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
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. However, fasting glucose provided a better contribution to predict cardiovascular events than HbA1c in Taiwanese patients with type 2 DM. 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. Variabilities in HbA1c and fasting glucose have been reported to be associated with cardiovascular disease. 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.

Measuring the blood pressure of the ankle was postulated as a screening method for PAD in the 1950s, and brought about ABI development. 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). 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. Furthermore, a combination of ABI and %MAP is useful in the prediction of all-cause mortality.

Recent evidence has shown that HbA1c variability is related to a decrease in ABI and an increase in %MAP in patients with DM. However, HbA1c variability is associated with not only changes in plasma glucose, but also several factors influencing the rate of glycation and hemoglobin level. 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, 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 × [serum creatinine (mg/dL)]−1.154 × [age (years)]−0.203 (× 0.742, if female) according to the Modification of Diet in Renal Disease equation, and an eGFR < 60 mL/min/1.73m² was defined as CKD. 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.\textsuperscript{26} 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% 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
Patients with high-risk PAD had lower proportions 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. Patients 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 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      | %MAP < 45% (n = 2175) | %MAP ≥ 45% (n = 402) | P      |
|----------------------|----------------|-----------------------|----------------------|--------|----------------------|----------------------|--------|
| 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/m²)          | 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 ± 2.3            | 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  |
| Triglycerides (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 m²) | 78 ± 28        | 79 ± 27               | 61 ± 31              | <0.001 | 80 ± 26              | 67 ± 32              | <0.001 |
| A1B                | 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 |
| Antplatelet, 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 |
| Alcohol-inhibiting agents, n (%) | 1082 (42.0%) | 974 (41.0%)          | 108 (54.0%)          | <0.001 | 889 (40.9%)          | 193 (48.0%)          | 0.009  |
| ACE inhibitor or ARB, n (%) | 189 (7.3%)     | 157 (6.6%)            | 32 (16.0%)           | <0.001 | 129 (5.9%)           | 60 (14.9%)           | <0.001 |
| β-Blockers, n (%)    | 525 (20.4%)    | 460 (19.4%)           | 65 (32.5%)           | <0.001 | 401 (18.4%)          | 124 (30.8%)          | <0.001 |
| Calcium channel blockers, 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). *P value between patients with ABI > 0.90 and ABI ≤ 0.90. **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.
**Table 2** Characteristics of the Enrolled Patients Categorized Based on a Combination of ABI and %MAP

|                  | ABI > 0.90 and %MAP | ABI > 0.90 and %MAP | ABI ≤ 0.90 and %MAP | ABI ≤ 0.90 and %MAP | 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 (64.6%)                         | 0.002   |
| Current smoking, n (%) | 254 (12.0%)  | 22 (8.5%)             | 9 (15.3%)             | 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           | 0.059   | 8.5 ± 2.0                            | 0.338   |
| Mean 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   |
| SD of fasting glucose (mmol/L) | 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 ± 2.6    | 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 ± 26.0  | 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          | 472 ± 2.0            | 40.9 ± 2.9          | 49.7 ± 3.3          | <0.001  | 47.1 ± 3.7                          | <0.001  |
| Antplatelet, 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
- β-Blocker, n (%) | 123 (5.8%) | 34 (13.1%) | 16 (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 (42.0%) | 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-Glucoside 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.
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. 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 OR (95% CI) | Model 1 OR (95% CI) | P     | Model 2 OR (95% CI) | P     | Model 3 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           | 1.904 (1.391–2.607) | <0.001           | 1.641 (1.320–2.039) | <0.001           |
| Male                     | 0.771 (0.627–0.948) | 0.013               | 0.676 (0.545–0.839) | <0.001           | 0.994 (0.800–1.323) | 0.958           | 1.099 (0.804–1.424) | 0.999           |
| CAD history              | 1.710 (1.213–2.411) | 0.002               | 1.495 (1.011–2.211) | 0.044            | 1.495 (1.011–2.211) | 0.044           | 1.099 (0.804–1.424) | 0.999           |
| Hypertension             | 1.190 (1.011–1.233) | 0.044               | 1.190 (1.011–1.233) | 0.044            | 1.190 (1.011–1.233) | 0.044           | 1.099 (0.804–1.424) | 0.999           |
| Fasting glucose ≥ 8 mmol/L | 1.158 (0.999–1.364) | 0.001               | 1.213 (1.011–1.233) | 0.044            | 1.213 (1.011–1.233) | 0.044           | 1.099 (0.804–1.424) | 0.999           |
| eGFR < 30 mL/min/1.73 m²  | 1.158 (0.999–1.364) | 0.001               | 1.213 (1.011–1.233) | 0.044            | 1.213 (1.011–1.233) | 0.044           | 1.099 (0.804–1.424) | 0.999           |
| Current use of antplatelet agents | 1.158 (0.999–1.364) | 0.001               | 1.213 (1.011–1.233) | 0.044            | 1.213 (1.011–1.233) | 0.044           | 1.099 (0.804–1.424) | 0.999           |
| Current use of insulin   | 1.158 (0.999–1.364) | 0.001               | 1.213 (1.011–1.233) | 0.044            | 1.213 (1.011–1.233) | 0.044           | 1.099 (0.804–1.424) | 0.999           |
| Current use of metformin | 1.158 (0.999–1.364) | 0.001               | 1.213 (1.011–1.233) | 0.044            | 1.213 (1.011–1.233) | 0.044           | 1.099 (0.804–1.424) | 0.999           |
| Current use of SGLT2 inhibitors | 1.158 (0.999–1.364) | 0.001               | 1.213 (1.011–1.233) | 0.044            | 1.213 (1.011–1.233) | 0.044           | 1.099 (0.804–1.424) | 0.999           |

Abbreviations: SD, standard deviation; CAD, coronary heart disease; eGFR, estimated glomerular filtration rate; PAD, peripheral artery disease; SGLT2, sodium glucose cotransporter 2.
improvement in myocardial metabolism, alteration in adipokines, and reduction in preload and afterload.\textsuperscript{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.\textsuperscript{53} In particular, previous studies have indicated that high variability in body mass index, blood pressure, and cholesterol level are predictors of cardiovascular disease.\textsuperscript{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.\textsuperscript{61,62} Finally, we did not collect hypoglycemia data, which is a factor linking high glucose variability and cardiovascular disease.\textsuperscript{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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