The Relationship Between Diabetes, Metabolic Syndrome, and Platelet Activity as Measured by Mean Platelet Volume

The National Health and Nutrition Examination Survey, 1999–2004

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OBJECTIVE—The association between platelet activity, diabetes, and glucometabolic control is uncertain. We aim to investigate mean platelet volume (MPV), a marker of platelet size and platelet activity, with the prevalence of diabetes, metabolic syndrome, and degree of glycemic control.

RESEARCH DESIGN AND METHODS—This is a retrospective analysis of 13,021 participants in the National Health and Nutrition Examination Survey from 1999 to 2004. Prevalence of diabetes was defined as nonfasting glucose >200 mg/dL, fasting glucose ≥126 mg/dL, or treatment with hypoglycemic agents. Presence of metabolic syndrome was determined by the National Cholesterol Education Program Adult Treatment Panel III definition. Odds ratios and 95% CIs were estimated by logistic regression.

RESULTS—MPV was significantly higher in subjects with diabetes (8.20 vs. 8.06 femtoliter [fL], $P < 0.01$) but not in subjects with metabolic syndrome (8.09 vs. 8.07 fL, $P = 0.24$). For the metabolic syndrome components, MPV was significantly higher in abdominal obesity ($P = 0.03$) and low HDL ($P = 0.04$), and not different in high blood pressure ($P = 0.07$), abnormal glucose metabolism ($P = 0.71$), or hypertriglyceridemia ($P = 0.46$). There was a significant correlation between MPV and glucose ($P < 0.0001$) and between MPV and hemoglobin A_{1c} ($P < 0.0001$) in subjects with diabetes. These correlations were no longer significant in those without diabetes. The adjusted odds of diabetes rose with increasing MPV levels and were most pronounced in subjects with MPV levels exceeding the 90th percentile (≥9.31 fL). The association between MPV and diabetes was most apparent in those with the poorest glucose control.

CONCLUSIONS—Mean platelet volume is strongly and independently associated with the presence and severity of diabetes.

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Platelets play a key role in the development of atherothrombosis, a major contributor of cardiovascular events (1). The contribution of platelets to cardiovascular events has been noted for decades. Since then, there have been numerous studies underlying the importance of platelets in thrombotic complications (1). To further solidify the importance of platelets in cardiovascular disease, medicines aimed at inhibiting platelet activity have been demonstrated to be very effective at decreasing myocardial infarction, stroke, and death (2).

Diabetes affects more than 25 million Americans and is the seventh leading cause of death in the U.S. (3). Metabolic syndrome, a precursor to diabetes, is an independent predictor of cardiovascular events (4). In a landmark study, Davì et al. (5) noted that thromboxane biosynthesis was elevated in subjects with cardiovascular disease who had inadequately controlled diabetes compared with healthy volunteers (5). Several studies since then have suggested that diabetic patients have altered platelet morphology and increased platelet activity (6,7). However, the importance of platelet activity in the setting of diabetes was noted in small selected populations, and specialized laboratory techniques were used to measure platelet activity.

Although several measurements of platelet activity have emerged as potential contributors to atherothrombosis, many of these measurements are time-consuming, expensive, use a high sample volume, or require specialty training (8,9). Alternatively, mean platelet volume (MPV) is a marker of platelet size that is easily determined on routine automated hemograms and routinely available at a relatively low cost. Subjects with a higher MPV have larger platelets that are metabolically and enzymatically more active and have greater prothrombotic potential than smaller platelets (10–13). In fact, several studies have demonstrated a significant association between higher MPV and an increased incidence of cardiovascular events and all-cause mortality (14–16).

In the current study, we hypothesized that a higher MPV would be independently associated with the prevalence of diabetes and that this association would be modified by the degree of glycemic control. We therefore sought to examine the relationship of MPV with diabetes, glucometabolic

control, and the metabolic syndrome in a large unselected population using the National Health and Nutrition Examination Survey (NHANES).

RESEARCH DESIGN AND METHODS

—The data source for this study was the 1999–2004 NHANES conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention. NHANES is a cross-sectional survey of the civilian, noninstitutionalized population of the U.S. Participants self-reported their age, race/ethnicity, and sex. Race/ethnicity was coded as non-Hispanic white, non-Hispanic black, Mexican American, and other. NHANES oversampled African Americans, Mexican Americans, and subjects aged 60 years and older. Participants with aged <21 years and a platelet count <100 and >450 ×10³/µL were excluded. Of a sample of 13,021 people who underwent detailed in-person interviews, physical examinations, and laboratory testing, 11,730 had data to classify them as with or without diabetes, and 10,775 had data on the five components of the metabolic syndrome (abdominal obesity, hypertension, hypertriglyceridemia, low HDL cholesterol, and abnormal glucose metabolism). The dataset with subjects having all nonmissing values for diabetes, the metabolic syndrome, and each component of the metabolic syndrome, is defined as the complete case dataset and is used for domain analysis.

