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ORIGINAL ARTICLE

Correlation between mean platelet volume and blood glucose levels after oral glucose loading in normoglycemic and prediabetic Japanese subjects

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ABSTRACT

Aims/Introduction: Mean platelet volume (MPV) reflects platelet activity, and high MPV is associated with thrombogenic activation and increased cardiovascular disease risk. Although a positive correlation between MPV and fasting plasma glucose (FPG) levels has been reported, the correlation between MPV and postprandial glucose levels remains unclear. The purpose of the present study was to evaluate the correlation between MPV and postprandial glucose levels in prediabetic and normoglycemic participants.

Materials and Methods: We evaluated 1,080 Japanese participants who underwent the 75-g oral glucose tolerance test (OGTT). Based on these results, the participants were divided into three groups: normal glucose tolerance group (NGT; n = 582), impaired fasting glucose group (IFG; n = 205) and impaired glucose tolerance group (IGT; n = 252). The relationship between MPV, FPG, and postchallenge glucose levels after 1 h (1 h-PG) and 2 h (2 h-PG) were analyzed.

Results: Bivariate correlation analyses showed a significant positive correlation between MPV and both FPG and 1 h-PG levels in the NGT group, as well as between MPV and 2 h-PG, total cholesterol, and low-density lipoprotein cholesterol in the IGT group. In contrast, no significant correlation was observed between MPV and postchallenge glucose levels in the IFG group. Multiple correlation analyses showed that FPG levels significantly correlated with MPV in the NGT and IGT groups. In addition, 1 h-PG and 2 h-PG levels correlated with MPV in the NTG and IGT groups, respectively.

Conclusions: These results suggest a possible mechanism by which subjects with postprandial hyperglycemia might be at increased cardiovascular risk.

INTRODUCTION

Platelets play an important role in the integrity of normal hemostasis; an accurate measure of the platelet size is considered a marker and determinant of platelet function[1]. Larger platelets with higher mean platelet volume (MPV) are hemostatically more reactive and produce higher amounts of the prothrombotic factor thromboxane A2, increasing the propensity to thrombosis[2]. Therefore, increased MPV is emerging as an independent risk factor for thromboembolism[3], stroke and myocardial infarction[4,5]. In patients with diabetes, MPV was higher compared with the normal glycemic controls; in addition, it has been proposed that an increase in MPV could play a role in the micro- and macrovascular complications related to diabetes[6,7].

Individuals with prediabetes are at a high risk of not only developing diabetes, but also adverse cardiovascular events later in life[8,9]. We previously reported that MPV in subjects with prediabetes is higher than that in normal subjects. Furthermore, MPV is positively associated with fasting plasma glucose (FPG)

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levels, not only in prediabetic subjects, but also in normoglycemic subjects[10]. Prediabetes is usually diagnosed on the basis of impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) levels[11]. IGT is defined as an elevated plasma glucose level (≥140 mg/dL, but <200 mg/dL) 2 h (2 h-PG) after undergoing a 75-g oral glucose tolerance test (OGTT) in individuals with FPG level <126 mg/dL. IFG is defined as FPG of 100–125 mg/dL with normal post-OGTT glucose levels (<140 mg/dL).

It is known that individuals with IGT and IFG have a tendency to develop diabetes; however, individuals with IGT are more likely to develop cardiovascular diseases (CVD) than those with IFG[12]. A meta-analysis showed that the risk of cardiovascular diseases is more strongly associated with postloading glucose levels than with FPG levels[13]. Furthermore, the normoglycemic subjects whose 2 h-PG levels do not return to FPG levels during OGTT are at a higher risk of death from CVD and other causes than those whose 2 h-PG level is less than or equal to their FPG levels[14]. These findings show that acute postprandial hyperglycemia is independently related to the risk of cardiovascular diseases not only in prediabetic, but also in normoglycemic subjects.

