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博 士 論 文

Association between mean platelet volume in the pathogenesis of type 2 diabetes mellitus and diabetic macrovascular complications in Japanese patients.

(2 型糖尿病の病態把握における平均血小板容積 MPV の有用性に関する検討)

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Abstract

Aims/Introduction: Mean platelet volume is a widely used biological marker of platelet function and activity. Increased mean platelet volume is associated with accelerated thrombopoiesis and an elevated risk of cardiovascular disease. However, it is not known whether higher mean platelet volume is related to the pathogenesis of type 2 diabetes and diabetic macrovascular complications in Japanese patients. Therefore, we analyzed mean platelet volume and its correlation with atherosclerosis in Japanese patients with type 2 diabetes and those who were prediabetic.

Materials and Methods: We divided the patients into 3 groups: normoglycemic patients (Control group, n = 56), prediabetic patients (Pre-DM group, n = 44), and type 2 diabetic patients (T2DM group, n = 115). We measured platelet parameters and evaluated arterial stiffness in the 3 groups.

Results: Significantly higher mean platelet volume was found in the T2DM and Pre-DM groups compared with the Control group. Mean platelet volume was significantly correlated with fasting blood glucose and glycated hemoglobin levels. Multiple linear regression analysis showed that MPV was positively correlated with HbA1c even after adjustment for confounding factors. In the evaluation of arterial stiffness by measuring the cardio-ankle vascular index and maximum intima-media thickness, MPV showed a positive correlation with these parameters.

Conclusions: These findings suggest that MPV was significantly increased in the early stage of type 2 diabetes. We showed positive correlations between MPV and HbA1c levels, and between MPV and arterial stiffness in Japanese patients with type 2 diabetes.

Introduction

Platelets have central roles in hemostasis and thrombosis[1]. When platelets are activated by vascular injury, they secrete various substances essential for mediating coagulation, thrombosis, inflammation, and atherosclerosis[2]. Therefore, evaluation of platelet hyperactivity is important. However, the optimal method for platelet testing is complicated and requires specialized equipment, making direct measurement of platelet activity impractical in routine practice. Generally, large platelets exhibit greater metabolic and enzymatic activity than small platelets[3, 4]. Mean platelet volume (MPV) is widely used as a biological marker of platelet function and activity[5]. MPV can be measured easily and cheaply by using an automated blood cell counter, which is routinely available in most hospitals. Increased MPV has been linked to the development of myocardial infarction[6] and atherosclerosis[7], as well as to increased risk of cardiovascular disease[7, 8].

The risk of cardiovascular disease is high in patients with an underlying disease, such as hypertension, dyslipidemia, and type 2 diabetes mellitus (T2DM). T2DM is a metabolic disorder and a critical factor in cardiovascular disease onset. Its pathogenesis is characterized mainly by insulin resistance and pancreatic β-cell failure. Microvascular complications (retinopathy, nephropathy, and neuropathy) and macrovascular complications (ischemic heart disease, peripheral vascular disease, and cerebrovascular disease) are features of T2DM associated with hyperglycemia. Higher MPV is observed in patients with metabolic disorders such as obesity[9] and T2DM[10-12]; however, these studies only reported increased MPV in patients with T2DM, and it is still unclear whether higher MPV is present in the early stage of T2DM. To our knowledge, no studies have examined whether increased MPV is associated with progression of atherosclerosis in patients with T2DM.

In this study, we hypothesized that MPV is associated with metabolic disorder in the early stage of T2DM in Japanese patients and that increased MPV results in the progression of diabetic macrovascular complications.

Materials and Methods

Subjects

The required number of patients in each group was determined statistically by R software, and we needed at least 41 patients in each group to perform the analysis. On the basis of this calculation, we analyzed the data of 215 patients (normoglycemic patients [Control group], n = 56; prediabetic patients [Pre-DM group], n = 44; and T2DM group, n = 115) from 2014 to 2015. They were classified into 3 groups based on criteria outlined by the American Diabetes Association[13]: Control (fasting blood glucose levels <110 mg/dL), Pre-DM (fasting blood glucose levels 100–125 mg/dL and glycated hemoglobin [HbA1c] 5.7%–6.4%), and T2DM (fasting blood glucose levels >126 mg/dL and HbA1c ≥6.5%). We could not divide the Pre-DM group into impaired fasting glucose and impaired glucose tolerance groups because an oral glucose tolerance test was not carried out. Patients with type 1 diabetes or an abnormal platelet count (<100 or >450 × 10^9 platelets/L) were excluded.

