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ORIGINAL ARTICLE

The inter-arm difference in systolic blood pressure is a novel risk marker for subclinical atherosclerosis in patients with type 2 diabetes

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Recent studies have suggested that the inter-arm blood pressure difference (IAD) is associated with cardiovascular events and mortality. The aim of this study was to assess whether the IAD could be a marker for subclinical atherosclerosis in patients with type 2 diabetes who are at high risk of cardiovascular disease (CVD). In a cross-sectional retrospective study of 206 Japanese patients with type 2 diabetes aged 49–76 years, we examined the correlation of the IAD with the carotid intima-media thickness (IMT), ankle-brachial index (ABI) or cardio ankle vascular index (CAVI). The IAD was positively correlated with the maximum IMT ($r=0.266$, $P<0.0001$), mean IMT ($r=0.209$, $P=0.00726$) or CAVI ($r=0.240$, $P=0.0005$). The IAD was higher in patients with CVD than in those without ($P=0.0020$). A multiple linear regression analysis demonstrated that the IAD was an independent determinant of maximum IMT ($\beta=0.169$, $P=0.0167$), mean IMT ($\beta=0.178$, $P=0.0153$), ABI ($\beta=-0.222$, $P=0.0033$) or CAVI ($\beta=0.213$, $P=0.0011$) after adjusting for known risk factors. The area under the receiver operating characteristic curve (AUC) of the IAD as a predictor of subclinical atherosclerosis was similar to the AUC of the Framingham 10-year coronary heart disease risk score. In conclusion, the IAD could be a novel risk marker for subclinical atherosclerosis in patients with type 2 diabetes.
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Keywords: ankle-brachial index; cardio ankle vascular index; carotid intima-media thickness

INTRODUCTION

Recent evidence suggests that the inter-arm blood pressure difference (IAD) correlates with cardiovascular events and mortality.[1–3] As it reflects the peripheral vascular sclerosis of the upper limbs,[4] the IAD can be the predictor of subclinical atherosclerosis and subsequent cardiovascular events.[3] However, this easily applied clinical tool is not used widely in current medical settings.[5,6]

Cardiovascular disease (CVD) is the primary cause of mortality and morbidity in patients with type 2 diabetes, and several risk factors, including smoking, hypertension and dyslipidemia, have been shown to accelerate the progression of CVD.[7,8] Thus, one of the main targets of practice in patients with type 2 diabetes is to detect early atherosclerotic changes. Currently, atherosclerosis markers, such as the carotid intima-media thickness (IMT), ankle-brachial index (ABI) and cardio ankle vascular index (CAVI), are widely used for clinical evaluations.[9,10] However, given that the number of diabetic patients is increasing rapidly, more easily applied and cost-effective clinical tools that can be utilized with limited medical resources are required to screen for early atherosclerosis.

To the best of our knowledge, no previous reports have examined the linear correlation between the IAD, carotid IMT, ABI or CAVI in patients with type 2 diabetes. Furthermore, few reports have demonstrated the correlation between the IAD and diabetic microangiopathy. In this study, we examined the relationship between the IAD and subclinical atherosclerosis markers, such as carotid IMT, ABI and CAVI, in patients with type 2 diabetes.

METHODS

Patients

We performed a cross-sectional retrospective study in 206 consecutive patients who were hospitalized for the treatment of type 2 diabetes in Matsushita Memorial Hospital from April 2009 to August 2012. We then evaluated the relationship of the IAD in systolic blood pressure (SBP) with the maximum IMT, mean IMT, ABI, CAVI, microvascular complications (including diabetic retinopathy and nephropathy) and various parameters, including serum cholesterol, serum creatinine (Cre), serum uric acid and hemoglobin A1c. All patients provided their demographic, medical history and medication usage details. Body mass index was calculated as weight in kilograms divided by

