Platelet markers correlate with glycemic indices in diabetic, but not diabetic-myelodysplastic patients with normal platelet count

Maria Dalamaga, Konstantinos Karmaniolas, Antigoni Lekka, George Antonakos, Apollon Thrasyvoulides, Evangelia Papadavid, Nikolaos Spanos and Amalia Dionyssiou-Asteriou

Abstract. Background: Altered thrombocyte morphology and function have been reported in patients with diabetes mellitus (DM) type 2. The aim of the present study was to determine the associations between platelet morphology markers and hemoglobin A1C (HbA1c), fasting glucose (FG), hypertension and coronary heart disease (CHD) in patients with myelodysplastic syndromes (MDS) and DM, in patients with DM and in controls.

Methods: This cross-sectional study included 30 cases with primary MDS with normal platelet count and non-insulin dependent diabetes, 30 non-insulin dependent diabetic patients and 30 non-diabetic, non-MDS controls matched on age and gender.

Results: After adjusting for body mass index, platelet number, CHD and hypertension, HbA1c and FG were significant predictors of mean platelet volume (MPV) and platelet distribution width (PDW) in diabetic patients. There was no correlation between platelet parameters and HbA1c or FG in diabetic MDS patients. In controls, FG and hypertension predicted significant differences in platelet morphology. Platelet count correlated with platelet morphology in diabetic MDS and control groups, but not in diabetics.

Conclusions: MPV and PDW are associated with glycemic indices in diabetic patients but not in diabetic MDS patients with normal platelet counts. Non-diabetic controls also exhibit FG related changes in platelet morphology. This suggests other factors inherent to bone marrow dysplasia, platelet turnover and biochemistry, or vascular environment affect platelet morphology in diabetic MDS patients even with normal platelet count. Platelet morphology in this population may be an early marker for myelodysplasia. These findings also support platelet morphology change as a marker for elevated macrovascular disease risk.

Keywords: Myelodysplastic syndrome, diabetes, glycohemoglobin, glucose, mean platelet volume

1. Introduction

Altered thrombocyte morphology and function have been reported in patients with diabetes mellitus type 2 [1]. Mean platelet volume (MPV) as well as platelet distribution width (PDW) have been evaluated as markers of platelet morphology and activation in many stud-
ies [1–3]. There is accumulating evidence that MPV reflects the state of thrombogenesis [4]. Diabetic patients present higher MPV values than normal controls matched on age and gender [1,5]. High MPV values are related with an increased risk of developing micro- and macrovascular diabetic complications such as cardiovascular disease [1,6,7]. Moreover, it has recently been reported that MPV is lower in thrombocytopenic patients with bone marrow disease and could act as a surrogate marker for the degree of bone marrow disease [8] in patients with myelodysplastic syndrome (MDS). However, the relationship of platelet parameters to the development of diabetic vascular disease and especially in MDS patients with diabetes mellitus (DM) and normal platelet count remains unclear. To the best of our knowledge, this is the first study in medical literature assessing the association of glycosylated hemoglobin (HbA1c) and fasting blood glucose with platelet parameters in diabetic MDS patients with normal platelet count.

Therefore, the aim of the present investigation was (1) to evaluate platelet markers such as MPV and PDW in diabetic MDS patients with normal platelet count, in patients with DM type 2 without microvascular diabetic complications, and in non-diabetic non-MDS healthy controls; and (2) to determine the associations between platelet parameters (MPV, PDW) and glycosylated hemoglobin and fasting blood glucose with platelet parameters in diabetic MDS patients with normal platelet count.

2. Materials and methods

In this study, both cases and controls were selected from patients of the Outpatient Department at the Veterans’ General Hospital of Athens (NIMTS). This hospital is the only Veterans’ Hospital in Athens Metropolitan area and the entire Southern Greece. The study included 90 patients divided into three groups. Group A comprised 30 cases with primary MDS and type 2 diabetes mellitus (21 men and 9 women) with a mean age of 72.6 ± 6.1, a mean duration of diabetes of 10.7 ± 4.2 years and a mean platelet count of 177.9 × 10^9/L ± 28.5 (range: 150–290 × 10^9/L). Eligible cases of this group included newly diagnosed patients with histologically confirmed primary MDS without underlying malignancy, prior to any therapeutic approach (transfusion and/or chemotherapy) under age 82, consecutively seen in the Outpatient Department of Internal Medicine-Hematology between March 1, 2000 and October 31, 2006. All cases were classified according to the FAB Cooperative Group scheme [9]. The following MDS subtypes were recognised: refractory anaemia (RA), refractory anaemia with ring sideroblasts (RARS) and refractory anaemia with excess blasts (RAEB).

