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ORIGINAL RESEARCH

Variability in Annual Fasting Glucose and the Risk of Peripheral Artery Disease in Patients with Diabetes Mellitus

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Purpose: High glucose concentrations and swings are associated with endothelial dysfunction. We examined the effects of variability in fasting plasma glucose on peripheral artery disease (PAD) in patients with diabetes mellitus (DM).

Patients and Methods: In this screening study for the risk factors of PAD, we retrospectively collected data on the ankle-brachial index (ABI) and the percentage of mean arterial pressure (% MAP) at the ankle between August 01, 2016 and July 31, 2017. We defined low ABI ≤0.90, high % MAP ≥45%, or both as high-risk PAD and others as low-risk PAD. We compared the standard deviation (SD) of the first fasting plasma glucose data available each year after January 01, 2007.

Results: In 2577 patients, a higher SD of annual fasting glucose was observed in those with an ABI ≤0.90 than in patients with an ABI >0.90 (2.6 ± 2.1 vs 2.2 ± 2.3, P = 0.009), and in patients with %MAP ≥45% than in those with %MAP <45% (2.4 ± 2.1 vs 2.2 ± 2.3, P = 0.034). A high-risk PAD was significantly associated with the SD (P = 0.032) but not with the mean (P = 0.338) of annual fasting glucose. The former was an independent risk factor for high-risk PAD (odds ratio = 1.424; 95% CI = 1.118–1.814; P = 0.004).

Conclusion: Variability but not mean of annual fasting plasma glucose was significantly associated with a high risk of PAD in patients with DM.

Keywords: ankle-brachial index, arterial stiffness, lower extremity arterial disease, percentage of the mean arterial pressure, standard deviation

Introduction

Peripheral artery disease (PAD) of the lower extremities is characterized by arterial occlusion caused by atherosclerosis.[1] PAD is associated with disability and mortality,[2,3] and carries considerable economic and humanistic burdens worldwide.[4,5] Based on the American Heart Association/American College of Cardiology guidelines set in 2016 for the management of patients with lower-extremity PAD, the resting ankle-brachial index (ABI) is the priority diagnostic test.[6] According to the definition of ABI ≤ 0.90, the global prevalence of PAD was 5.56% in adults ≥ 25 years of age,[7] and the lifetime risk of PAD was 19%–30% in the USA.[8,9]

Diabetes mellitus (DM) is a metabolic disorder associated with several chronic complications, including PAD.[10] Because the number of people with DM is growing worldwide, DM is a major risk factor that increases PAD prevalence significantly.[11] According to a report from the International Diabetes Federation, the global number of patients with DM was 463 million in 2019 and will rise to approximately 700 million by 2045 in the population aged 20–79 years.[12,13]

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Among traditional markers for glycemic control, hemoglobin A1c (HbA1c) level was shown to be more strongly associated with PAD development than the fasting glucose level in patients with established DM in the Atherosclerosis Risk in Communities study.[14] However, fasting glucose provided a better contribution to predict cardiovascular events than HbA1c in Taiwanese patients with type 2 DM.[15] It was recently reported that normal coronary artery was associated with a higher HbA1c level compared with documented coronary atherosclerosis on coronary computed tomography angiography in patients with type 2 DM.[16] Variabilities in HbA1c and fasting glucose have been reported to be associated with cardiovascular disease.[17–19] However, in the Multi-Ethnic Study of Atherosclerosis study, mean fasting glucose was the important predictor of cardiovascular events and mortality, and variability of fasting glucose was not significantly associated with cardiovascular events or mortality after adjustment for mean fasting glucose during follow-up.[20]

Measuring the blood pressure of the ankle was postulated as a screening method for PAD in the 1950s, and brought about ABI development.[21] However, the ABI values would unexpectedly increase due to arterial stiffness and reduce the sensitivity of the PAD diagnosis, especially in older people or those with DM and chronic kidney disease (CKD).[22–24] It has been reported that the percentage of mean arterial pressure (%MAP) calculated using pulse volume recording at the ankle could enhance the sensitivity for the diagnosis of PAD.[25,26] Furthermore, a combination of ABI and %MAP is useful in the prediction of all-cause mortality.[27]

Recent evidence has shown that HbA1c variability is related to a decrease in ABI and an increase in %MAP in patients with DM.[28] However, HbA1c variability is associated with not only changes in plasma glucose, but also several factors influencing the rate of glycation and hemoglobin level.[29] There is a lack of investigation to assess the relationship between %MAP and glucose variability. Since a combination of low ABI and high %MAP carries a high mortality risk in patients with DM,[30] we hypothesized that glucose variability is associated with ABI and %MAP in patients with DM. Therefore, this screening study investigated whether glucose variability, as estimated by the standard deviation (SD) of annual fasting plasma glucose, is significantly associated with PAD, reflected by either high %MAP or low ABI, in patients with DM.