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height in meters squared. Type 2 diabetes was diagnosed according to the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus.[11] Retinopathy was assessed by the state of mydriasis by ophthalmologists who were blinded to the IAD and was graded as follows: NDR, no diabetic retinopathy; SDR, simple diabetic retinopathy; and PDR, proliferative, including pre-proliferative diabetic retinopathy. If the findings in the left and right fundi were discordant, the worse side was taken as representative of the subject. CVD was defined as previous myocardial or cerebral infarction based on the clinical history or physical examination. The subjects were classified as nonsmokers, past smokers or current smokers according to a self-administered questionnaire. Patients with thoracic aortic dissection, aortic aneurysm, aortic coarctation, syphilitic aortitis, aortic syndrome (Takayasu's disease), and atrial fibrillation or atrial flutter were excluded. Moreover, patients with advanced renal dysfunction (serum Cre $>176.8\,\mu mol\,l^{-1}$), malignant disease, liver cirrhosis, congestive heart failure or hematologic disease were excluded from this study. Approval for the study was obtained from the local research ethics committee, and informed consent was obtained from all patients.

Biochemical analysis

Fasting blood samples were obtained in the morning. Serum triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, serum Cre and serum uric-acid levels were assessed using standard enzymatic methods. Hemoglobin A1c was assayed using high-performance liquid chromatography and was expressed as National Glycohemoglobin Standardization Program units. C-reactive protein was assessed using immunoturbidimetry. Urinary albumin and Cre concentrations were determined using early-morning spot urine. Nephropathy was graded as follows: normoalbuminuria, urinary albumin excretion (UAE) $<30\,mg\,g^{-1}$ Cre; microalbuminuria, 30–$300\,mg\,g^{-1}$ Cre; or macroalbuminuria, $>300\,mg\,g^{-1}$ Cre. UAE was measured with an immunoturbidimetric assay.

Measurement of blood pressure, ankle-brachial index and CAVI

Blood pressure, ABI and CAVI were calculated using the Fukuda Vascular Screening system VaSera VS-1000 (Fukuda Denshi Bunkyo, Tokyo, Japan). Patients rested for 5 min, and then the blood pressures were measured at both upper arms and ankles using an oscillometric method to obtain the ABI and CAVI. A difference in SBP between the arms was expressed as the absolute difference, and these differences were determined for each patient. We calculated the BP difference as the absolute value of right −left (|right −left|). CAVI was calculated in the following manner: $CAVI = a\ [(2\rho/\Delta P) \times \ln(Ps/Pd)PWV^2] + b$, where Ps is SBP, Pd is diastolic blood pressure, PWV is pulse wave velocity (Hasegawa's method), ΔP is Ps −Pd, ρ is blood density and a and b are constants. The SBP and CAVI were evaluated as the larger value of the left or right side, and the ABI was evaluated as the smaller value of the left or right side. The clinic blood pressure was also measured by one nurse trained in the technique of BP measurement, using an appropriate cuff size with an oscillometric monitor with a manual inflator (model HEM412C, Omron Healthcare Muko, Kyoto, Japan). Patients rested for 5 min before the measurements. The patient's arm was kept at the heart level during the measurement.

Measurement of carotid IMT

One trained physician, who was blinded to the IAD, conducted the ultrasonographic scanning of the carotid arteries using a real-time, B-mode ultrasound imaging with a 10-MHz annular array probe (Xario system, Toshiba, Minato, Tokyo, Japan) that provided an axial resolution of 0.1 mm to evaluate early atherosclerosis. We used the guidelines from the Japan Society of Ultrasonic Medicine.[12] With the patients placed in the supine position, the extracranial common carotid artery, carotid bifurcation and internal carotid artery were scanned. The site of the greatest thickness, including the plaque lesions, was sought along the arterial walls. IMT was measured as the distance between two parallel echogenic lines corresponding to the blood-intima and media-adventitia interface on the far wall of the artery. Three determinations of IMT were performed at the thickest point, maximum IMT and two adjacent points (1 cm upstream and 1 cm downstream from this site). These three determinations were averaged to obtain the mean IMT.