Group B consisted of 30 patients with type 2 diabetes mellitus (21 men and 9 women) with a mean age of 70.2 ± 6.1 and a mean duration of diabetes of 13.2 ± 3.6 years. These were patients without neoplastic and infectious conditions from the Outpatient Diabetologic Department of the same hospital matched to cases of group A on age (± 5 years) and gender.

Group C (healthy controls) included 30 non-diabetic individuals (21 men and 9 women) with a mean age of 73.5 ± 5.9 without neoplastic and infectious conditions seen in the Outpatient Laboratory Department from individuals coming for an annual check-up examination of the same hospital and matched to cases of group A on age (± 5 years) and gender. No control developed MDS or any malignancy. For every eligible case of group A, an attempt was made to randomly identify a case of group B and a control of group C admitted to the Outpatient Department of Veterans’ Hospital as closely as possible in time to the corresponding case.

Exclusion criteria for all participants in the study were detection of abnormal platelet count (less than 150 × 10^9/L), abnormal leucocyte count (greater than 10 × 10^9/L), presence of iron deficiency anemia or hemolytic anemia. None of the patients and controls had any thrombotic disease or had received anticoagulant or antiplatelet medication. Furthermore, all patients were not smokers (or were ex-smokers for at least 2 years) and didn’t present hypertriglyceridemia (serum triglycerides greater than 180 mg/dL) or hyperbilirubinemia (serum bilirubin greater than 1.5 mg/dL). All study participants were fully informed of the aim of the study and gave written consent for their participation and their agreement that the results of this study may well be presented or published, solely in the interests of science, provided that their anonymity is maintained. The study protocol was approved by the Committee of NIMTS Hospital.

Platelet count, MPV and PDW were measured in blood samples anticoagulated with sodium citrate within 90 min after collection by venipuncture. Each measurement was performed in two different automated blood cell counters (Sysmex XE 2100 and Cell Dyn 1700). During the study period, the anticoagulant, its dilution, the blood cell counters as well as the time from venipuncture and the conditions of sample storage remained invariable. HbA1c was measured using
Table 1: Demographic and clinical data of diabetic MDS patients (Group A), diabetic patients (Group B) and healthy controls (Group C)

| Parameters                        | Group A         | Group B         | Group C         | p value |
|-----------------------------------|-----------------|-----------------|-----------------|---------|
| Number of patients                | 30              | 30              | 30              | –       |
| Age, years, mean (SD)             | 72.6 (6.1)      | 70.2 (6.1)      | 73.5 (5.9)      | NS      |
| Gender (male/female)              | 21 / 9          | 21 / 9          | 21 / 9          | NS      |
| Duration of diabetes, years, mean (SD) | 10.7 (4.2) | 13.2 (3.6)      | –               | 0.02    |
| Fasting blood glucose, mmol/L, mean (SD) | 7.8 (0.9) | 8.5 (0.9)      | 5.1 (0.5)       | < 0.001 |
| HbA1c, %, mean (SD)               | 7.1 (1.1)       | 8.1 (0.8)       | 5.2 (0.4)       | < 0.001 |
| Mean platelet count, × 10^9/L, mean (SD) | 177.9 (28.5) | 261.2 (36.1)   | 268.9 (47.6)    | < 0.001 |
| MPV, fL, mean (SD)                | 9.5 (1.2)       | 13.0 (9.9)      | 11.2 (1.2)      | < 0.001 |
| Body Mass Index, kg/m², mean (SD) | 13.1 (0.9)      | 16.4 (1.3)      | 13 (1.7)        | < 0.001 |
| Arterial hypertension (yes/no)    | 9 / 21          | 8 / 22          | 4 / 26          | NS      |
| Treatment for hypertension (yes/no) | 2 / 28        | 4 / 26          | 1 / 29          | NS      |
| Coronary artery disease (yes/no)  | 4 / 26          | 4 / 26          | 1 / 29          | NS      |
| FAB MDS category (N of patients and %) | RA (17 (56.7)) | 17 (56.7)       | 17 (56.7)       |        |
|                                   | RARS (10 (33.3)) | 10 (33.3)      | 10 (33.3)       |        |
|                                   | RAEB (3 (10))   | 3 (10)          | 3 (10)          |        |

†NS = Non-significant.
∂SD = Standard Deviation.