Patients and Methods

Study Design and Subjects

We conducted this screening study to investigate the risk factors of PAD at Taichung Veterans General Hospital in Taiwan. We retrospectively reviewed the medical information of patients with DM who had undergone assessments of ABI with %MAP between August 01, 2016 and July 31, 2017. We collected anthropometric and biochemical data within 3 months of ABI assessment, as well as the first available data of fasting plasma glucose levels each year before the ABI assessment. Patients were excluded if they (1) did not have complete laboratory data within three months of ABI assessment, (2) had a history of lower-extremity surgery, (3) had end-stage renal disease, (4) had evidence of non-compressible vessels as indicated by ABI values > 1.40 in both lower limbs; and (5) fewer than three data points of annual fasting plasma glucose before ABI assessment. Data collection was performed by reviewing electronic medical records from January 01, 2007.

Biochemistry Assessments

Biochemical data measured in the central laboratory of our hospital were collected, including fasting plasma glucose, HbA1c, total cholesterol, triglycerides, and creatinine. Plasma glucose levels were measured using the oxidase-peroxidase method (Wako Diagnostics, Tokyo, Japan). HbA1c was measured using cation-exchange high-performance liquid chromatography (certified by the NGSP; G8, TOSOH, Tokyo, Japan). Total cholesterol, triglycerides, and creatinine levels were measured using commercial kits (Beckman Coulter, Fullerton, USA). The estimated glomerular filtration rate (eGFR) value was calculated as $186 \times [\text{serum creatinine (mg/dL)}]^{-1.154} \times [\text{age (years)}]^{-0.203}$ ($\times$ 0.742, if female) according to the Modification of Diet in Renal Disease equation, and an eGFR < 60 mL/min/1.73m^2 was defined as CKD.[31] The glucose variability was evaluated using the SD of the annual fasting glucose levels.

The Profile of PAD

ABI values were measured using a validated automatic device (VP-1000 Plus; Omron Healthcare Co. Ltd., Kyoto, Japan). The brachial-ankle pulse wave velocity (baPWV) values were calculated as the ratio of the brachial-ankle path to the brachial-ankle pulse transmission time. Only the lower ABI value and higher baPWV value between the lower limbs of the same patient were recorded

for analyses. %MAP, which was determined based on the ankle pulse volume waveforms, indicates the height of the mean arterial wave area divided by the peak amplitude. The reproducibility of ABI, %MAP, and baPWV has been shown in a previous study.[28] We collected only the data of the last ABI record in patients with repeated ABI assessments during the enrollment period. Abnormal ABI was defined as an ABI value ≤ 0.90 and abnormal %MAP was defined as a %MAP value ≥ 45%. Finally, high-risk PAD was defined as abnormal ABI, abnormal %MAP, or both.

Statistical Analysis

Continuous data are presented as the mean ± SD. Categorical data are presented as numbers (percentages). High fasting glucose was defined as a plasma glucose level ≥ 8 mmol/L which was the average plasma level of fasting glucose detected around the ABI assessment. Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg, diastolic blood pressure (DBP) ≥ 90 mmHg, history of hypertension, or current use of antihypertensive drugs. Statistical analyses were performed using the independent sample *t*-test to compare the differences in continuous variables between two groups. One-way analysis of variance was conducted to detect the differences in continuous variables among more than two groups. Chi-square tests were used to detect differences in categorical variables. Multivariate logistic regression analysis was carried out to evaluate factors associated with high-risk PAD. Statistical analyses were performed using SPSS 22.0 (IBM., Armonk, NY, USA).

Results

A total of 2861 patients were assessed, and 2577 patients who met the study criteria were enrolled; 2377 were assigned to ABI > 0.90 and 200 to ABI ≤ 0.90. We then divided the patients into four subgroups based on whether %MAP was ≥ 45% or not. Overall, we defined ABI > 0.90 and %MAP < 45% as the low-risk PAD group (n = 2117), and the remaining patients (n = 460) were categorized into the high-risk PAD group (Figure 1).

The demographic and clinical characteristics of the enrolled patients are shown in Table 1. The mean age of the enrolled patients was 66 ± 10 years, and 1364 (52.9%) were male. Patients with an ABI ≤ 0.90 were significantly older than those with an ABI > 0.90 (72 ± 12 vs 65 ± 10 years, P < 0.001). Patients with an ABI ≤ 0.90 had a higher proportion of coronary artery disease (CAD; 31.5% vs 9.0%, P < 0.001), a higher proportion of hypertension (98.5% vs 78.0%, P < 0.001), higher SBP (143 ± 24 vs 136 ± 19 mmHg, P < 0.001), lower DBP (74 ± 12 vs 77 ± 11 mmHg, P < 0.001), higher triglycerides (1.7 ± 1.1 vs 1.5 ± 1.2, P = 0.014), and lower eGFR (61 ± 31 vs 79 ± 27 mL/min/1.73m^2, P < 0.001) than those with an ABI > 0.90. Moreover, a higher %MAP (47.1 ± 5.1 vs 40.5 ± 3.8%, P < 0.001) and baPWV (2015 ± 686 vs 1856 ± 437 cm/sec, P < 0.001) were also noted in patients with ABI ≤ 0.90, compared to those with ABI > 0.90.