Statistical analysis

StatView software (version 5.0; SAS Institute, Cary, NC, USA) was used for the statistical analyses, except for the receiver operating characteristic curve analyses, and $P<0.05$ was considered to be statistically significant. The mean, median or frequencies of potential confounding variables were calculated. Skewed variables, such as triglycerides, C-reactive protein and UAE, were presented as median (interquartile range), and continuous variables were presented as the mean ± s.d. As the triglycerides, C-reactive protein and UAE levels showed a skewed distribution, logarithmic (log) transformation was performed before the correlation and regression analyses. An unpaired Student's *t*-test or an analysis of variance followed by the Tukey–Kramer *post hoc* test was conducted to assess the statistical significance of the between-group differences. The relationships between the IAD, maximum IMT, mean IMT, ABI, CAVI, age, glycemic control or other variables were examined using a linear regression analysis. A multivariate linear regression analysis was performed to adjust the confounding factors of the relationship between the IAD and maximum IMT and the mean IMT, ABI or CAVI. The potential confounding factors included age, sex, diabetes disease duration, body mass index, SBP, heart rate, hemoglobin A1c, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, log (triglycerides), serum Cre, uric acid,

Table 1 Clinical characteristics of patients

n	*206*
Age (years)	62.4 ± 13.5
Sex (male/female)	120/86
Duration of diabetes (years)	12.1 ± 10.5
Body mass index ($kg\,m^{-2}$)	25.1 ± 4.7
Systolic blood pressure (mm Hg)	141.5 ± 19.9
Diastolic blood pressure (mm Hg)	85.1 ± 11.9
Inter-arm blood pressure difference (mm Hg)	6.0 ± 5.1
Heart rate (beats per min)	72.3 ± 14.1
Hemoglobin A1c (%)	10.2 ± 2.0
High-density lipoprotein cholesterol ($mmol\,l^{-1}$)	1.3 ± 0.5
Low-density lipoprotein cholesterol ($mmol\,l^{-1}$)	2.9 ± 1.0
Triglycerides ($mmol\,l^{-1}$)	1.6 (1.0–2.5)
C-reactive protein ($mmol\,l^{-1}$)	9.1 (3.8–19.1)
Creatinine ($\mu mol\,l^{-1}$)	70.7 ± 41.5
Uric acid ($\mu mol\,l^{-1}$)	341.4 ± 626.3
Smoking (none/past/current)	130/46/30
Retinopathy (NDR/SDR/PDR)	120/56/30
Nephropathy (normo-/micro-/macroalbuminuria)	103/78/25
Cardiovascular disease (−/+)	161/45
Urinary albumin excretion ($mg\,g^{-1}$ creatinine)	29.9 (11.2–97.0)
Insulin treatment (−/+)	147/59
Antidiabetes drugs (−/+)	55/151
Anti-gout drugs (−/+)	187/19
Anti −platelets (−/+)	169/37
ACE-I/ARB (−/+)	129/77
CCB (−/+)	139/67
Diuretics (−/+)	178/28
Statins (−/+)	128/78
Fibrates (−/+)	205/1
Maximum intima-media thickness	1.3 ± 0.7
Mean intima-media thickness	0.9 ± 0.3
Ankle-brachial index	1.1 ± 0.6
Cardio ankle vascular index	9.2 ± 2.0

Abbreviations: ACE-I, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CCB, calcium channel blockers; NDR, no diabetic retinopathy; PDR, proliferative diabetic retinopathy; SDR, simple diabetic retinopathy.
Data are number of patients, mean ± s.d. or median (interquartile range).

log (C-reactive protein) and smoking status. Receiver operator characteristic analyses were performed to calculate the area under the receiver operating characteristic curve (AUC) of the IAD or the Framingham 10-year coronary heart disease risk score (FRS) for subclinical atherosclerosis, which was defined as the maximum IMT $\geqslant$1.55 mm and mean IMT $\geqslant$1.05 mm, according to previous reports.[13] We used the ROCKIT (http://xray.bsd.uchicago.edu/krl/roc_soft.htm) for calculation and comparison of the receiver operating characteristic curves in the present study.