History of diabetes was defined as a random glucose >200 mg/dL, fasting blood glucose ≥126 mg/dL, or treatment with insulin or oral hypoglycemic agents. We used the metabolic syndrome definition published as part of the National Cholesterol Education Program Adult Treatment Panel III recommendations (17). The fasting blood glucose threshold of ≥100 mg/dL set by the American Diabetes Association was used as part of the definition for abnormal glucose metabolism (18). Abdominal obesity was defined as a waist circumference >102 cm (40 inches) in men and >88 cm (35 inches) in women. History of hypertension was defined as systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg. The hypertension definition could also be met by a self-report of current use of antihypertensive medication or whether the patient responded yes to the question: "Have you ever been told by a doctor or other health professional that you had hypertension, also called

high blood pressure?" Hypertriglyceridemia was identified by triglycerides ≥150 mg/dL, and low HDL cholesterol was identified by HDL cholesterol <40 mg/dL in men or <50 mg/dL in women.

Laboratory analysis

The mean platelet volume (MPV), platelet count, and other blood cell indices were measured using a Beckman Coulter method of counting and sizing, automatic diluting, and mixing. An automated chemical analyzer (Beckman Syncrom LX20, Beckman Coulter, Fullerton, CA) was used to determine nonfasting total cholesterol, triglycerides, and HDL cholesterol levels. Fasting glucose was measured using a hexokinase method.

Statistical analysis

NHANES uses a complex, multistage, probability-sampling design to select participants representative of the civilian, noninstitutionalized U.S. population. All analyses accounted for the complex sampling method following the NHANES analytic guidelines (19). Because the goodness-of-fit tests for normal distribution of the MPV show that the MPV is not normally distributed ($P < 0.01$), the median (interquartile [IQR]) for MPV was used in the descriptive analyses. In regression analyses on the MPV, however, the continuous MPV was used according to the central limit theorem because the sample size is quite large (20).

To test the MPV level differences between presence and absence of diabetes, the metabolic syndrome, and each component of the metabolic syndrome, we obtained P values by using linear regression of continuous MPV on those dichotomous variables mentioned above (Table 1). We also obtained Wald χ^2 P values by using logistic regression of presence and absence of diabetes, the metabolic syndrome, and each component of

the metabolic syndrome on continuous MPV (Table 2).

Associations between MPV and glucose or HbA_{1c} were examined using Pearson correlation coefficients. To explore the relationship between MPV and the prevalence of diabetes, logistic regression was used with diabetes as the dichotomous outcome and MPV as the main predictor. We built models hierarchically for categoric MPV. First, we added in demographics such as age, sex, and race into the logistic regression model. This was followed by platelet count and BMI in the next step. Lastly, we sequentially added HDL cholesterol, waist circumference, high blood pressure, and triglycerides to the logistic regression model (when waist circumference was included, BMI was excluded). All P values presented are two-tailed; $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SAS 9.2 software to account for the complex sampling design. Domain statement was used in all analyses to ensure the correctness of variance estimates.

RESULTS—Baseline characteristics of the sample population are detailed in the Supplementary Table. Among the 13,021 subjects, 48% were men, 73% were non-Hispanic white, and the mean age was 47 years (range 21–85 years). The prevalence of cardiovascular disease, as defined by a history of myocardial infarction or stroke, in the overall population was 5.6%. Of the 11,730 subjects (90%) for whom diabetes status was available, 1,558 had diabetes, for an unadjusted weighted prevalence of 9.7%. There were 4,034 subjects with metabolic syndrome, for an unadjusted weighted prevalence of 31%.