The characteristics of the patients with %MAP ≥ 45% and %MAP < 45% are also shown in Table 1. Patients with %MAP ≥ 45% were older (P < 0.001) and more likely to be female (P = 0.002). Higher SBP and lower DBP (P < 0.001 and P = 0.002, respectively), higher proportion of CAD (P < 0.001) and hypertension (P < 0.001), lower eGFR (P < 0.001), lower ABI (P < 0.001), and higher baPWV (P < 0.001) were observed in patients with %MAP ≥ 45% than in those with %MAP < 45%.

Notably, the SD of annual fasting glucose was significantly higher in patients with ABI ≤ 0.90 than in those with ABI > 0.90 (2.6 ± 2.1 vs 2.2 ± 2.3 mmol/L, P = 0.009). The SD of annual fasting glucose was significantly higher in patients with %MAP ≥ 45% than in those with %MAP < 45% (2.4 ± 2.1 vs 2.2 ± 2.3 mmol/L, P = 0.034). However, the mean level of annual fasting glucose showed no significant difference between patients with ABI ≤ 0.90 and ABI > 0.90 (8.6 ± 2.1 vs 8.4 ± 2.1 mmol/L, P = 0.326) or between patients with %MAP ≥ 45% and %MAP < 45% (8.5 ± 2.1 vs 8.4 ± 2.1 mmol/L, P = 0.229).

Several factors were associated with both ABI < 0.90 and %MAP ≥ 45%. Hence, we divided all patients into four groups: ABI > 0.90 with %MAP < 45%, ABI > 0.90 with %MAP ≥ 45%, ABI ≤ 0.90 with %MAP <45%, and ABI ≤ 0.90 with %MAP ≥ 45%. The characteristics of the patients in these four groups are shown in Table 2. The mean level of annual fasting glucose was not significantly different among these four groups (P for trend = 0.229, Figure 2). However, the SD of annual fasting glucose showed a significantly positive trend from the ABI > 0.90 with %MAP < 45% group to the ABI ≤ 0.90 with %MAP ≥ 45% group (P for trend = 0.005, Figure 2).

We defined the ABI > 0.90 with %MAP < 45% group as low-risk PAD and the other three groups, those were the ABI > 0.90 with %MAP ≥ 45%, ABI ≤ 0.90 with %MAP <45%, and ABI ≤ 0.90 with %MAP ≥ 45% groups, as high-risk PAD (Table 2). Patients with high-risk PAD had a higher SD of annual fasting glucose than those with low-risk PAD. Patients with high-risk PAD were older (71 ± 12