RESULTS

The clinical characteristics of 206 patients with type 2 diabetes enrolled in this study are shown in Table 1. Among the 206 patients, the mean IAD was 6.0 ± 5.1 mm Hg. Relationships between the IAD and other variables are shown in Table 2. The IAD was positively correlated with the maximum IMT, mean IMT, CAVI or log (UAE). The IAD was higher in the patients with proliferative diabetic retinopathy than in those with no diabetic retinopathy ($P<0.0001$) or simple diabetic retinopathy ($P=0.0021$), and the IAD was higher in the patients with macroalbuminuria than in those with normoalbuminuria ($P=0.0004$) or microalbuminuria ($P=0.0037$). The IAD was higher in the patients with CVD than in those without CVD ($P=0.0020$; Table 3).

A multiple linear regression analysis demonstrated that the IAD was an independent determinant of the maximum IMT ($\beta=0.169$, $P=0.0167$), mean IMT ($\beta=0.178$, $P=0.0153$), ABI ($\beta=-0.222$, $P=0.0033$) or CAVI ($\beta=0.213$, $P=0.0011$) after adjusting for age, sex, diabetes disease duration, body mass index, SBP, heart rate, hemoglobin A1c, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, log (triglycerides), Cre, uric acid, log (C-reactive protein), and smoking status or concomitant medications (Table 4).

The AUCs for the IAD and FRS for the maximum IMT $\geqslant$1.55 mm were 0.617 ($P=0.159$) and 0.656 ($P=0.060$), respectively ($P=0.3064$). The optimal cutoff points were 8.0 and 13.0 for the IAD and FRS, respectively (Figure 1a). The AUCs for the IAD and FRS for the mean IMT $\geqslant$1.05 mm were 0.589 ($P=0.030$) and 0.708 ($P<0.001$), respectively ($P=0.3339$). The optimal cutoff points for the IAD and FRS were 9.0 and 20.0, respectively (Figure 1b).

Table 2 Correlation between the inter-arm blood pressure difference and other variables

	R	P-*value*
Age (years)	0.170	0.0143
Duration of diabetes (years)	0.012	0.8659
Body mass index (kg m^{-2})	0.061	0.3840
Systolic blood pressure (mm Hg)	0.289	<0.0001
Heart rate (beats per min)	0.076	0.2771
Hemoglobin A1c (%)	−0.037	0.5970
High-density lipoprotein cholesterol (mmol l^{-1})	0.003	0.9673
Low-density lipoprotein cholesterol (mmol l^{-1})	−0.102	0.1445
Logarithm of triglycerides	−0.088	0.2066
Creatinine (μmol l^{-1})	−0.079	0.2617
Uric acid (μmol l^{-1})	−0.087	0.2159
Logarithm of C-reactive protein	0.067	0.3415
Logarithm of urinary albumin excretion	0.238	0.0006
Maximum intima-media thickness	0.266	<0.0001
Mean intima-media thickness	0.209	0.0026
Ankle-brachial index	−0.098	0.1608
Cardio ankle vascular index	0.240	0.0005

DISCUSSION

Our study showed that the IAD correlates with the atherosclerosis markers, including the maximum IMT, mean IMT, ABI and CAVI. The association was independent of the SBP, glycemic control, duration of diabetes and other conventional CVD risk factors. Moreover, as predictors of subclinical atherosclerosis, the AUCs of the IAD, including the maximum and mean IMTs, were similar to the AUCs of the FRS, which is a useful predictive score for future CVD.

The diastolic blood pressure -IAD did not correlate with the markers for subclinical atherosclerosis, including the maximum IMT ($r=0.069$, $P=0.3338$), mean IMT ($r=0.058$, $P=0.4126$), ABI ($r=0.013$, $P=0.8525$) or CAVI ($r=-0.018$, $P=0.7958$). The diastolic blood pressure IAD could not be a marker of subclinical atherosclerosis, contrary to the SBP-IAD.