Although several studies have reported a positive association between MPV and FPG levels in diabetes[6,15], and in IGT[16,17], only one report has addressed the correlation between MPV and 2 h-PG levels after OGTT in IGT[18]. Furthermore, no study has compared MPV and 2 h-PG levels after OGTT in individuals with normal glucose tolerance (NGT). We hypothesized that MPV was related to the postloading glucose levels after OGTT in normoglycemic and prediabetic subjects. The aim of the present study was to evaluate the relationship between MPV and postloading glucose levels in the non-diabetic Japanese population.

MATERIALS AND METHODS

Study Population and Samples

The present study included 1080 participants aged 35 years and older who underwent a 75-g OGTT from January 2008 to December 2012 at Iida Municipal Hospital in Nagano, Japan, during a routine health check-up. A standard 75-g OGTT was carried out for each participant after overnight fasting (>12 h). Blood samples were collected at 0, 1 and 2 h after OGTT. The glucose tolerance status of a participant was classified on the basis of the criteria of the American Diabetes Association 2011 as follows: NGT (FPG <100 mg/dL and 2 h-PG levels <140 mg/dL), IFG (FPG of 100–125 mg/dL, and 2 h-PG levels <140 mg/dL) and IGT (FPG ≤125 mg/dL, and 2 h-PG levels of 140–199 mg/dL)[19].

Participants with diabetes or those receiving hypoglycemics were excluded. Participants with abnormal platelet counts (<100 and >400 × 10^3/μL) or receiving antiplatelet medication (aspirin, ticlopidine and clopidogrel) were also excluded. On the basis of the OGTT results, participants with NGT (n = 582), IFG (n = 205) and IGT (n = 252) were selected for the present study. Informed consent was obtained from all subjects who agreed to participate in the study.

The venous blood samples were mixed with dipotassium ethylenediaminetetraacetic acid and tested within 30 min of collection to minimize variations as a result of sample aging. MPV and platelets were measured using an automatic blood counter (XE-5000; Sysmex Corp., Kobe, Japan). Glucose, uric acid, lipid profiles and high-sensitivity C-reactive protein were determined by standard methods. Following were the criteria for dyslipidemia: serum low-density lipoprotein (LDL) cholesterol ≥140 mg/dL, high-density lipoprotein (HDL) cholesterol <40 mg/dL, triglycerides ≥150 mg/dL or having been treated for dyslipidemia[20]. Hypertension was defined as SBP ≥140 mmHg, DBP ≥90 mmHg or presently taking any medication prescribed for hypertension[21]. The body mass index (BMI) was calculated as weight/height^2 (kg/m^2).

A questionnaire was used to obtain information about familial medical history and the participants' lifestyle, such as smoking habits and alcohol consumption. Familial history of diabetes was defined as having one or more relatives (parent or sibling) with diabetes. Individuals who had smoked <100 cigarettes during their lifetime were considered non-smokers, those who had smoked ≥100 cigarettes and were currently not smoking were considered former smokers, and those who had smoked ≥100 cigarettes and were currently smoking were considered current smokers. The following criteria were defined for alcohol consumption groups: drinking never or rarely (0–5 times/year), occasionally (1–5 times/month) and regularly (1–7 times/week).

Statistical Analysis

Statistical analyses were carried out using the SPSS software version 15.0 (SPSS Inc, Chicago, IL, USA). One-way analysis of variance was used to compare the clinical characteristics among the three groups followed by the Bonferroni post-hoc test for continuous variables. The χ^2-test was used to compare the categorical parameters.

Pearson's correlation coefficients were calculated to evaluate the relationships between MPV and several clinical variables (age, sex, blood pressure [SBP/DBP], BMI, uric acid, total cholesterol (TC), HDL cholesterol, LDL cholesterol, high-sensitivity C-reactive protein, smoking and alcohol consumption). The distribution of triglycerides was skewed; hence, we carried out Pearson's linear correlation using log-transformed values instead of the raw data. To assess independent relationships between MPV and the clinical variables, a multiple linear regression analysis was carried out. Data were expressed as mean ± standard deviation. A P-value of <0.05 was considered statistically significant.