3. Results

Table 1 depicts the demographic and clinical characteristics of patients and controls as well as the histologic subtype of MDS patients according to the FAB classification scheme. The mean age of diabetic MDS patients was 72.6 years (± 6.1), of diabetic patients 70.2 years (± 6.1) and of hospital controls 73.5 years (± 5.9). Male patients in each group were 21 (70%) and female 9 (30%). The predominant histologic subtype of MDS was RA (56.7%) with about more than half of all MDS cases diagnosed in this category.

Mean platelet count in diabetic MDS patients (Group A) was significantly lower than that in diabetic patients...
(p < 0.001) and controls (p < 0.001), but platelet count in all groups was within normal ranges (150–400 × 10^9/L). MPV and PDW in diabetic patients were significantly higher than those in diabetic MDS patients (p < 0.001) and controls (p < 0.001). Fasting blood glucose and HbA1c in diabetic patients were significantly higher than those in diabetic MDS patients (p = 0.006 and p < 0.001 respectively) and controls (p < 0.001). BMI in diabetic patients was significantly higher than BMI in diabetic MDS patients (p < 0.001) and controls (p < 0.001).

In the group of diabetic MDS patients (Group A), there were no correlations between MPV and fasting glucose (r = −0.157, p = 0.408), and MPV and HbA1c (r = 0.014, p = 0.941). In Group A, MPV correlated significantly with PDW (r = 0.853, p < 0.001). MPV and PDW were statistically significantly higher in diabetic MDS patients with hypertension (p = 0.03 and 0.02 respectively) and in diabetic MDS patients with CHD (p = 0.02 and 0.05 respectively).

In the group of diabetic patients (Group B) there were statistically significant correlations between MPV and fasting glucose (r = 0.825, p < 0.001), MPV and HbA1c (r = 0.877, p < 0.001), and MPV and PDW (r = 0.694, p < 0.001). PDW correlated significantly with fasting serum glucose (r = 0.66; p < 0.001) and HbA1c (r = 0.579, p < 0.001). MPV and PDW were statistically significantly higher in diabetic patients with hypertension (p < 0.001) and in diabetic patients with CHD (p = 0.03 and 0.006 respectively). Overall, in patients with diabetes (Group A and B), MPV and PDW were statistically significantly higher in patients with CHD (p = 0.024 and p = 0.036 respectively) and hypertension (p = 0.05).

In controls (Group C), MPV correlated significantly with fasting glucose (r = 0.763, p < 0.001) but not with HbA1c (r = −0.118, p = 0.536). Similarly, PDW correlated significantly with fasting glucose (r = 0.439, p = 0.015) but not with HbA1c (r = −0.024, p = 0.9).

Multiple linear regression models were performed in order to explore the association between MPV and HbA1c, fasting blood glucose, adjusting for confounding factors such as age, gender, BMI, platelet count, CHD, hypertension in diabetic MDS patients, in diabetic patients and finally in controls (Tables 2, 3 and 4). Adjusting for age, gender, BMI, platelet number, CHD and hypertension, neither HbA1c nor fasting blood glucose presented any statistically significant association with MPV (p = 0.55 and p = 0.26 respectively, Table 2a) or PDW (p = 0.66 and p = 0.28 respectively, Table 2b) in diabetic MDS patients. Only platelet count was significantly associated with MPV and PDW (p < 0.001 and p = 0.03 respectively). Adjusting for age, gender, BMI, platelet number, CHD and hypertension, HbA1c and fasting blood glucose were the only statistically significant predictors of MPV (p < 0.001, Table 3a) and PDW (p = 0.014 and 0.007 respectively, Table 3b) in diabetic patients. Finally, controlling for the aforementioned variables, fasting blood glucose, platelet count and the presence of hypertension were statistically significant predictors of MPV in healthy controls (Table 4a).

Further adjustment for hypertensive treatment in all models for all Groups (A, B and C) didn’t alter the results.

| Independent variables | b | SE_b | t statistic | p value |
|-----------------------|---|------|-------------|---------|
| **Model 1**           |   |      |             |         |
| HbA1c                 | 0.08 | 0.14 | 0.61 | 0.55 |
| Hypertension          | 0.32 | 0.35 | 0.89 | 0.38 |
| CHD                   | 0.81 | 0.5  | 1.62 | 0.12 |
| BMI                   | 0.06 | 0.15 | 0.4  | 0.69 |
| Platelet number       | 0.02 | 0.01 | 4.57 | <0.001* |
| **Model 2**           |   |      |             |         |
| Fasting blood glucose | −0.17 | 0.14 | −1.16 | 0.26 |
| Hypertension          | 0.33 | 0.34 | 0.97 | 0.34 |
| CHD                   | 0.89 | 0.5  | 1.79 | 0.09 |
| BMI                   | 0.1  | 0.14 | 0.77 | 0.45 |
| Platelet number       | 0.02 | 0.01 | 4.04 | <0.001* |