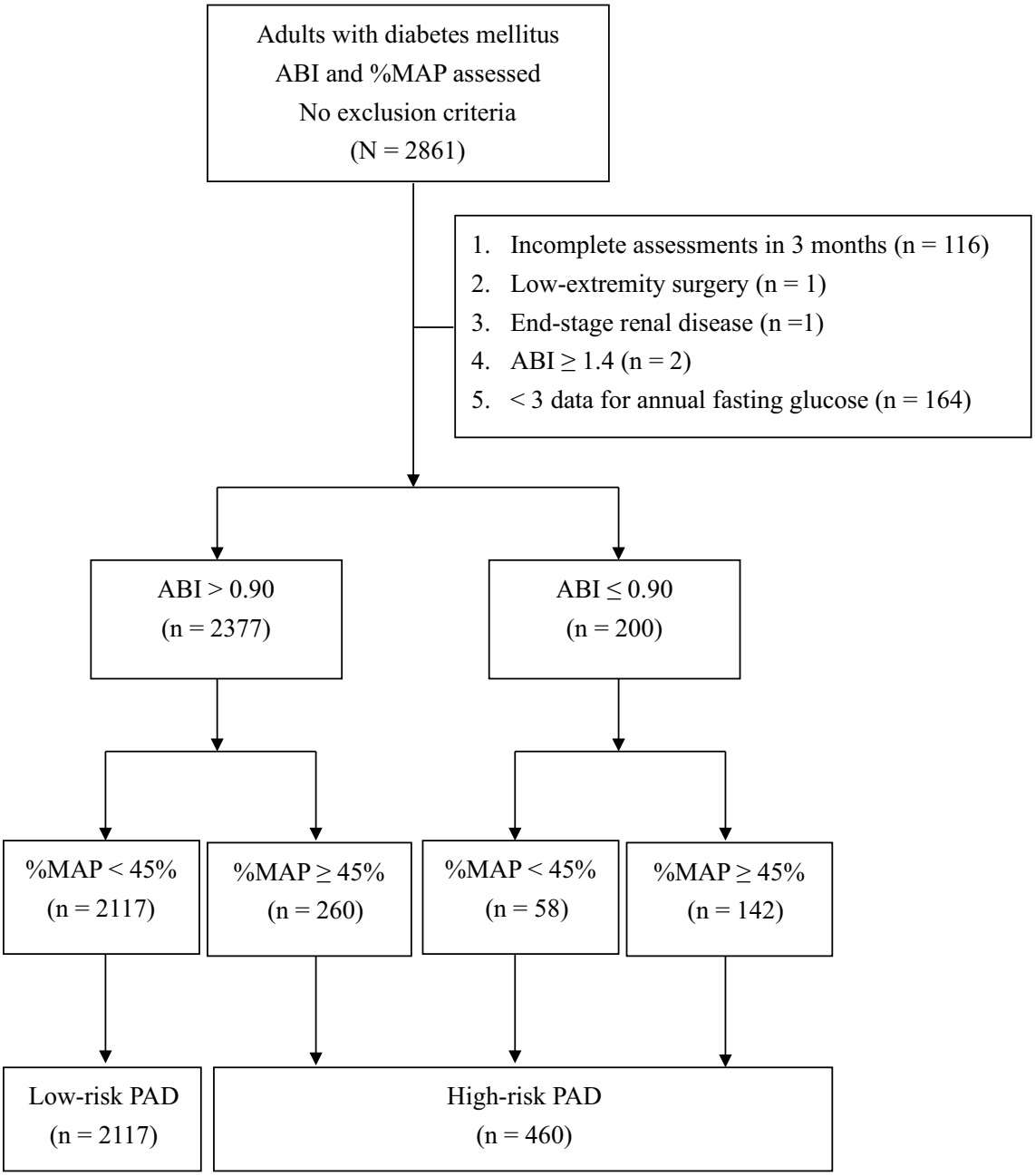

Figure 1 Flowchart for the enrollment and evaluation of study participants (%MAP: percentage of the mean arterial pressure; ABI: ankle-brachial index; PAD: peripheral artery disease).

vs 65 ± 10 years, P < 0.001), lower proportion of male gender (46.3% vs 54.4%, P = 0.002), higher proportion of CAD (21.3% vs 8.5%, P < 0.001), lower eGFR (67 ± 32 vs 80 ± 26 mL/min/1.73m^2, P < 0.001), higher proportions of current using antiplatelet agents (46.1% vs 26.8%, P < 0.001) and insulin (29.3% vs 22.2%, P = 0.001), and lower proportions of current using metformin (28.9% vs 37.8%, P < 0.001) and sodium glucose cotransporter 2 (SGLT2) inhibitors (5.4% vs 11.1%, P < 0.001) than those with low-risk PAD. Patient with high-risk PAD also had higher proportion of hypertension than those with low-risk PAD (90.4% vs 77.2%, P < 0.001).

Since a cutoff value for the SD of annual fasting glucose is not available in clinical practice, we conducted the analyses of receiver operating characteristic curve to differentiate high-risk PAD based on the SD of annual fasting glucose. Using a cut off of 1.274 mmol/L provided a relatively high sensitivity (70.0%) and

Table 1 Characteristics of Enrolled Patients Categorized Based on ABI Value or %MAP Value