RESULTS

The characteristics of the 582 NGT participants, 205 IFG participants and 252 IGT participants in the present study are summarized in Table 1. MPV, age, male-to-female ratio, BMI,

Table 1 | Clinical and metabolic characteristics of study participants according to fasting plasma glucose

	NGT	IFG	IGT	*P*-values
No. patients	582	205	252	
Men (%)	60.5	77.07	86.8	<0.001
MPV (fl)	9.92 ± 0.69	10.00 ± 0.80	10.09 ± 0.80	0.104
Count of platelets (10^3 cells/μL)	219.3 ± 53.2	227.3 ± 56.0	210.4 ± 48.9	0.455
Age (years)	54.55 ± 7.90	55.83 ± 7.59	58.61 ± 10.14	<0.001
BMI (kg/m^2)	22.64 ± 2.95	23.78 ± 2.96	24.35 ± 3.64	<0.001
SBP (mmHg)	119.91 ± 16.15	125.28 ± 15.59	126.08 ± 16.60	<0.001
DBP (mmHg)	73.25 ± 11.47	76.20 ± 11.05	76.10 ± 11.43	<0.001
UA (mg/dL)	5.47 ± 1.34	5.93 ± 1.30	6.05 ± 1.22	<0.001
TC (mg/dL)	204.36 ± 32.04	204.02 ± 32.84	204.49 ± 32.59	0.989
TG (mg/dL)	109.41 ± 79.56	116.72 ± 69.55	148.07 ± 75.0	<0.001
Log TG	1.97 ± 1.15	2.08 ± 0.24	2.00 ± 1.99	<0.001
HDL-C (mg/dL)	66.94 ± 15.61	63.20 ± 14.15	60.79 ± 14.23	<0.001
LDL-C (mg/dL)	117.63 ± 27.61	119.17 ± 29.51	118.56 ± 25.76	0.894
hsCRP (mg/dL)	0.070 ± 0.186	0.073 ± 0.297	0.115 ± 0.159	<0.001
Log hsCRP	−1.28 ± 0.22	−0.16 ± 0.24	−1.09 ± 0.46	<0.001
FPG (mg/dL)	91.56 ± 53.35	106.63 ± 105.25	103.30 ± 10.42	<0.001
1 h-PG (mg/dL)	128.30 ± 76.62	149.94 ± 52.70	189.07 ± 37.05	<0.001
2 h-PG (mg/dL)	102.30 ± 59.70	110.22 ± 109.00	161.06 ± 15.55	<0.001
Hypertension (%)	13.23	20.49	26.19	<0.001
Dyslipidemia (%)	31.96	36.10	39.29	<0.001
Familial history of diabetes (%)	10.65	17.07	21.83	<0.001
Smoking status (%)				
Current	17.18	20.00	19.84	<0.001
Former	31.96	33.66	38.49	
Never	50.86	46.34	50.00	
Alcohol ingestion (%)				
Regularly	23.71	27.32	27.78	<0.001
Occasionally	35.05	37.07	40.48	
Never or rarely	41.24	35.61	31.75	

Data are shown as the mean ± standard deviation and percentage (%). *P*-values were calculated using the ANOVA and χ^2-tests. BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; hsCRP; high-sensitivity C-reactive protein; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; LDL-C, low-density lipoprotein cholesterol; MPV, mean platelet volume; NGT, normal glucose tolerance; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; UA, uric acid.

SBP and DBP, uric acid levels, lipid profiles, high-sensitivity C-reactive protein level, smoking status, and alcohol consumption were different in all three groups.

In bivariate correlation analyses of MPV and other parameters in the NGT subjects, MPV showed a significant positive correlation with FGP and 1 h-PG levels. In the IGT participants, MPV showed a significant positive correlation with 2 h-PG levels, TC and LDL cholesterol. In contrast, in the participants with IFG levels, no significant correlation was observed between MPV and postchallenge glucose levels during OGTT (Table 2).