Table 3 Comparisons of the inter-arm blood pressure difference in various groups

	Inter-arm blood pressure difference	P-*value*
Retinopathy (NDR/SDR/PDR)	4.93 ± 4.24/6.28 ± 4.56/9.70 ± 7.04*,**	<0.0001
Nephropathy (normo-/micro-/macroalbuminuria)	5.28 ± 5.19/5.90 ± 4.23/9.24 ± 5.92†,††	0.0459
Cardiovascular disease (−/+)	5.42 ± 5.10/8.04 ± 4.46	0.0020
Smoking (none/past/current)	6.15 ± 5.34/5.87 ± 5.14/5.50 ± 3.68	0.5303
Insulin treatment (−/+)	5.91 ± 5.06/6.16 ± 5.18	0.7565
Antidiabetic drugs (−/+)	5.56 ± 4.61/6.20 ± 5.23	0.4341
Anti-gout drugs (−/+)	6.08 ± 5.14/5.33 ± 4.85	0.5873
Antiplatelets (−/+)	5.80 ± 5.27/7.21 ± 4.06	0.1449
ACE-I and/or ARB (−/+)	5.90 ± 4.20/6.25 ± 6.44	0.6437
CCB (−/+)	5.81 ± 4.17/6.49 ± 6.75	0.3829
Diuretics (−/+)	5.99 ± 5.31/6.25 ± 3.38	0.8187
Statins (−/+)	5.68 ± 4.36/6.51 ± 6.23	0.2688

Abbreviations: ACE-I, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CCB, calcium channel blockers; NDR, no diabetic retinopathy; PDR, proliferative diabetic retinopathy; SDR, simple diabetic retinopathy.
*$P<0.0001$ vs NDR.
**$P=0.0021$ vs SDR.
†$P=0.0004$ vs normoalbuminuria.
††$P=0.0037$ vs microalbuminuria.

Table 4 Multivariate linear regression analysis on the relationship between the IAD and markers of subclinical atherosclerosis

	Maximum IMT		*Mean IMT*		*ABI*		*CAVI*	
	B	P-*value*	*β*	P-*value*	*β*	P-*value*	*β*	P-*value*
Age (years)	0.311	0.0002	0.213	0.0119	0.039	0.6506	0.377	<0.0001
Sex (male/female)	0.058	0.4129	0.108	0.1437	−0.127	0.0899	0.178	0.0063
Duration of diabetes (years)	0.101	0.1994	0.047	0.5647	0.065	0.4272	−0.006	0.9270
Body mass index (kg m^{-2})	−0.071	0.3709	−0.147	0.0745	0.112	0.1812	−0.222	0.0025
Systolic blood pressure (mm Hg)	0.224	0.0019	0.070	0.3482	0.250	0.0011	0.049	0.4496
Heart rate (beats per min)	−0.033	0.6414	0.031	0.6782	−0.074	0.3224	0.115	0.0765
Hemoglobin A1c (%)	0.043	0.5505	0.081	0.2785	0.016	0.8291	−0.053	0.4181
HDL-C (mmol l^{-1})	−0.046	0.5276	−0.052	0.4956	−0.253	0.0011	0.117	0.0785
LDL-C (mmol l^{-1})	−0.046	0.5048	0.113	0.1175	−0.024	0.7474	−0.005	0.9334
Log (triglycerides)	0.096	0.1938	0.05	0.9446	−0.034	0.6651	0.083	0.2171
Creatinine (μmol l^{-1})	−0.065	0.3599	0.09	0.8968	−0.140	0.0606	0.105	0.1024
Uric acid (μmol l^{-1})	−0.038	0.5652	0.073	0.2882	−0.028	0.6854	0.038	0.5312
Log (C-reactive protein)	−0.001	0.9846	0.016	0.8363	−0.151	0.0619	0.048	0.4892
Smoking status	−0.042	0.5309	−0.044	0.5442	−0.032	0.6599	−0.042	0.5076
ACEI/ARB	−0.013	0.8544	0.024	0.7465	0.007	0.9234	0.026	0.6919
Statins	−0.052	0.4882	0.031	0.6923	−0.007	0.9249	−0.012	0.8627
IAD	0.169	0.0167	0.178	0.0153	−0.214	0.0044	0.213	0.0010

Abbreviations: ABI, ankle brachial index; CAVI, cardio ankle vascular index; HDL-C, high-density lipoprotein cholesterol; IAD, inter-arm blood pressure; IMT, intima-media thickness; LDL-C, low-density lipoprotein cholesterol; Log, logarithm.