Table 1 reports the median MPV levels in participants with and without diabetes, the metabolic syndrome, and its individual components. MPV was

Table 1—MPV levels (fL) according to the presence or absence of diabetes, the metabolic syndrome, and each component of the metabolic syndrome

Characteristic	Present	Absent	P
Diabetes	8.20 (7.62–8.82)	8.06 (7.55–8.65)	0.0073
Metabolic syndrome	8.09 (7.58–8.74)	8.07 (7.55–8.69)	0.2372
Abdominal obesity	8.09 (7.58–8.71)	8.05 (7.54–8.63)	0.0262
High blood pressure	8.08 (7.57–8.73)	8.06 (7.55–8.63)	0.0665
Abnormal glucose metabolism	8.10 (7.58–8.75)	8.10 (7.63–8.72)	0.7063
Low HDL cholesterol	8.09 (7.58–8.70)	8.06 (7.55–8.68)	0.0435
Hypertriglyceridemia	8.06 (7.55–8.63)	8.07 (7.56–8.71)	0.4646

Data are presented as median (IQR). P values were obtained by linear regression.

Table 2—Prevalence of diabetes (stratified by glycemic control) and metabolic syndrome components by MPV quartile

| | MPV quartile | | | | |
	1st $n = 3,297$	2nd $n = 3,775$	3rd $n = 2,849$	4th $n = 3,100$	P
Diabetes					
HbA$_{1c}$ ≤6.5%	46.7 (3.1)	40.5 (4.7)	40.5 (2.8)	36.3 (2.8)	0.7831
HbA$_{1c}$ 6.6–8%	27.7 (2.9)	34.1 (3.6)	30.8 (3.3)	30.2 (2.9)	0.1002
HbA$_{1c}$ ≥8%	25.6 (3.4)	25.4 (4.1)	28.7 (2.3)	33.5 (2.6)	0.0666
Metabolic syndrome	32.9 (1.2)	33.0 (1.6)	34.6 (1.1)	35.2 (1.1)	0.2317
Abdominal obesity	47.6 (1.4)	49.9 (1.3)	50.6 (1.5)	51.6 (1.2)	0.0223
High blood pressure	40.5 (1.3)	40.7 (1.5)	40.9 (1.3)	43.8 (1.2)	0.0649
Abnormal glucose metabolism	44.7 (2.3)	43.0 (2.1)	41.2 (1.8)	44.4 (1.4)	0.7048
Low HDL cholesterol	32.2 (1.5)	31.2 (1.3)	35.1 (1.2)	33.5 (0.9)	0.0343
Hypertriglyceridemia	32.3 (1.0)	31.7 (1.0)	32.1 (0.9)	30.4 (1.1)	0.4603

Data are shown as percent (SE). P values were obtained by linear regression.

Figure 1—*Prevalence of diabetes is shown stratified by mean MPV quartiles. The SE for the prevalence of diabetes is 0.7 in the 1st MPV quartile, 0.7 for the 2nd MPV quartile, 0.5 for the 3rd MPV quartile, and 0.7 for the 4th MPV quartile.*
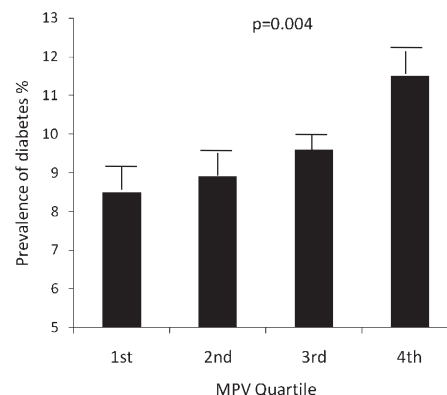
significantly higher in the subjects with diabetes (8.20 vs. 8.06 femtoliter [fL], $P = 0.007$). There was no significant difference in MPV between subjects with and without the metabolic syndrome (8.09 vs. 8.07 fL, $P = 0.24$). For the individual components of the metabolic syndrome, MPV was significantly higher in subjects with abdominal obesity ($P = 0.03$) and low HDL cholesterol ($P = 0.04$), and was not significantly different in those with high blood pressure ($P = 0.07$), abnormal glucose metabolism ($P = 0.71$), or hypertriglyceridemia ($P = 0.46$). Median (IQR) MPV levels (in fL) increased with the number of components of the metabolic syndrome: 8.05 (7.54–8.67) if no components were present, 8.07 (7.55–8.66) if one component was present, 8.06 (7.56–8.65) if two components were present, 8.07 (7.58–8.73) if three components were present, 8.12 (7.57–8.73) if four components were present, and 8.23 (7.60–8.81) if five components were present. However, this finding failed to reach statistical significance ($P = 0.09$).