	All (N = 2577)			ABI > 0.90 (n = 2377)			ABI ≤ 0.90 (n = 200)			P[a]	%MAP < 45% (n = 2175)			%MAP ≥ 45% (n = 402)			P[b]
Age (year)	66	±	10	65	±	10	72	±	12	<0.001	65	±	10	71	±	12	<0.001
Male, n (%)	1364		(52.9%)	1255		(52.8%)	109		(54.5%)	0.697	1180		(54.3%)	184		(45.8%)	0.002
Current smoking, n (%)	300		(11.6%)	276		(11.6%)	24		(12.0%)	0.960	263		(12.1%)	37		(9.2%)	0.115
CAD, n (%)	277		(10.7%)	214		(9.0%)	63		(31.5%)	<0.001	190		(8.7%)	87		(21.6%)	<0.001
BMI (kg/m^2)	25.8	±	4.0	25.8	±	4.0	26.2	±	4.0	0.130	25.9	±	3.9	25.6	±	4.3	0.280
Systolic BP (mmHg)	137	±	20	136	±	19	143	±	24	<0.001	136	±	19	144	±	24	<0.001
Diastolic BP (mmHg)	77	±	11	77	±	11	74	±	12	<0.001	77	±	11	75	±	13	0.002
Fasting glucose (mmol/L)	8.0	±	2.8	8.0	±	2.8	8.2	±	3.2	0.342	8.0	±	2.8	8.1	±	3.1	0.747
Mean of fasting glucose (mmol/L)	8.4	±	2.1	8.4	±	2.1	8.6	±	2.1	0.326	8.4	±	2.1	8.5	±	2.1	0.229
SD of fasting glucose (mmol/L)	2.2	±	2.3	2.2	±	2.3	2.6	±	2.1	0.009	2.2	±	2.3	2.4	±	2.1	0.034
HbA1c (%)	7.3	±	1.4	7.3	±	1.4	7.4	±	1.4	0.374	7.3	±	1.4	7.4	±	1.3	0.337
Total cholesterol (mmol/L)	4.1	±	0.8	4.1	±	0.8	4.1	±	0.9	0.627	4.1	±	0.8	4.1	±	0.8	0.325
Triglyceride (mmol/L)	1.5	±	1.2	1.5	±	1.2	1.7	±	1.1	0.014	1.5	±	1.2	1.5	±	1.0	0.730
eGFR (mL/min/1.73 m^2)	78	±	28	79	±	27	61	±	31	<0.001	80	±	26	67	±	32	<0.001
ABI	1.1	±	0.1	1.1	±	0.1	0.7	±	0.2	<0.001	1.1	±	0.1	0.9	±	0.2	<0.001
PWV (cm/sec)	1868	±	463	1856	±	437	2015	±	686	<0.001	1829	±	407	2082	±	651	<0.001
%MAP	41.0	±	4.3	40.5	±	3.8	47.1	±	5.1	<0.001	39.7	±	3.0	48.0	±	2.8	<0.001
Antiplatelet, n (%)	779		(30.2%)	647		(27.2%)	132		(66.0%)	<0.001	590		(27.1%)	189		(47.0%)	<0.001
Statins, n (%)	1854		(71.9%)	1711		(72.0%)	143		(71.5%)	0.949	1566		(72.0%)	288		(71.6%)	0.931
Hypertension, n (%)	2050		(79.5%)	1853		(78.0%)	197		(98.5%)	<0.001	1691		(77.7%)	359		(89.3%)	<0.001
Antihypertensive agents, n (%)																	
ACE inhibitor or ARB, n (%)	1082		(42.0%)	974		(41.0%)	108		(54.0%)	<0.001	889		(40.9%)	193		(48.0%)	0.009
α-Blocker, n (%)	189		(7.3%)	157		(6.6%)	32		(16.0%)	<0.001	129		(5.9%)	60		(14.9%)	<0.001
β-Blocker, n (%)	525		(20.4%)	460		(19.4%)	65		(32.5%)	<0.001	401		(18.4%)	124		(30.8%)	<0.001
Calcium channel blocker, n (%)	136		(5.3%)	113		(4.8%)	23		(11.5%)	<0.001	110		(5.1%)	26		(6.5%)	0.298
Diuretics, n (%)	258		(10.0%)	209		(8.8%)	49		(24.5%)	<0.001	176		(8.1%)	82		(20.4%)	<0.001
Insulin therapy, n (%)	604		(23.4%)	534		(22.5%)	70		(35.0%)	<0.001	488		(22.4%)	116		(28.9%)	0.006
Oral antihyperglycemic drugs																	
Insulin secretagogues, n (%)	1000		(38.8%)	928		(39.0%)	72		(36.0%)	0.440	837		(38.5%)	163		(40.5%)	0.469
Metformin, n (%)	933		(36.2%)	885		(37.2%)	48		(24.0%)	<0.001	822		(37.8%)	111		(27.6%)	<0.001
Thiazolidinediones, n (%)	562		(21.8%)	524		(22.0%)	38		(19.0%)	0.362	481		(22.1%)	81		(20.1%)	0.417
α-Glucosidase inhibitor, n (%)	271		(10.5%)	257		(10.8%)	14		(7.0%)	0.117	228		(10.5%)	43		(10.7%)	0.968
DPP4 inhibitors	1512		(58.7%)	1402		(59.0%)	110		(55.0%)	0.306	1281		(58.9%)	231		(57.5%)	0.630
SGLT2 inhibitors	259		(10.1%)	251		(10.6%)	8		(4.0%)	0.005	237		(10.9%)	22		(5.5%)	0.001

Notes: Continuous data are presented as mean ± SD, and categorical data are presented as numbers (percentages). [a]P value between patients with ABI > 0.90 and ABI ≤ 0.90. [b]P value between patients with %MAP < 45% and %MAP ≥ 45%.

Abbreviations: %MAP, percentage of the mean arterial pressure; ABI, ankle-brachial index; CAD, coronary heart disease; BMI, body mass index; BP, blood pressure; SD, standard deviation; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate; baPWV, brachial-ankle pulse wave velocity; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor antagonist; DPP4, dipeptidyl peptidase-4; SGLT2, sodium glucose cotransporter 2.

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Table 2 Characteristics of the Enrolled Patients Categorized Based on a Combination of ABI and %MAP