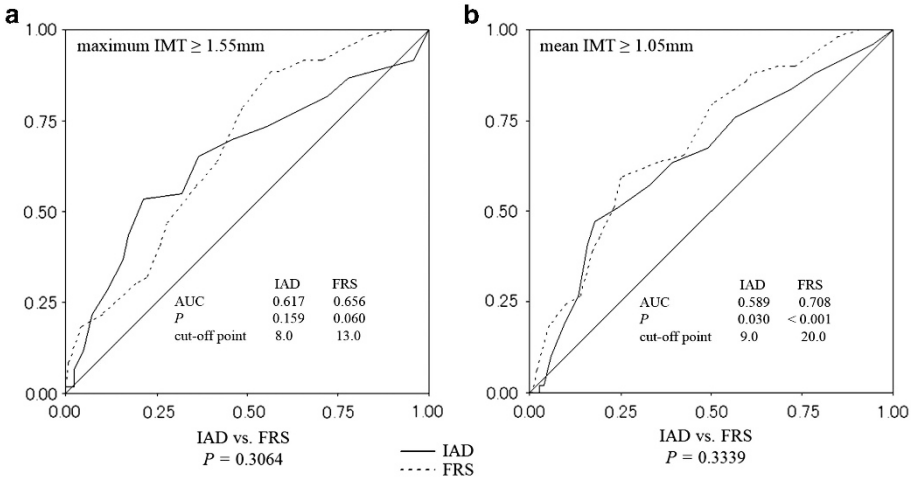

Figure 1 Receiver operating characteristic (ROC) curve and area under the ROC curve (AUC) showing the ability of inter-arm blood pressure difference (IAD) and Framingham 10-year coronary heart disease risk score (FRS) to predict maximum intima-media thickness (IMT)⩾1.55 mm and mean IMT⩾1.05 mm. We compared AUC (95% confidence interval (CI)) between the two groups using the ROCKIT.

The IAD is an easily applied clinical tool. An appreciation of the presence of the IAD is recommended to accurately diagnosis and manage of hypertension, as the current guidelines of American College of Cardiology Foundation and American Heart Association recommend assessing at the initial visit.[14] Historically, the IAD has been dismissed as a normal variant.[15] O'Shea and Murphy[16] suggested an anatomical explanation for this phenomenon while Frank *et al.*[17] described it as a sign of aortic aneurysm or vascular disease. However, some studies have suggested that the difference is caused by atherosclerotic changes of the large vessels, which gives the IAD a prognostic value as a marker for predicting cardiovascular events.[18,19] Peripheral vascular disease is proposed to be the underlying mechanism of the IAD.[18,19] Moll *et al.*[20] suggested that 83% of patients with an IAD in SBP had evidence of innominate subclavian artery stenosis. Clark *et al.*[21] suggested that the IAD may be a marker for peripheral vascular disease. Moreover, Okada *et al.*[22] demonstrated that an IAD in SBP and a difference between the lower limbs could be a novel risk marker for diabetic nephropathy in patients with type 2 diabetes. Together, these findings indicate that the IAD might correlate with micro- and macrovascular complications in patients with type 2 diabetes.