To examine the correlations of postprandial glucose with MPV, multiple correlation analyses were carried out to adjust the variables (BMI, SBP, DBP, TC and LDL cholesterol) that were significant in the bivariate correlation analyses. Multiple correlation analyses showed that in the NTG participants, FPG and 1 h-PG levels had significant linear relationships with MPV. Furthermore, in the IGT participants, FPG and 2 h-PG levels significantly correlated with MPV, even after adjustment for the aforementioned confounding factors. In the IGT participants, the 2 h-PG levels remained as the first independent predictors. However, in the IFG participants, FPG and postprandial glucose levels had no significant relationship with MPV (Table 3). In addition, multiple regression analysis using dummy variables for glucose tolerance, representing NGT, IFG and IGT, showed that glucose tolerance status was independently associated with MPV (data not shown).

DISCUSSION

Mean platelet volume, a determinant of platelet activation, is an emerging risk factor for atherothrombosis. Hyperglycemia increases platelet reactivity directly and by promoting glycation of platelet proteins[22]; increased MPV has also been reported in diabetes[6,15], IGT[16,17] and gestational diabetes[23]. We have previously reported that MPV is positively and independently correlated with FPG levels, not only in prediabetic subjects, but also

Table 2 | Correlations between mean platelet volumes and various parameters

	NGT		IFG		IGT	
	n = 582		*n* = 205		*n* = 252	
	r	*P*-values	*r*	*P*-values	*r*	*P*-values
FPG (mg/dL)	0.083	0.0453	0.0414	0.5552	0.1137	0.1631
1 h-PG (mg/dL)	0.088	0.0388	0.1000	0.1535	0.0146	0.8625
2 h-PG (mg/dL)	0.0503	0.2259	0.0360	0.6081	0.1338	0.0100
Sex	0.1064	0.3421	0.1435	0.5445	0.3767	0.3871
Age (years)	0.0717	0.084	0.0482	0.4924	–0.0072	0.9301
BMI (kg/m^2)	0.0026	0.2144	0.1464	0.0362	0.0056	0.9458
SBP (mmHg)	0.0032	0.9390	0.1770	0.0111	0.1581	0.0517
DBP (mmHg)	0.0070	0.8666	0.2154	0.0019	0.1237	0.1290
UA (mg/dL)	0.0259	0.5334	0.1039	0.1381	0.1306	0.1088
TC (mg/dL)	0.0035	0.9325	0.0814	0.2458	0.1732	0.0328
Log TG	–0.6093	0.8238	0.0495	0.4812	0.0656	0.4218
HDL-C (mg/dL)	0.0030	0.9430	–0.0561	0.4245	–0.0379	0.6427
LDL-C (mg/dL)	0.0358	0.3892	0.0726	0.3006	0.2543	0.0016
Log hsCRP	0.0114	0.7845	0.0245	0.7643	0.0716	0.4331

Coefficients (*r*) and *P*-values are calculated using the Pearson's correlation model. 1 h-PG, 1 h post-challenge plasma glucose; 2 h-PG, 2 h post-challenge plasma glucose; BMI, body mass index; DBP, diastolic blood pressure, FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; LDL-C, low-density lipoprotein cholesterol; Log hsCRP, log-transformed high-sensitivity C-reactive protein; Log TG, log-transformed triglyceride; NGT, normal glucose tolerance; SBP, systolic blood pressure; UA, uric acid; TC, total cholesterol.

in normoglycemic subjects, after correcting for the confounding variables[10].

Coban *et al.*[18] reported a positive correlation between MPV and 2 h-PG during OGTT in modest IGT subjects. However, they did not evaluate the confounding factors that are considered to have a pronounced impact on MPV, such as blood pressure, dyslipidemia, high-sensitivity C-reactive protein or smoking status[24]. In the present study, we confirmed the aforementioned positive correlation in an adequate sample size of IGT subjects, even after correcting for the confounding variables. Our cross-sectional study cannot explain why 2 h-PG levels are associated with elevated MPV in IGT subjects. However, we hypothesized that transient and acute hyperglycemia, which induces oxidative stress, results in an elevated MPV[24]. In the IGT subjects, it has been shown that the association between 2 h-PG levels and the risk of death from cardiovascular disease and other causes is independent of FPG levels[25]. The present results might partly explain the increase in cardiovascular events in patients with postchallenge glucose excursions.