	ABI > 0.90 and %MAP < 45% (n = 2117)			ABI > 0.90 and %MAP ≥ 45% (n = 260)			ABI ≤ 0.90 and %MAP < 45% (n = 58)			ABI ≤ 0.90 and %MAP ≥ 45% (n = 142)			P[a]		ABI ≤ 0.90 or %MAP ≥ 45% (n = 460)			P[b]
Age (year)	65	±	10	70	±	12	67	±	12	74	±	11	<0.001		71	±	12	<0.001
Male, n (%)	1151		(54.4%)	104		(40.0%)	29		(50.0%)	80		(56.3%)	<0.001		213		(46.3%)	0.002
Current smoking, n (%)	254		(12.0%)	22		(8.5%)	9		(15.5%)	15		(10.6%)	0.281		46		(10.0%)	0.258
CAD, n (%)	179		(8.5%)	35		(13.5%)	11		(19.0%)	52		(36.6%)	<0.001		98		(21.3%)	<0.001
BMI (kg/m^2)	25.8	±	3.9	25.6	±	4.5	27.4	±	3.8	25.8	±	4.0	0.022		25.9	±	4.3	0.918
Systolic BP (mmHg)	135	±	19	144	±	24	140	±	21	145	±	25	<0.001		144	±	24	<0.001
Diastolic BP (mmHg)	77	±	11	76	±	12	76	±	11	73	±	13	<0.001		75	±	12	0.001
Fasting glucose (mmol/L)	8.0	±	2.8	8.0	±	2.9	8.4	±	2.8	8.2	±	3.4	0.781		8.1	±	3.0	0.526
Mean of fasting glucose (mmol/L)	8.4	±	2.1	8.5	±	2.0	8.3	±	2.0	8.7	±	2.2	0.509		8.5	±	2.0	0.338
SD of fasting glucose (mmol/L)	2.2	±	2.3	2.3	±	2.0	2.3	±	2.0	2.7	±	2.2	0.034		2.4	±	2.1	0.032
HbA1c (%)	7.3	±	1.4	7.4	±	1.3	7.5	±	1.5	7.4	±	1.4	0.563		7.4	±	1.4	0.197
Total cholesterol (mmol/L)	4.1	±	0.8	4.1	±	0.8	4.0	±	0.8	4.1	±	0.9	0.306		4.1	±	0.8	0.157
Triglyceride (mmol/L)	1.5	±	1.2	1.4	±	1.0	1.7	±	1.2	1.7	±	1.0	0.033		1.5	±	1.0	0.784
eGFR (mL/min/1.73 m^2)	80	±	26	73	±	31	73	±	32	56	±	29	<0.001		67	±	32	<0.001
ABI	1.1	±	0.1	1.1	±	0.1	0.8	±	0.1	0.7	±	0.2	<0.001		0.9	±	0.2	<0.001
PWV (cm/sec)	1830	±	404	2070	±	604	1798	±	505	2103	±	731	<0.001		2046	±	641	<0.001
%MAP	39.6	±	3.0	47.2	±	2.0	40.9	±	2.9	49.7	±	3.3	<0.001		47.1	±	3.7	<0.001
Antiplatelet, n (%)	567		(26.8%)	80		(30.8%)	23		(39.7%)	109		(76.8%)	<0.001		212		(46.1%)	<0.001
Statins, n (%)	1525		(72.0%)	186		(71.5%)	41		(70.7%)	102		(71.8%)	0.995		329		(71.5%)	0.869
Hypertension, n (%)	1634		(77.2%)	219		(84.2%)	57		(98.3%)	140		(98.6%)	<0.001		416		(90.4%)	<0.001
Antihypertensive agents																		
ACE inhibitor or ARB, n (%)	857		(40.5%)	117		(45.0%)	32		(55.2%)	76		(53.5%)	0.002		225		(48.9%)	0.001
α-Blocker, n (%)	123		(5.8%)	34		(13.1%)	6		(10.3%)	26		(18.3%)	<0.001		66		(14.3%)	<0.001
β-Blocker, n (%)	388		(18.3%)	72		(27.7%)	13		(22.4%)	52		(36.6%)	<0.001		137		(29.8%)	<0.001
Calcium channel blocker, n (%)	102		(4.8%)	11		(4.2%)	8		(13.8%)	15		(10.6%)	<0.001		34		(7.4%)	0.034
Diuretics, n (%)	167		(7.9%)	42		(16.2%)	9		(15.5%)	40		(28.2%)	<0.001		91		(19.8%)	<0.001
Insulin therapy, n (%)	469		(22.2%)	65		(25.0%)	19		(32.8%)	51		(35.9%)	<0.001		135		(29.3%)	0.001
Oral antihyperglycemic drugs																		
Insulin secretagogues, n (%)	817		(38.6%)	111		(42.7%)	20		(34.5%)	52		(36.6%)	0.487		183		(39.8%)	0.673
Metformin, n (%)	800		(37.8%)	85		(32.7%)	22		(37.9%)	26		(18.3%)	<0.001		133		(28.9%)	<0.001
Thiazolidinediones, n (%)	471		(22.2%)	53		(20.4%)	10		(17.2%)	28		(19.7%)	0.654		91		(19.8%)	0.272
α-Glucosidase inhibitor, n (%)	227		(10.7%)	30		(11.5%)	1		(1.7%)	13		(9.2%)	0.143		44		(9.6%)	0.516
DPP4 inhibitors, n (%)	1251		(59.1%)	151		(58.1%)	30		(51.7%)	80		(56.3%)	0.644		261		(56.7%)	0.380
SGLT2 inhibitors, n (%)	234		(11.1%)	17		(6.5%)	3		(5.2%)	5		(3.5%)	0.003		25		(5.4%)	<0.001

Notes: Continuous data are presented as the mean ± SD, and categorical data are presented as numbers (percentages). [a]P value among four groups [b]P value between the ABI > 0.90 with %MAP < 45% group and the ABI ≤ 0.90 or %MAP ≥ 45% group.

Abbreviations: %MAP, percentage of the mean arterial pressure; ABI, ankle-brachial index; CAD, coronary heart disease; BMI, body mass index; BP, blood pressure; SD, standard deviation; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate; baPWV, brachial-ankle pulse wave velocity; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor antagonist; DPP4, dipeptidyl peptidase-4; SGLT2, sodium glucose cotransporter 2.