Measurement of platelet parameters

Venous blood was sampled using K3-ethylenediaminetetraacetic acid tubes. The samples were tested within 1 h of collection to ensure variations due to sample aging were minimized. We measured platelet count and MPV using an ADVIA® 2120i Hematology

System (Siemens, Munich, Germany), which employs two-angle laser flow cytometry with sodium dodecyl sulfate treatment for isovolumetric sphering measurement of erythrocytes and platelets. As a result, platelets and other blood cells can be discriminated accurately.

Biochemical measurements

Biochemical analyses of fasting blood glucose levels, C-reactive protein, triglycerides, and high- and low-density lipoprotein cholesterol were determined by standard methods. HbA1c was analyzed using high-performance liquid chromatography (HLC723-G9; Tosoh Bioscience, Japan). The clinical laboratory of Nara Prefecture General Medical Center performed all laboratory measurements.

Assessment of arterial stiffness

The cardio-ankle vascular index (CAVI) is a measure of the arterial stiffness of the arterial tree between the origin of the aorta and the ankle. This assessment is independent of blood pressure during measurement. CAVI assessment was carried out using a VaSera VS-1500A system (Fukuda Denshi, Tokyo, Japan)[14].

Ultrasonography of carotid intima-media thickness (IMT)

B-mode ultrasonographic imaging of the carotid artery was performed using an ultrasound imaging system (LOGIQ S8; GE Healthcare Japan, Japan)[15]. Maximum IMT was used because it has been reported to be more useful than mean IMT for evaluating the progression of carotid artery disease[16-19].

Statistical analysis

One-way analysis of variance (ANOVA) was used for comparisons among 3 groups. If ANOVA revealed a significant difference, we used the Tukey-Kramer test for multiple comparisons to identify which group differed. Student's *t* test was used for comparisons between 2 groups. Pearson's correlation model was used to calculate correlations between MPV and several parameters (fasting blood glucose levels, HbA1c levels, CAVI, and maximum IMT). To examine the relationships between MPV and diabetic parameters after adjustment for clinical characteristics (age, sex, body mass index, blood pressure, smoking status, and type of antidiabetic medication), multiple linear regression analysis was performed. Data are presented as the mean ± standard deviation. $P < 0.05$ was considered to indicate statistical significance.

Results

Platelet size is positively correlated with glucose intolerance

Table 1 summarizes patients' characteristics, while Table 2 shows the types of antidiabetic medication taken in the T2DM group. The clinical conditions of the Control group are shown in Table 3. No significant difference was evident between all groups for age, body mass index, C-reactive protein, low- and high-density lipoprotein cholesterol, or diastolic blood pressure. The only significant differences observed in the T2DM group compared with the Control group were significantly increased triglycerides and systolic blood pressure.