There is increasing epidemiological evidence for the association of postprandial glucose levels and macrovascular complications, even in NGT subjects[26]. To our knowledge, ours is the first study to evaluate the correlation between MPV and blood glucose levels after an oral glucose load in NGT subjects. The present results showed a significant correlation between MPV and 1 h-PG levels in these subjects. However, no correlation was observed between MPV and 2 h-PG levels in NGT subjects. Although the importance of postchallenge glucose levels during OGTT, other than 2 h-PG levels, has not been clearly defined, it has been shown that NGT subjects with elevated 1 h-PG levels develop carotid atherosclerosis, a sign of early cardiovascular atherosclerosis[27]. Furthermore, elevated 1 h-PG levels during OGTT are associated with an increase in cardiovascular mortality and morbidity, and all causes of mortality in the general population[28,29]. Therefore, the present results suggest that the relationship between elevated MPV and 1 h-PG levels might be closely associated with cardiovascular risk factors in NGT subjects.

In the present study, we could not confirm the correlation between MPV and 2 h-PG levels in IFG subjects. IFG and IGT subjects differ not only with respect to FPG and 2 h-PG levels, but also with respect to the shape of the plasma glucose concentration curve after a glucose load during OGTT and a mixed meal[30,31]. IFG, characterized by fasting hyperglycemia, is associated with decreased hepatic insulin resistance and decreased first-phase insulin secretion. Conversely, IGT, characterized by elevated postchallenge glucose levels, is associated with peripheral insulin resistance and impairment of both

Table 3 | Associations of fasting plasma glucose, 1 h postchallenge plasma glucose and 2 h postchallenge plasma glucose with mean platelet volume adjusted for body mass index, blood pressure, and total and low-density lipoprotein cholesterol

	NGT		IFG		IGT	
	n = 582		*n* = 205		*n* = 252	
	Standardized β	*P*-values	Standardized β	*P*-values	Standardized β	*P*-values
FPG (mg/dL)	0.011	0.010	0.006	0.384	0.013	0.032
1 h-PG (mg/dL)	0.018	0.006	0.009	0.201	0.031	0.070
2 h-PG (mg/dL)	0.005	0.295	0.090	0.565	0.009	0.015

1 h-PG, 1 h post-challenge plasma glucose; 2 h-PG, 2 h post-challenge plasma glucose; FPG, fasting plasma glucose; IFG,impaired fasting glucose; IGT, impaired glucose tolerance; NGT, normal glucose tolerance.

early- and late-phase insulin secretions[31–33]. Platelet function is directly regulated by insulin through a functional insulin receptor found on platelets[22,34]. Therefore, these differences between pathophysiological mechanisms of abnormal glucose homeostasis underlying IFG and IGT could contribute to the differences in the correlations between MPV and 2 h-PG levels. To our knowledge, this is the first study to investigate the correlation between MPV and glucose levels after glucose loading in IFG subjects. However, further studies on IFG subjects are required to confirm our findings.

Recent studies have shown seasonal changes in MPV levels. In the Chinese population, Peng *et al.*[35] showed that MPV was lower during summer (11.2–14.7 fl) than during winter (11.8–15.6 fl). Although there are four seasons in Japan, extreme seasonal differences in the numbers of subjects who underwent a 75-g OGTT in the present study were not observed. Therefore, we believe that any seasonal MPV changes in our subjects were small.

The present study had several limitations. First, only a single 75-g OGTT was used, which might have not reflected a patient's status over a long period. In addition, single measurements were subject to intra-individual variability; this might have caused an imprecise classification of participants, thus affecting the results. Second, our findings are based only on the Japanese population; different results might be observed in other ethnic groups. Third, the present study was retrospective, and did not investigate the relationship between MPV and past clinical events.

In conclusion, the present study showed positive correlations between MPV and 2 h-PG levels in IGT subjects, and between MPV and 1 h-PG levels in NGT subjects. Increased platelet activity could contribute to an increased risk of cardiovascular disease in both IGT and NGT subjects.

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