The fact that the IAD correlates not only with carotid IMT, ABI and CAVI but also with retinopathy and nephropathy supports that there is a common underlying mechanism, including age, duration of diabetes, SBP, hemoglobin A1c and low-density lipoprotein cholesterol, in the development of micro- and macroangiopathy in patients with type 2 diabetes. Therefore, we have excluded retinopathy and nephropathy as the potential confounding factors in these

multivariate linear regression analyses. Cheung *et al.*[23] have reported that diabetic retinopathy is an independent predictor of CVD. As for the nephropathy, Simons *et al.*[24] have suggested that an abnormal UAE correlates with CVD in both diabetic and nondiabetic populations. The micro- and macroangiopathy share the common components, including endothelial dysfunction, inflammation, neovascularization, apoptosis and hypercoagulation. Brownlee[25] have shown that a single unifying process of diabetes complications is the hyperglycemia-induced overproduction of superoxide by the mitochondrial electron transport chain. The mitochondrial overproduction of superoxide activates four damaging pathways: the polyol pathway, hexosamine pathway, protein kinase C pathway and advanced glycation end products' formation. In addition, Araki *et al.*[26] have demonstrated that both increased UAE and brachial-ankle PWV are independent factors associated with the abnormal formation of spontaneous microaggregation of platelets in patients with type 2 diabetes. Therefore, the IAD suggests new avenues to detect micro- and macrovascular complications. Further research is needed to better assess the relationship between the IAD and micro- and macrovascular complications in patients with type 2 diabetes.

Study limitations

To our knowledge, this report is the first to investigate the linear correlation between the IAD and markers of subclinical atherosclerosis and microangiopathy in patients with type 2 diabetes. However, this study has some limitations that require consideration. First, this study used a cross-sectional retrospective design that did not permit the determination of causality. Second, this single-site study used a relatively small sample size. Thus, the study population might not accurately represent the underlying population. Third, it would be interesting to compare the IAD in this study with the IADs in clinical or home settings to examine the relationships between the markers for subclinical atherosclerosis. Unfortunately, we do not have the IAD data from clinics or home blood pressure monitoring. Finally, this study included only Japanese patients; therefore, cultural and socio-demographic differences may have affected our results.

CONCLUSION

The IAD in SBP was positively correlated with the markers of subclinical atherosclerosis, including carotid IMT, ABI and CAVI. Assessing the IAD could be one of the most easily applied clinical tools for detecting macrovascular complications in patients with type 2 diabetes.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