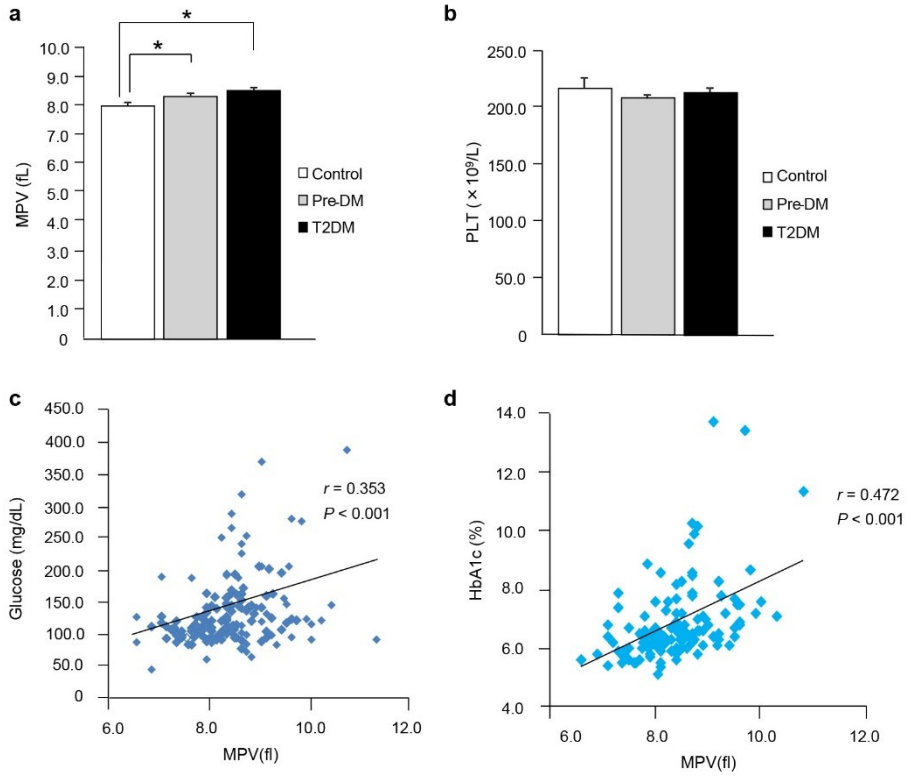

Fig. 1

Fig. 1. Mean platelet volume (MPV) levels in the 3 groups and the correlation between MPV and fasting blood glucose and HbA1c levels.

(a) MPV levels and (b) platelet counts (PLT) for the normoglycemic patients (Control group), prediabetic patients (Pre-DM group), and type 2 diabetic patients (T2DM group). (c) Correlation between MPV and fasting blood glucose levels. (d) Correlation between MPV and HbA1c levels. *$P < 0.05$.

There was a significant increase in MPV in the T2DM and Pre-DM groups compared with the Control group (Fig. 1a). No significant difference was seen in platelet counts among the 3 groups (Fig. 1b). MPV was positively correlated with fasting blood glucose and HbA1c levels (Fig. 1c and d). To examine whether MPV was affected by the type of antidiabetic medication, we performed multiple linear regression analysis. However, there was no positive relationship between MPV and the type of antidiabetic medication in the T2DM group after adjusting for medication type (Table 4).

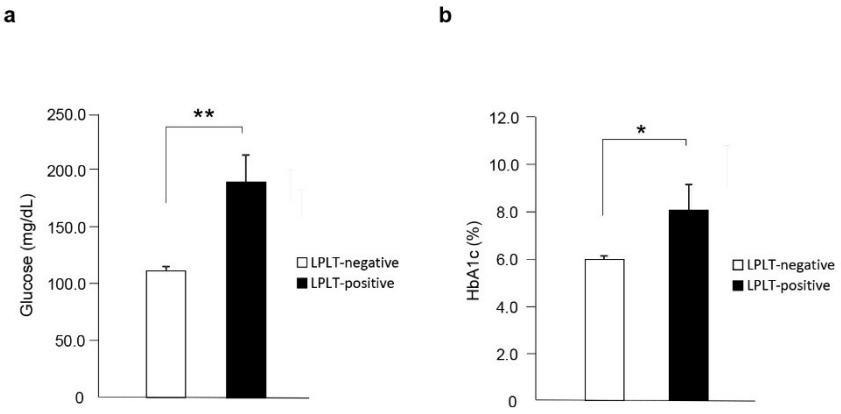

Fig. 2

Fig. 2. Measurement of fasting blood glucose and HbA1c levels in the large platelet (LPLT)-negative and -positive groups.

(a) Fasting blood glucose levels and (b) HbA1c levels for the LPLT-negative and -positive groups. LPLT-negative, <10% large platelets in the blood; LPLT positive, ≥10% large platelets in the blood. *$P < 0.05$, **$P < 0.01$.

In addition to MPV, the ADVIA 2120i Hematology System can measure another marker of platelet size, namely, the large platelet (LPLT) morphology flag. When ≥10% of platelets in the blood are larger than 20 fL, the LPLT flag becomes positive. In LPLT-positive patients, fasting blood glucose and HbA1c levels were significantly increased compared with LPLT-negative patients (Fig. 2a and b). Moreover, we performed multiple linear regression analysis to determine the independent relationships between MPV and HbA1c among the confounding factors. MPV was positively correlated with HbA1c and blood pressure even after adjustment for the confounding factors (Table 5).