Significant correlations were found between MPV and fasting blood glucose ($P < 0.0001$) and between MPV and HbA$_{1c}$ ($P < 0.0001$) in the population with diabetes. These correlations were no longer significant in the nondiabetic population ($P = 0.13$ and $P = 0.08$, respectively). Subjects in higher MPV quartiles were more likely diabetic (8.5% [SE 0.7] in quartile 1, 8.9% [0.7] in quartile 2, 9.6% [0.5] in quartile 3, and 11.5% [0.7] in quartile 4; $P = 0.004$; Fig. 1). This difference was most apparent in diabetic subjects with poor glycemic control (Table 2).

To better understand the relationship between glycemic control and diabetes, we evaluated MPV in diabetic subjects stratified by HbA$_{1c}$. Median (IQR) MPV (in fL) increased with HbA$_{1c}$: 8.09 (7.55–8.74) if HbA$_{1c}$ ≤6.5%, 8.24 (7.7–8.82) if HbA$_{1c}$ was 6.6–7.9%, and 8.35 (7.77–8.91) if HbA$_{1c}$ >8% ($P = 0.02$). The prevalence of metabolic syndrome was not different when evaluated by MPV quartiles (Table 2); however, the prevalence of abdominal obesity and low HDL was higher with increasing MPV quartiles.

The estimated prevalence of diabetes increased with increasing MPV. The odds of having diabetes rose with increasing MPV levels and became statistically significant with MPV levels in excess of the 90th percentile (Table 3). Compared with subjects with MPV levels less than the 50th percentile (8.07 fL), subjects with higher MPVs had a graded increase in the odds of diabetes: odds ratio (OR) 1.21 (95% CI 0.98–1.49) for MPV >75th percentile (8.69 fL), 1.48 (1.19–1.84) for MPV >90th percentile (9.31 fL), and 2.17 (1.22–3.85) for MPV >99th percentile (10.57 fL). In a multivariable model adjusted for age, sex, and race/ethnicity, MPV was associated with prevalence of diabetes: OR 1.15 (0.94–1.42) for MPV >75th percentile, 1.40 (1.12–1.75) for MPV >90th percentile, and 2.03 (1.13–3.67) for MPV >99th percentile. In further analyses also adjusting for BMI and platelet count, the association between higher MPV and diabetes was present with some attenuation of the magnitude: OR 1.36 (0.99–1.89) for MPV >90th percentile and 1.68 (0.83–3.39) for MPV >99th percentile. When the components of metabolic syndrome (HDL cholesterol, waist circumference, high blood pressure, and triglycerides) were sequentially added to the model, the odds of diabetes remained elevated with increasing levels of MPV. Finally, no significant interaction was detected between MPV and cardiovascular disease.

CONCLUSIONS—This is the largest study to date to examine MPV with diabetes and correlate MPV to the degree of glycemic control in a large unselected population. Several small studies have noted a higher MPV in patients with diabetes (21–26). However, the data correlating MPV to glycemic control are conflicting and from relatively small or single-center populations (21–26). Although one study correlated MPV to the presence of metabolic syndrome (27), no study has evaluated MPV and the individual components of the metabolic syndrome. The current analysis is the largest study of platelet activity in diabetes and the only study to evaluate the complex relationship between MPV and diabetes, glycemic control, and the metabolic syndrome with its individual components.

In the current study, platelet activity, as measured by MPV, is significantly higher in the diabetic population and, in particular, in those subjects with diabetes and poor glycemic control. This is consistent with an observational study of 150 subjects by Coban et al. (24) that demonstrated a graded association between MPV and the glucometabolic state (diabetes > impaired fasting glucose > healthy control subjects). This is also consistent with a study of 105 subjects that demonstrated MPV was higher in the 35 subjects with diabetes and a HbA$_{1c}$ level >7% compared with

Table 3—Odds of diabetes with elevated MPV levels

Cut point percentile	MPV fL	Diabetes %	Unadjusted OR (95% CI)	P	Adjusted OR* (95% CI)	P	Adjusted OR† (95% CI)	P	Adjusted OR‡ (95th percentile)	P
≥50th	≥8.07	16.70	1.07 (0.90–1.27)	0.467	1.05 (0.88–1.26)	0.560	0.98 (0.82–1.17)	0.803	0.91 (0.76–1.09)	0.317
≥75th	≥8.69	18.51	1.21 (0.98–1.49)	0.071	1.15 (0.94–1.42)	0.179	1.11 (0.88–1.40)	0.368	1.06 (0.84–1.33)	0.633
≥90th	≥9.31	21.72	1.48 (1.19–1.84)	<0.001	1.40 (1.12–1.75)	0.003	1.36 (0.99–1.89)	0.061	1.27 (0.95–1.71)	0.111
≥99th	≥10.57	28.91	2.17 (1.22–3.85)	0.009	2.03 (1.13–3.67)	0.018	1.68 (0.83–3.39)	0.146	1.81 (0.90 3.64)	0.098