* statistically significant when p ≤ 0.05.

| Independent variables | b | SE_b | t statistic | p value |
|-----------------------|---|------|-------------|---------|
| **Model 1**           |   |      |             |         |
| HbA1c                 | −0.06 | 0.14 | −0.44 | 0.66 |
| Hypertension          | 0.35 | 0.38 | 0.93 | 0.36 |
| CHD                   | 0.57 | 0.53 | 1.08 | 0.29 |
| BMI                   | 0.04 | 0.16 | 0.31 | 0.76 |
| Platelet number       | 0.01 | 0.006 | 2.24 | 0.03* |
| **Model 2**           |   |      |             |         |
| Fasting blood glucose | −0.009 | 0.008 | −1.1 | 0.28 |
| Hypertension          | 0.28 | 0.36 | 0.77 | 0.45 |
| CHD                   | 0.76 | 0.53 | 1.41 | 0.17 |
| BMI                   | 0.02 | 0.15 | 0.17 | 0.87 |
| Platelet number       | 0.01 | 0.006 | 2.2 | 0.05* |

* statistically significant when p ≤ 0.05.
4. Discussion

Diabetes mellitus constitutes a complex disease which is characterized by chronic hyperglycemia, metabolic abnormalities and long-term macrovascular and microvascular abnormalities involving the blood vessels, eyes, kidneys and nerves. Platelet parameters such as high platelet counts and mainly high MPV have been reported in diabetic patients and they are likely to be associated with an increased risk of vascular disease [1,13]. Higher MPV in diabetic patients indicates larger platelet size suggesting stimulated thrombopoiesis and augmented platelet activation [3,13]. Platelet hyperactivity is accompanied by an increased production of thromboxane A2 and/or a decreased synthesis of prostacycline as larger platelets produce more serotonin, thromboxane A2, β-thromboglobulin and secrete more membrane receptors such as CD63 and CD62 [14,15].

In agreement with other studies [1,5], our study showed that diabetic patients presented significantly higher MPV and PDW than age- and gender-matched non-diabetic controls. Furthermore, both in univariate analysis and after adjustment for confounders, we found that there was a positive correlation between MPV and HbA1c, or fasting blood glucose in diabetic patients. One possible mechanism of increased MPV in DM is osmotic swelling due to raised blood glucose and some glucose metabolites [16] and perhaps due to a shorter life span of platelets in diabetic patients [17].

The table below shows the results of multiple linear regression analysis of MPV and PDW in diabetic patients adjusting for age and gender (matched variables), HbA1c (model 1), fasting blood glucose (model 2), hypertension, CHD, BMI and platelet count (as independent variables); regression coefficients (b), standard error of b (SEb) and t statistic with corresponding p-value. HbA1c and fasting blood glucose were not introduced simultaneously in a model because of co-linearity.

| Independent variables | b     | SEb   | t statistic | p value |
|-----------------------|-------|-------|-------------|---------|
| **Model 1**           |       |       |             |         |
| HbA1c                 | 0.88  | 0.14  | 7.17        | <0.001* |
| Hypertension          | 0.53  | 0.13  | 1.37        | 0.09    |
| CHD                   | 0.12  | 0.29  | 0.97        |         |
| BMI                   | 0.003 | 0.04  | 0.97        |         |
| Platelet number       | −0.0007 | 0.003 | −0.24      | 0.81    |
| **Model 2**           |       |       |             |         |
| Fasting blood glucose | 0.87  | 0.16  | 5.26        | <0.001* |
| Hypertension          | 0.23  | 0.57  | 0.57        | 0.09    |
| CHD                   | 0.01  | 0.98  | 0.01        |         |
| BMI                   | 0.04  | 0.63  | 0.63        |         |
| Platelet number       | −0.003 | 0.003 | −1.04      | 0.31    |

*statistically significant when p ≤ 0.05.