Next, we examined the possibility that MPV could change according to variations in glucose levels. We defined an improvement of hyperglycemia when fasting blood glucose levels were decreased by <160 mg/dL or HbA1c levels were decreased by >0.5% in 1 year, regardless of the type of treatment used. Then, 38 patients in the T2DM group were observed to have achieved an improvement of fasting blood glucose (Fig. 3a) and HbA1c (Fig. 3b) levels after treatment for 1 year. We found that MPV after treatment was significantly reduced compared with that before treatment (Fig. 3c).

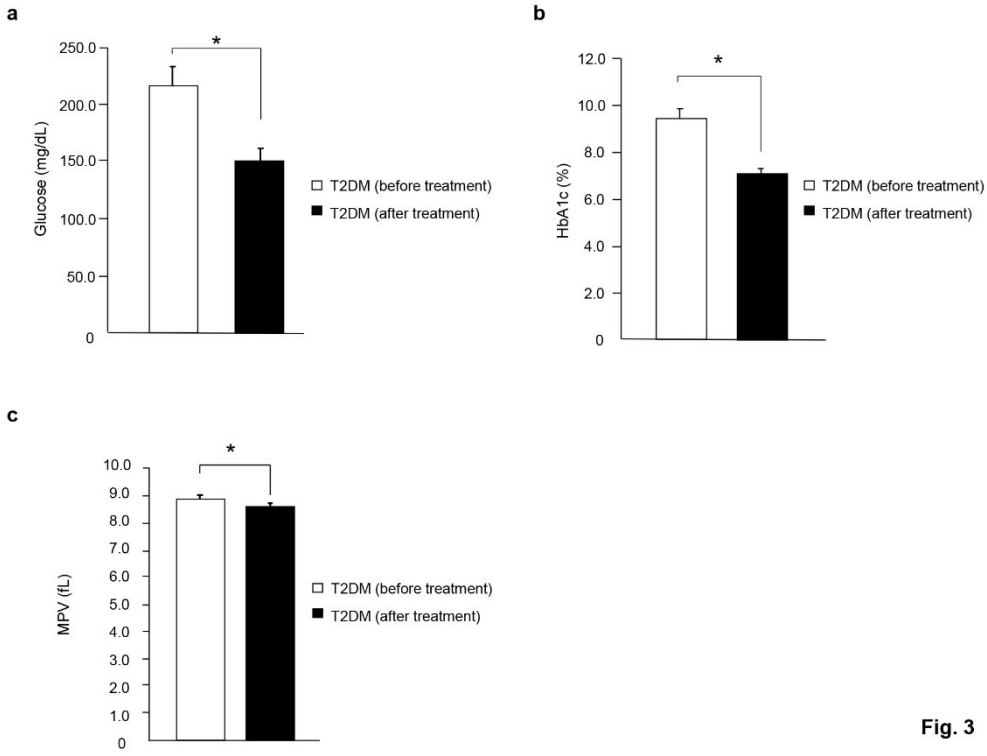

Fig. 3. Clinical characteristic changes and mean platelet volume (MPV) in the type 2 diabetic patients (T2DM) group before and after treatment.

(a) Fasting blood glucose levels, (b) HbA1c levels, and (c) MPV for the T2DM before treatment group and after treatment group. *$P < 0.05$.

Progression of atherosclerosis in patients with T2DM is positively correlated with

increased MPV

To evaluate how MPV is related to arterial stiffness, we measured CAVI and maximum IMT, which are widely used markers of arterial stiffness. A significant increase in CAVI and maximum IMT was found in the T2DM group compared with the Control group (Fig. 4a, b). Furthermore, there was a significant increase in CAVI in the Pre-DM group compared with the Control group (Fig. 4a). Atherosclerosis has been found in the early stage of T2DM[20, 21]. Indeed, we found that MPV and CAVI were positively correlated (Fig. 4c). However, the relationship between increased MPV and atherosclerotic condition in the T2DM group was not completely clear. We included T2DM patients with mild atherosclerosis ($8.0 < CAVI < 9.0$) in the group of patients without atherosclerosis[14] and analyzed MPV in these patients. MPV was observed to be significantly increased in the T2DM group without atherosclerosis compared with the Control group (Fig. 4d).