P values were obtained by linear regression. *Adjusted for age, sex, and race/ethnicity. †Adjusted for age, sex, race/ethnicity, BMI, and platelet count. ‡Adjusted for age, sex, race/ethnicity, platelet count, HDL cholesterol, waist circumference, high blood pressure, and triglycerides.

subjects with diabetes and a HbA_{1c} <7% (25). Furthermore, MPV was decreased at the 3-month follow-up in the 30 diabetic patients in whom glycemic control was improved with intensive diet and pharmacotherapy (25).

Although the underlying mechanism of higher MPV in diabetic subjects is incompletely understood, it has been suggested that increased MPV in diabetes may be due to osmotic swelling as a result of hyperglycemia (28). Another postulated mechanism from a study in mice demonstrated that insulin causes megakaryocytes to produce larger platelets (29). Alternatively, increased platelet size may reflect the presence of high platelet turnover and younger platelets (30). Larger platelets and younger platelets are both believed to be more physiologically active, have greater prothrombotic potential, and may be less responsive to antiplatelet therapy (11,31). These data may help explain the increased cardiovascular risk and worse responsiveness to antiplatelet therapy observed in diabetes (32,33).

The current study demonstrates a significant correlation of MPV with degree of glycemic control *only* in the diabetic population and not in the nondiabetic population. Among subjects with metabolic syndrome, the group with abnormal glucose metabolism (versus normal glucose metabolism) did not have a significantly higher MPV. These data suggest that hyperglycemia alone (without diabetes) is insufficient to see a difference in platelet activity. An underlying abnormal glucometabolic state and poor glycemic control is necessary to observe a higher MPV.

Of note, there was no significant difference in MPV in subjects with and without metabolic syndrome, suggesting that the association of metabolic syndrome to cardiovascular events may not be through the mechanism of increased platelet activity. Only one small study of 345 subjects previously examined the relationship between metabolic syndrome and MPV (27). Although higher MPV was demonstrated in subjects referred for coronary angiography with metabolic syndrome compared with those without metabolic syndrome, many of the patients with metabolic syndrome also had coronary artery disease, whereas those without metabolic syndrome had only angiographically normal coronary arteries. Subjects with coronary artery disease are known to have higher MPV than those without coronary artery disease (14,15), and that elevated MPV is associated with atherosclerosis rather than metabolic syndrome itself is highly plausible.

The current study found that MPV was significantly higher in subjects with low HDL cholesterol and abdominal obesity. HDL cholesterol and obesity have consistently been associated with markers of platelet activity (34–36). In fact, infusion of reconstituted HDL in subjects with diabetes resulted in a reduction of ex vivo platelet aggregation (37). Furthermore, weight loss in subjects with obesity was also associated with a decrease in platelet activity (38). In addition to being a marker of risk, platelet activity may serve as a potential therapeutic target.

Limitations

This is an observational study, and because of the cross-sectional design, we cannot establish a causal relationship between MPV and diabetes and degree of glycemic control. However, our findings do support the link between an underlying abnormal glucometabolic state, poor glycemic control, and platelet activity as measured by MPV. Second, the MPV value evaluated in this study represents only one point in time. Third, although specific instructions were given to run the blood count within 2 h of collection, sites were allowed to run the sample up to a maximum of 24 h, and, therefore, we are unable to determine time-sensitive EDTA-induced platelet swelling (39). Nonetheless, any bias introduced would have biased the results toward the null hypothesis. Fourth, our study did not account for use of medications affecting platelet activity; however, there are data suggesting that MPV is not influenced by platelet-directed therapies and therefore, this would unlikely affect the study results (40). Finally, the findings are limited to the cohort studied here, which included noninstitutionalized adults from the U.S., and, thus, exclude hospitalized patients and may not be applicable to other nationalities.

In conclusion, MPV is strongly and independently associated with the presence of diabetes. Furthermore, glucose control modifies the association of MPV and diabetes. These data suggest a potential role of platelet activity measurement in subjects with diabetes. Large prospective studies correlating vascular complications of diabetes with MPV should be considered and may support the role of monitoring MPV in the diabetic population.

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