The table below shows the results of multiple linear regression analysis of MPV and PDW in healthy controls adjusting for age and gender (matched variables), HbA1c (model 1), fasting blood glucose (model 2), hypertension, CHD, BMI and platelet count (as independent variables); regression coefficients (b), standard error of b (SEb) and t statistic with corresponding p-value. HbA1c and fasting blood glucose were not introduced simultaneously in a model because of co-linearity.

| Independent variables | b     | SEb   | t statistic | p value |
|-----------------------|-------|-------|-------------|---------|
| **Model 1**           |       |       |             |         |
| HbA1c                 | 0.68  | 0.26  | 2.66        | 0.014*  |
| Hypertension          | 1.09  | 1.65  | 2            | 0.06    |
| CHD                   | 0.19  | 1.49  | 0.15        |         |
| BMI                   | 0.0007| 0.14  | 0.89        |         |
| Platelet number       | 0.0002| 0.05  | 0.96        |         |
| **Model 2**           |       |       |             |         |
| Fasting blood glucose | 0.04  | 0.29  | 0.007       |         |
| Hypertension          | 0.7   | 1.19  | 0.24        |         |
| CHD                   | 0.39  | 0.62  | 0.54        |         |
| BMI                   | 0.24  | 1.39  | 0.07        |         |
| Platelet number       | 0.0002| 0.05  | 0.96        |         |

*statistically significant when p ≤ 0.05.
Alternatively, this may also suggest that platelet activation is related to glycemic control, an issue of current debate [1,5,18,19].

In contrast, we found no correlation between platelet parameters and HbA1c or fasting blood glucose in diabetic MDS patients with normal platelet count after adjusting for age, gender, BMI, platelet count, presence of CHD and hypertension. To the best of our knowledge, this is the first study in medical literature evaluating the association of glycemic control and platelet parameters in diabetic MDS patients with normal platelet count.

MDS constitutes a heterogeneous group of acquired clonal disorders of the stem cell, characterized by ineffective hematopoiesis leading to one or more peripheral blood cytopenias associated typically with a normocellular or hypercellular bone marrow [20]. Thrombocytopenia in MDS (< 100 × 10^9/L) ranges from 40% to 65% [21]. Recently, it has been reported that MPV is lower in thrombocytopenic patients with bone marrow disease and could be used as a surrogate prognostic marker for the degree of bone marrow disease in MDS patients [8]. In our study, all MDS patients had normal platelet count (mean: 177.9 × 10^9/L; range: 150–290 × 10^9/L) but presented lower MPV (mean: 9.5 fL; range: 8–12 fL) than diabetics and controls. Low MPV in myelodysplastic patients with normal platelet count may represent a disease marker for bone marrow dysplasia as well as a prognostic marker for MDS status [8]. Based upon the non-associations of HbA1c as well as fasting blood glucose with MPV in this group of patients, it could be inferred that indices of glycemic control didn’t contribute to platelet morphology and that other factors inherent to bone marrow dysplasia pathogenesis, platelet turnover, platelet biochemistry, or vascular environment could be more important determinants of platelet size and function. Platelet dysfunction and especially hypoactivity has been reported in MDS patients with platelet count greater than 80 × 10^9/L [22]. Moreover, independently of the category of diabetic patients (MDS patients versus DM patients), CHD (as an example of DM macrovascular complication) and hypertension were associated with increased MPV in univariate analysis only, in agreement with studies reporting that MPV is associated with increased cardiovascular morbidity [7] and hypertension [23].

In non-diabetic, non-MDS controls, fasting blood glucose, platelet number and the presence of hypertension predicted significantly platelet morphology represented by MPV. This finding is consistent with a similar study reporting that mean platelet volume is significantly higher in hypertensive patients indicating the importance of platelet morphology and function as emerging risk factors for atherothrombosis [23].

The main limitation of our study is the relatively small sample size which is due to the rare incidence of MDS patients with co-existing DM. Nevertheless, we are able to observe statistically significant associations between glycemic control indices and platelet morphologic parameters in diabetics with or without MDS, and to show these groups respond differently. The inclusion of a non-diabetic MDS control group would be necessary to further explore the relationship.

In conclusion, higher MPV and higher PDW are associated with higher mean glycosylated hemoglobin and higher fasting glucose in diabetic, but not matched diabetic myelodysplastic patients presenting with normal platelet counts. This may reflect MPV as a disease marker for diabetes control and thrombotic risk in diabetics. Moreover, it points to non-glycemic factors in the diabetic MDS patient including undetected bone marrow dysplasia, platelet biochemical variations, platelet turnover rates, or vascular changes. Further study is needed to assess the association of platelet morphology with macrovascular disease or risk; to determine the impact of risk reducing interventions; and to elucidate these findings in the setting of bone marrow dysfunction.

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Conflict of interest statement

There is no any conflict of interest

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