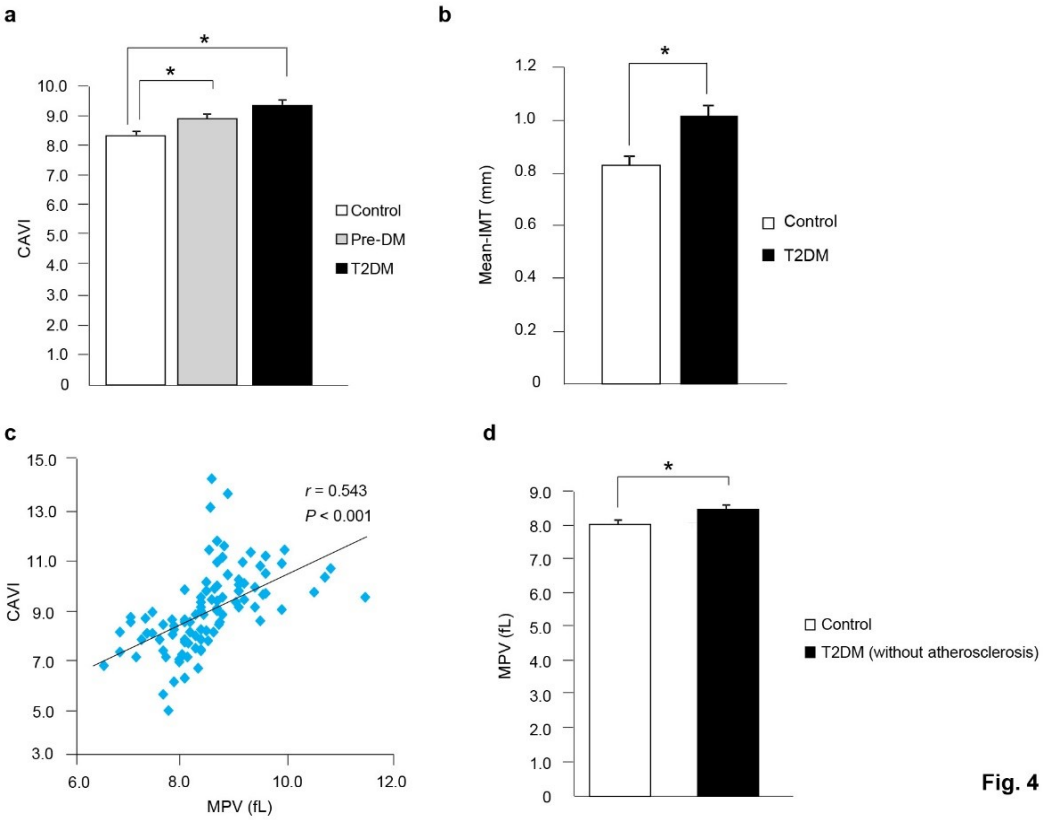

Fig. 4. Assessment of arterial stiffness in the 3 groups and examination of the effect of atherosclerosis on mean platelet volume (MPV).

(a) Cardio-ankle vascular index (CAVI) levels in normoglycemic patients (Control group) prediabetic patients (Pre -DM group), and type 2 diabetic patients (T2DM group) . (b) Maximum intima-media thickness (IMT) for the Control and T2DM groups. (c) Correlation between MPV and CAVI levels. (d) Comparison of MPV between the Control group and T2DM patients without atherosclerosis. *$P < 0.05$.

Discussion

Our findings demonstrated that increased MPV and diabetic conditions are positively correlated in Japanese patients with T2DM. Moreover, we observed a significant increase in MPV in the early stage of T2DM according to the findings in the Pre-DM group. In this study, we examined the association between platelet size and hyperglycemia by analyzing LPLT, which revealed that platelet size might be influenced by chronic hyperglycemia because LPLT was positively associated with HbA1c levels. Multiple linear regression analysis showed that there was no positive relationship between MPV and the type of antidiabetic medication used in the T2DM group after making adjustments for medication type. Furthermore, we found that MPV could be changed by improving hyperglycemia in Japanese patients with T2DM. A significant decrease in MPV due to the improvement of hyperglycemia via 6 months of metformin treatment has been shown in patients with T2DM[22]. These results suggested that platelet size was influenced in the early stage of T2DM, and baseline treatment did not have a positive association with MPV. The chronic change in blood glucose levels may be associated with MPV. Factors reported to affect MPV include the length of time from venous blood sampling to testing[5], seasonal changes[23], and hypertension[24]. However, we tested all blood samples within 1 h from sampling and observed no seasonal differences in the recruited patients. Therefore, these factors did not affect our results. In the T2DM group, we observed significant elevation in only systolic blood pressure compared with the Control group. In addition, multiple linear regression analysis showed that MPV was positively correlated with HbA1c levels and blood pressure after adjustment for confounding factors. From these results, we could not completely discount the influence of blood pressure, but at the very least, blood pressure did not affect MPV and arterial stiffness in the Pre-DM group. Nevertheless, the