1 Clark CE, Taylor RS, Shore AC, Campbell JL. The difference in blood pressure readings between arms and survival: primary care cohort study. *BMJ* 2012; **344**: e1327.
2 Agarwal R, Bunaye Z, Bekele DM. Prognostic significance of between-arm blood pressure differences. *Hypertension* 2008; **51**: 657–662.
3 Clark CE, Campbell JL, Powell RJ. The interarm blood pressure difference as predictor of cardiovascular events in patients with hypertension in primary care: cohort study. *J Hum Hypertens* 2007; **21**: 633–638.
4 Clark CE, Powell RJ. The differential blood pressure sign in general practice: prevalence and prognostic value. *Fam Pract* 2002; **19**: 439–441.
5 Gosse P. Blood pressure should be measured in both arms on the first consultation. *J Hypertens* 2002; **20**: 1045–1046.
6 Materson B. Inter-arm blood pressure differences. *J Hypertens* 2004; **22**: 2267–2268.
7 Isomaa B, Almgren P, Tuomi T, Forsén B, Lahti K, Nissén M, Taskinen MR, Groop L. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 2001; **24**: 683–689.
8 Multiple Risk Factor Intervention Trial Research Group. Multiple risk factor intervention trial. Risk factor changes and mortality results. *JAMA* 1982; **248**: 1465–1477.
9 Hayashi C, Ogawa O, Kubo S, Mitsuhashi N, Onuma T, Kawamori R. Ankle brachial pressure index and carotid intima-media thickness as atherosclerosis markers in Japanese diabetes. *Diab Res Clin Pract* 2004; **66**: 269–275.
10 Wakabayashi I, Masuda H. Relationships between vascular indexes and atherosclerotic risk factors in patients with type 2 diabetes mellitus. *Angiology* 2008; **59**: 567–573.
11 Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 2003; **26**: S5–20.
12 Terminology and Diagnostic Criteria Committee, Japan Society of Ultrasonics in Medicine. Subcommittee for Preparing Guidelines for Ultrasound Diagnosis of Carotid Artery: Standard method for ultrasound evaluation of carotid artery lesions. *Jpn J Med Ultrasonics* 2009; **36**: 501–518.
13 Irie Y, Sakamoto K, Kubo F, Okusu T, Katura T, Yamamoto Y, Umayahara Y, Katakami N, Kaneto H, Kashiyama T, Ueda Y, Kosugi K. Association of coronary artery stenosis with carotid atherosclerosis in asymptomatic type 2 diabetic patients. *J Atheroscler Thromb* 2010; **18**: 337–344.
14 Aronow WS, Fleg JL, Pepine CJ, Artinian NT, Bakris G, Brown AS, Ferdinand KC, Forciea MA, Frishman WH, Jaigobin C, Kostis JB, Mancia G, Oparil S, Ortiz E, Reisin E, Rich MW, Schocken DD, Weber MA, Wesley DJ, Harrington RAACCF Task Force. ACCF/AHA 2011 Expert Consensus Document on Hypertension in the Elderly: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *Circulation* 2011; **123**: 2434–2506.
15 Clark CE, Campbell JL, Evans PH, Millward A. Prevalence and clinical implications of the inter-arm blood pressure difference: a systematic review. *J Hum Hypertens* 2006; **20**: 923–931.
16 O'Shea JC, Murphy MB. Ambulatory blood pressure monitoring: which arm? *J Hum Hypertens* 2000; **14**: 227–230.
17 Frank SM, Norris EJ, Christopherson R, Beattie C. Right and left arm blood pressure discrepancies in vascular surgery patients. *Anesthesiology* 1991; **75**: 457–463.
18 Orme S, Ralph SG, Birchall A, Lawson-Matthew P, McLean K, Channer KS. The normal range for inter-arm differences in blood pressure. *Age Ageing* 1999; **28**: 537–542.
19 Kimura A, Hashimoto J, Watabe D, Takahashi H, Ohkubo T, Kikuya M, Imai Y. Patient characteristics and factors associated with inter-arm difference of blood pressure measurements in a general population in Ohasama, Japan. *J Hypertens* 2004; **22**: 2277–2283.
20 Moll F, Six J, Mutsaerts D. Misleading upper extremity blood pressure measurements in vascular occlusive disease. *Bruit* 1983; **8**: 18–19.
21 Clark CE. Difference in blood pressure between arms might reflect peripheral vascular disease. *BMJ* 2001; **323**: 399–400.
22 Okada H, Fukui M, Tanaka M, Matsumoto S, Mineoka Y, Nakanishi N, Asano M, Yamazaki M, Hasegawa G, Nakamura N. A difference in systolic blood pressure between arms and between lower limbs is a novel risk marker for diabetic nephropathy in patients with Type 2 diabetes. *Hypertens Res* 2013; **36**: 403–407.
23 Cheung N, Wang JJ, Klein R, Couper DJ, Sharrett AR, Wong TY. Diabetic retinopathy and the risk of coronary heart disease: the atherosclerosis risk in communities study. *Diabetes Care* 2007; **30**: 1742–1746.
24 Simons PC, Algra A, Bots ML, Grobbee DE, van der Graaf Y. Common carotid intima-media thickness and arterial stiffness: indicators of cardiocvascular risk in high-risk patients. The SMART Study (Second Manifestations of ARTerial disease). *Circulation* 1999; **100**: 951–957.
25 Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. *Diabetes* 2005; **54**: 1615–1625.
26 Araki S, Matsuno H, Haneda M, Koya D, Kanno Y, Itho J, Kishi A, Isshiki K, Sugimoto T, Maegawa H, Kashiwagi A, Uzu T. Correlation between albuminuria and spontaneous platelet microaggregate formation in type 2 diabetic patients. *Diabetes Care* 2009; **32**: 2062–2067.