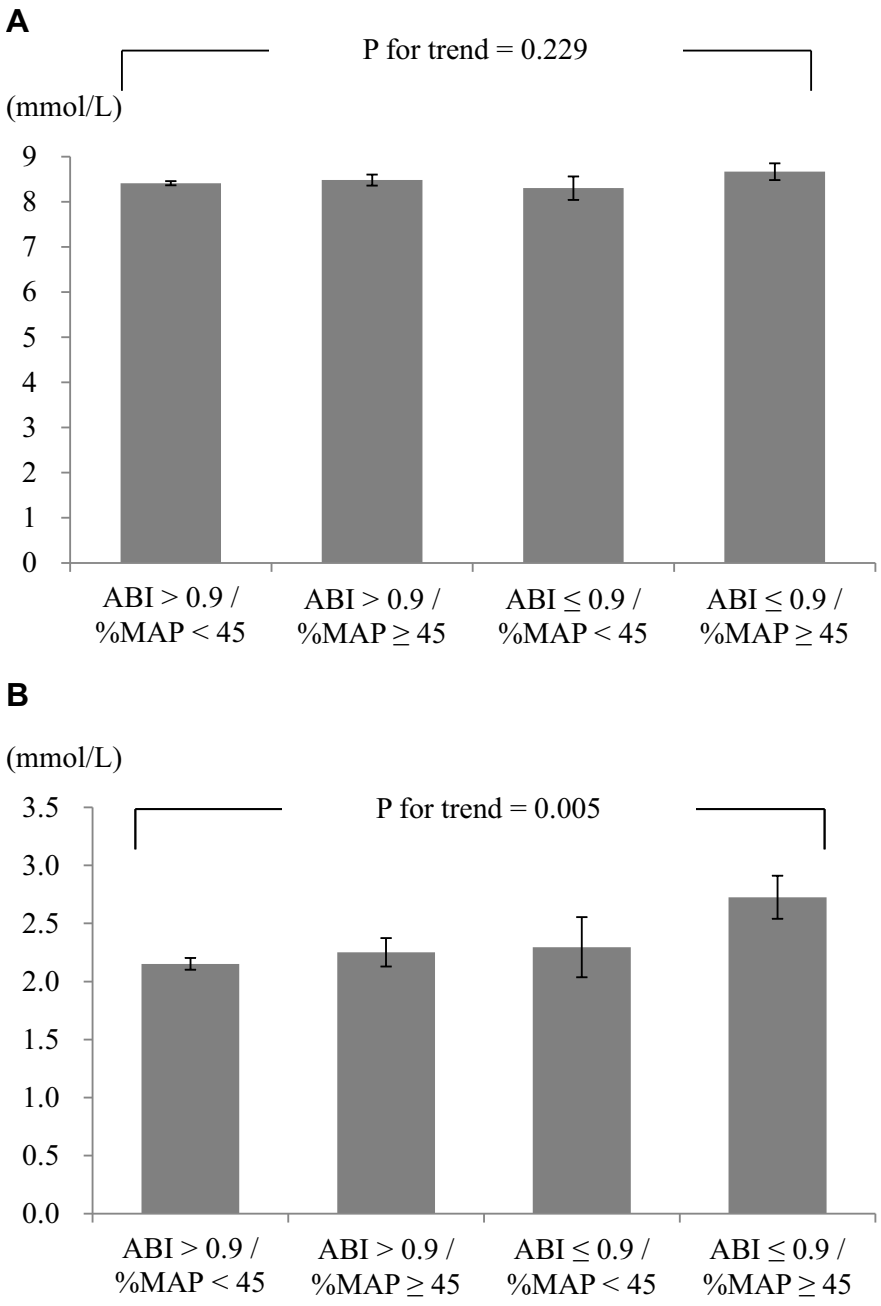

Figure 2 (**A**) Mean and (**B**) SD of fasting plasma glucose levels among the four groups.

specificity (41.3%) for differentiating high-risk PAD. An SD of annual fasting glucose ≥ 1.274 mmol/L provided an increased risk with odds ratio (OR) of 1.424 (95% CI = 1.118–1.814, P = 0.004) for high-risk PAD compared with an SD of annual fasting glucose < 1.274 mmol/L after adjustment for the associated risk factors, selected from Table 2, including age, gender, CAD history, hypertension, fasting glucose level, eGFR, and current use of antiplatelet agents, insulin, metformin, or SGLT2 inhibitors (Table 3).

Discussion

The main results of this study were that the SD of annual fasting glucose was significantly associated with a low ABI and a high %MAP in patients with DM. However, the mean annual fasting glucose level was not significantly associated with ABI or %MAP. Glycemic variability plays an important role in vasculopathy, and higher HbA1c variability has been linked to higher risks of microvascular complications, cardiovascular disease, and mortality.[32,33] The SD of annual HbA1c has also been reported to be

Table 3 Logistic Regression Analysis Showing the Factors Associated with High-Risk PAD