mechanism by which MPV was increased in patients with T2DM remains unclear. Platelet size is determined during megakaryopoiesis, and there is a positive association between platelet morphology and levels of thrombopoietin and interleukin-6 (IL-6), which regulate megakaryocyte ploidy[25, 26]. Hyperglycemia increases the production of thrombopoietin by neutrophils in the liver via the receptor for advanced glycation end products[27]. IL-6 is well known for linking inflammation and insulin resistance in T2DM[28, 29]. Thrombopoietin and IL-6 production might be regulated by diabetic conditions, such as hyperglycemia and hyperinsulinemia, which leads to increased platelet size. Gieger et al. performed a meta-analysis of genome-wide association studies for platelet indices and identified an association between some single nucleotide polymorphisms and MPV[30]. In fact, the present study included some patients with low MPV. These genetic variants may contribute to other mechanisms that regulate MPV independently of diabetic conditions. Another study identified four genetic variants associated with MPV and arterial stiffness[31], and one of them corresponded with the results of Gieger et al. Further research focusing on these molecules or genes is needed.

We examined MPV as a biomarker for predicting macrovascular complications in Japanese patients with T2DM. In patients with coronary artery disease, MPV is reported to be a potentially useful prognostic biomarker[32]. The population-based Gutenberg Health Study showed a strong association between MPV and arterial stiffness. Furthermore, higher MPV was considered a potential marker of platelet activation and increased stiffness of the arterial vessel wall[31]. Our results revealed a positive association between higher MPV and progression of atherosclerosis in the T2DM and Pre-DM groups. In addition, we showed the possibility that progression of atherosclerosis in T2DM was due to increased MPV. In light of this possible relationship, we suggest that measuring

MPV may be important in terms of evaluating atherosclerosis and cardiovascular outcomes in Japanese patients with T2DM.

This study has several limitations. First, due to its retrospective nature, we could not examine how increased MPV is related to future clinical events. Second, we were unable to divide the Pre-DM group into impaired fasting glucose and impaired glucose tolerance groups because we did not have oral glucose tolerance test data. Third, we could not analyze platelet activity or functions because we did not have any suitable methods or specialized equipment. Thus, the correlation between platelet functions and MPV is still unclear.

In conclusion, these findings suggest that increased MPV is positively associated with HbA1c levels in Japanese T2DM patients and is positively related to the progression of atherosclerosis. Measuring MPV could be a beneficial marker for determining diabetes-induced macrovascular complications in patients with T2DM.

Acknowledgments

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Disclosure

The authors declare no conflicts of interest.

Ethics Approval

The protocol for this research project has been approved by a suitably constituted ethics committee of the institution and it conforms to the provisions of the Declaration of Helsinki. Institutional Review Board of Nara Prefecture General Medical Center, Approval No. 398.

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Table 1. Clinical characteristics of the patients (N = 215).

Variable	Control (n = 56)	Pre-DM (n = 44)	T2DM (n = 115)
Male/female (n)	31/25	34/10	70/45
Age (years)	70.3 ± 1.5	71.9 ± 0.8	71.9 ± 1.5
BMI (kg/m^2)	22.4 ± 0.4	23.2 ± 0.5	23.8 ± 0.4
Duration of DM (years)	0	0	10.3 ± 0.6
Smoking (yes/no)	6/50	12/32	41/74
FBG (mg/dL)	96 ± 2.3	108.1 ± 2.3**	172.6 ± 6.6*
HbA1c (%)	5.63 ± 0.1	6.1 ± 0.1**	7.9 ± 0.2*
CRP (mg/dL)	0.17 ± 0.1	0.19 ± 0.1	0.1 8 ±0.1
Triglycerides (mg/dL)	125.4 ± 11.7	130 ± 10.0	130.6 ± 9.0
LDL (mg/dL)	105.8 ± 5.0	105.1 ± 6.3	106.6 ± 2.71
HDL (mg/dL)	49.7 ± 2.3	48.2 ± 2.6	49.2 ± 1.2
SBP (mmHg)	130.6 ± 1.9	131.8 ± 2.2	139.3 ± 1.8*
DBP (mmHg)	81.4 ± 1.2	82.2 ± 1.2	81.3 ± 1.2

