raises the possibility of using the combination of brachial IMT and FMD for risk assessment. Previous studies showed the efficacy of the combined use of noninvasive vascular tests including carotid IMT, FMD, and pulse wave velocity to predict cardiovascular events [24, 25, 26]. Nagai et al. [24] reported that the combination of carotid IMT and brachial-ankle pulse wave velocity improved the prediction of future cardiovascular events better than each test alone in Japanese subjects of advanced age. Brachial FMD has been reported to be strongly associated with future cardiovascular events [3, 4, 5, 6, 7, 8, 9, 10]. Therefore, combined assessment of brachial IMT and FMD is of clinical interest.

In the Japan Diabetes Complications Study (JDCS), the crude incidence of myocardial infarction in patients with diabetes was 3.84 per 1,000 patient-years [27], which was higher than that in the general population (0.64–1.42 per 1,000 patient-years) [28, 29]. Silent myocardial infarctions were more common in patients with than without diabetes [30]. Moreover, traditional cardiac risk factors were not associated with abnormal stress test results in patients with diabetes [31]. Thus, detecting groups at high risk of developing CAD among patients with diabetes is difficult. Because the increase in CAC is closely associated with the prevalence of obstructive CAD, the measurement of CAC is a useful tool for risk stratification. However, radiation exposure and use of CT scanners in usual clinical practice remain problematic. According to our findings, measurement of the brachial IMT and FMD is simple and effective for detecting patients with diabetes at high risk of CAD.

This study has several limitations. First, this was a single-center study that included only 292 Japanese patients with diabetes mellitus. This study also excluded patients with a history of coronary artery disease because the presence of a coronary stent or bypass graft might lead to an inaccurate CAC score. Because these patients had a higher prevalence of risk factors than the general population, the results may not be applicable to the general population or to other ethnicities. Second, our study did not provide direct molecular insights into this relationship. Because of the cross-sectional nature of the study, a causal relationship between brachial IMT and the presence of CAC cannot be concluded. Third, data on coronary CT angiography were not available in this study. The direct association of brachial IMT with coronary plaque volumes and morphology could not be evaluated.

In conclusion, the present study demonstrates that thicker IMT of the brachial artery was associated with the presence of CAC in patients with diabetes. The measurement of brachial IMT in addition to FMD may be of use for risk assessment in patients with diabetes. Future studies are needed to confirm our finding and evaluate the usefulness of brachial IMT as a surrogate marker of future cardiovascular events.

Compliance with Ethical Standards

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

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (ethics committees of Okayama University Hospital and Okayama City Hospital) and with the 1964

Helsinki declaration and its later amendments or comparable ethical standards. The first and last authors take complete responsibility for the integrity of the data and the accuracy of the data analysis.

Informed consent: Written informed consent was obtained from all individual participants included in the study.

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Figure legends

Figure 1. Flow diagram of enrollment in the present study

CT, computed tomography; PCI, percutaneous coronary intervention

Figure 2. Comparison of the brachial IMT measured with the software and the brachial IMT measured manually. The graphs on the left show the correlations between the measurements with the software and manual measurements. The graphs on the right show the Bland–Altman plots for the two methods. The straight lines represent the mean differences between the two methods, and the dotted lines represent the limits of agreements. *Difference = manual measurement − measurement with software

IMT, intima-media thickness

Figure 3. Receiver operating characteristic curve analysis of brachial IMT and FMD for discriminating patients with coronary artery calcification

AUC, area under the curve; FMD, flow-mediated dilation; IMT, intima-media thickness