	Crude			Model 1			Model 2			Model 3		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
SD of fasting glucose ≥ 1.274 mmol/L	1.641	1.320 2.039	<0.001	1.595	1.278 1.989	<0.001	1.458	1.158 1.836	0.001	1.424	1.118 1.814	0.004
Age ≥ 65 years				2.612	2.105 3.242	<0.001	2.148	1.717 2.688	<0.001	2.049	1.633 2.570	<0.001
Male				0.771	0.627 0.948	0.013	0.676	0.545 0.839	<0.001	0.664	0.535 0.825	<0.001
CAD history							1.904	1.391 2.607	<0.001	1.870	1.364 2.564	<0.001
Hypertension							1.710	1.213 2.411	0.002	1.698	1.203 2.396	0.003
Fasting glucose ≥ 8 mmol/L							0.994	0.800 1.235	0.958	1.000	0.804 1.244	0.999
eGFR < 30 mL/min/1.73 m^2							1.495	1.011 2.211	0.044	1.369	0.921 2.035	0.120
Current use of antiplatelet agents							1.570	1.233 1.998	<0.001	1.569	1.231 2.000	<0.001
Current use of insulin										1.102	0.853 1.423	0.456
Current use of metformin										0.819	0.648 1.035	0.095
Current use of SGLT2 inhibitors										0.586	0.376 0.914	0.018

Abbreviations: SD, standard deviation; CAD, coronary heart disease; eGFR, estimated glomerular filtration rate; PAD, peripheral artery disease; SGLT2, sodium glucose cotransporter 2.

correlated with high-risk PAD in patients with DM.[28] HbA1c is clinically used as a glycemic marker to diagnose DM and monitor glucose control in DM.[34] The HbA1c level reflects a longer glycemic duration than the fasting glucose level, and several underlying conditions can influence the HbA1c level independent of glucose.[35] Therefore, HbA1c variability may result from unstable underlying diseases associated with chronic complications.[29,36–39] We used the SD of annual fasting glucose to reflect glucose variability, which has a stronger association with ABI and %MAP than the mean of annual fasting glucose level in the present study.

In accordance with our study, a higher variability in fasting glucose has been reported to be associated with an increased prevalence of lower-extremity PAD in people without DM.[40] Several mechanisms might be involved in glucose variability linked to cardiovascular disease such as the activation of inflammatory pathways, increase in oxidative stress, and non-enzymatic glycation.[41] Glucose swings might provoke a more specific triggering impact than chronic sustained hyperglycemia on oxidative stress, which could contribute to cardiovascular events.[42–44]

Yang et al[45] reported variability of fasting glucose, estimated by the coefficient of variation, to be significantly associated with PAD which was defined using clinical diagnostic coding instead of ABI in a retrospective cohort study. However, use of administrative data has been reported to be not sensitive for PAD detection.[46] Interestingly, we noted that a synergistic effect of low ABI and high %MAP on the association with the SD of annual fasting glucose. Emanuelsson et al[47] reported that a higher 1 mmol/L of glucose level was associated with an increased risk ratio of 1.19 for PAD. Mongraw-Chaffin et al[20] also reported that mean fasting glucose is a better indicator of cardiovascular disease than the one-off measurement of the fasting glucose and variability in the fasting glucose. However, our study showed that the mean of annual fasting glucose levels was not significantly different between patients with high- and low-risk PAD.

A recent trial on cardiovascular outcome revealed that canagliflozin might be associated with an increased risk of amputation.[48] Overall, however, SGLT2 inhibitors do not increase the PAD risk according to meta-analyses.[49,50] Notably, current use of SGLT2 inhibitors provided a significantly low risk (OR = 0.586) for high-risk PAD in the present study. SGLT2 inhibitors are considered to have cardiorenal benefits.[51] The mechanisms for the cardioprotective benefits of SGLT2 inhibitors include

improvement in myocardial metabolism, alteration in adipokines, and reduction in preload and afterload.[52]

The present study had several limitations. First, we collected only the annual fasting plasma glucose data rather than all available data on glucose. The advantages of using only the annual fasting glucose data were the interval of the data being similar and avoidance of bias resulting from frequent measurements. Second, our findings cannot be applied to patients with ABI > 1.4 since they were excluded because the role of %MAP remains unclear in the high-ABI population. Third, although several risk factors associated with PAD were assessed in the multivariate regression model, some other risk factors were not analyzed in this study.[53] In particular, previous studies have indicated that high variability in body mass index, blood pressure, and cholesterol level are predictors of cardiovascular disease.[54–60] Fourth, because only a few patients used glucagon like peptide-1 receptor (GLP-1R) agonists, we did not include those data. It has been reported that treatment with GLP-1R agonists might have protective effects against cardiovascular disease.[61,62] Finally, we did not collect hypoglycemia data, which is a factor linking high glucose variability and cardiovascular disease.[63–65]

Conclusions

A high SD of annual fasting glucose is an independent risk factor for high-risk PAD, defined as ABI ≤ 0.90, %MAP ≥ 45%, or both. Our results suggest that a stable fasting plasma glucose level is important for the clinical treatment in patients with DM.

Ethical Approval and Informed Consent

The study complied with the Declaration of Helsinki. The Institutional Review Board of Taichung Veterans General Hospital approved the protocol (ethical approval code: CE17234A) and waived the need for informed consent due to retrospective collection of data. Anonymous medical record data were obtained from the Clinical Informatics Research & Development Center of Taichung Veterans General Hospital after delinking the identification code.

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Disclosure

The authors report no conflicts of interest in this work.

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