Data are presented as the mean ± standard deviation and percentage (%) for the Control, Pre-DM, and T2DM groups. *P*-values were calculated using analysis of variance and the Tukey-Kramer test for multiple comparisons.

BMI, body mass index; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; CRP, C-reactive protein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure.*$P < 0.05$, Control vs. T2DM; **$P < 0.05$, Control vs Pre-DM.

Table 2. Type of antidiabetic medication taken by patients in the T2DM group.

Antidiabetic medication	**n (%)**
Sulfonylurea	24 (26.1)
Glinide	2 (2.1)
Metformin	17 (18.5)
Alpha-glucosidase inhibitor	19 (20.7)
Thiazolidinedione	6 (6.5)
DPP-4 inhibitor	54 (58.7)
GLP-1 receptor agonist	1 (1.1)
SGLT-2 inhibitor	2 (2.1)
Insulin	32 (34.8)

DPP-4; dipeptidyl peptidase; GLP-1; glucagon like peptide-1; SGLT-2; sodium-glucose cotransporter 2.

Table 3. Clinical conditions of the Control group.

Clinical condition	**n (%)**
Hypertension	14 (25.0)
Angina	11 (19.6)
Dyslipidemia	8 (14.3)
Chronic kidney disease	6 (10.7)
Arrhythmia	3 (5.3)
Hyperuricemia	3 (5.3)
Rheumatoid arthritis	2 (3.6)
Thyroid dysfunction	2 (3.6)
Gastritis	2 (3.6)
Neurological disorders	2 (3.6)
Iron deficiency anemia	2 (3.6)
Systemic lupus erythematosus	1 (1.8)

Table 4. Correlation with MPV and type of antidiabetic medication according to multiple linear regression analysis.

Characteristic	Regression coefficient β	SE	95% CI		*P* value
			lower	upper	
Sulfonylurea	0.000	0.177	−0.355	0.351	0.998
Glinide	−0.438	0.498	−1.429	0.553	0.377
Metformin	0.013	0.206	−0.397	0.423	0.933
Alpha-glucosidase inhibitor	0.232	0.190	−0.147	0.612	0.226
Thiazolidinedione	0.438	0.301	−0.182	1.048	0.165
DPP-4 inhibitor	−0.321	0.177	−0.673	0.029	0.072
GLP-1 receptor agonist	−0.471	0.717	−1.898	0.957	0.514
SGLT-2 inhibitor	0.081	0.502	−0.917	1.079	0.871
Insulin	−0.121	0.192	−0.505	0.262	0.530

CI, confidence interval; DPP-4; dipeptidyl peptidase; GLP-1; glucagon like peptide-1; SE, standard error; SGLT-2; sodium-glucose cotransporter 2.

Table 5. Correlation between MPV and clinical characteristics according to multiple linear regression analysis.

Characteristic	Regression coefficient β	SE	95% CI		*P* value
			lower	upper	
Age (years)	0.009	0.006	−0.001	0.020	0.089
Sex	0.179	0.119	−0.055	0.414	0.132
BMI (kg/m^2)	0.006	0.014	−0.023	0.034	0.692
SBP (mmHg)	0.007	0.003	0.001	0.014	0.003*
DBP (mmHg)	−0.015	0.001	−0.028	−0.003	0.016*
Smoking status	0.023	0.125	−0.223	0.271	0.851
Fasting blood glucose (mg/dL)	0.001	0.001	−0.001	0.003	0.265
HbA1c (%)	0.106	0.041	0.027	0.187	0.001**

BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; SBP, systolic blood pressure; SE, standard error. *$P < 0.05$, **$P < 0.01$.