Table 1. Baseline characteristics of the study population

Variables	Total (n = 292)	CAC score = 0 (n = 81)	CAC score > 0 (n = 211)	p value
Age, y	65 ± 12	57.4 ± 12.6	68.2 ± 9.5	<0.001
Male sex	171 (59)	36 (44)	135 (64)	0.002
Body mass index, kg/m^2	24.4 ± 4.4	24.3 ± 4.9	24.4 ± 4.3	0.775
Hypertension	190 (65)	40 (49)	150 (71)	<0.001
Dyslipidemia	173 (59)	46 (57)	127 (60)	0.566
Smoking	90 (31)	26 (32)	64 (30)	0.897
Systolic blood pressure, mmHg	124.3 ± 18.7	121.7 ± 18.0	125.4 ± 18.9	0.129
Diastolic blood pressure, mmHg	72.8 ± 10.5	73.7 ± 11.7	72.4 ± 10.0	0.37
Heart rate, bpm	67.1 ± 11.4	67.6 ± 12.6	66.9 ± 11.0	0.652
Triglycerides, mg/dL	136.9 ± 111.6	130.2 ± 106.3	139.6 ± 113.8	0.522
HDL cholesterol, mg/dL	52.7 ± 16.4	55.7 ± 19.4	51.5 ± 14.9	0.077
LDL cholesterol, mg/dL	106.3 ± 30.7	108.4 ± 32.8	105.5 ± 29.9	0.457
Hemoglobin A1c, %	7.5 ± 1.9	8.4 ± 2.4	7.1 ± 1.6	<0.001
Flow-mediated dilation, %	5.3 ± 1.9	6.0 ± 2.8	5.1 ± 2.4	0.006
Brachial IMT, mm	0.33 ± 0.07	0.31 ± 0.07	0.34 ± 0.06	<0.001
Statin use	180 (62)	38 (47)	142 (67)	0.002
Anti-hypertensive agent use	209 (72)	45 (56)	164 (78)	<0.001
Anti-diabetic agent use	254 (87)	70 (86)	184 (87)	0.858

Data are presented as n (%) or mean ± standard deviation.

CAC, coronary artery calcification; HDL, high-density lipoprotein; LDL, low-density lipoprotein; IMT, intima-media thickness

Table 2. Correlation of FMD and brachial IMT with clinical variables

	Brachial IMT		FMD	
	r	p value	r	p value
FMD, %	−0.250	<0.001		
Age, y	0.309	<0.001	−0.287	<0.001
Systolic blood pressure, mmHg	0.146	0.013	−0.168	0.004
Diastolic blood pressure, mmHg	0.109	0.064	−0.076	0.199
Heart rate, bpm	0.113	0.065	0.032	0.604
LDL cholesterol, mg/dL	−0.065	0.272	0.125	0.034
HDL cholesterol, mg/dL	0.015	0.797	0.021	0.717
Triglycerides, mg/dL	0.030	0.629	−0.032	0.611
Hemoglobin A1c, %	−0.087	0.140	0.176	0.003
Log-transformed (CAC score+1)	0.304	<0.001	−0.244	<0.001

HDL, high-density lipoprotein; LDL, low-density lipoprotein; IMT, intima-media thickness; FMD, flow-mediated dilation; CAC, coronary artery calcification

Table 3. Predictors of the presence of coronary artery calcification

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
Age of >60 years	6.024 (3.387–10.713)	<0.001	6.025 (3.091–11.747)	<0.001
Male sex	2.220 (1.319–3.737)	0.003	2.720 (1.392–5.318)	0.003
Smoking	0.921 (0.531–1.598)	0.77	0.761 (0.361–1.603)	0.473
Hypertension	2.562 (1.510–4.347)	<0.001	1.808 (0.992–3.296)	0.053
Dyslipidemia	1.164 (0.693–1.957)	0.566	1.093 (0.601–1.987)	0.772
FMD of <5.1%	1.617 (0.965–2.708)	0.068	0.769 (0.410–1.440)	0.412
Brachial IMT of >0.32 mm	2.589 (1.528–4.385)	<0.001	2.034 (1.098–3.770)	0.024

OR, odds ratio; CI, confidence interval; IMT, intima-media thickness; FMD, flow-mediated dilation

Table 4. CAC score according to brachial IMT and FMD

		Brachial IMT	
		≤0.31 mm	>0.31 mm
FMD	≥6.5%	0 (0, 133), n = 65	31 (0, 183), n = 47
	<6.5	6 (0, 159), n = 80	150 (17, 564), n = 154

CAC, coronary artery calcification; IMT, intima-media thickness; FMD, flow-mediated dilation

Values are expressed as median (25^{th} percentile, 75^{th} percentile).