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Are platelet indices useful in the evaluation of type 2 diabetic patients?

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Os índices plaquetários são úteis na avaliação de pacientes diabéticos tipo 2?

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ABSTRACT

Introduction: Long-term complications of diabetes *mellitus* are a leading cause of death in people with diabetes. Recent studies suggest that platelets with altered morphology could be associated with an increased risk for developing vascular complications in diabetes. **Objective:** To evaluate the platelet parameters in diabetic patients and correlate these indices with microvascular and macrovascular complications of the disease. **Materials and methods:** We analyzed platelet parameters and biochemical data of patients seen in outpatient clinics of a university hospital. Individuals aged between 30 and 60 years were included, 100 patients with type 2 diabetes *mellitus* (T2DM) (DM group) and 100 non-diabetic patients (control group). **Results:** We observed increase in plateletcrit (PCT): $0.21 \pm 0.054\%$ vs $0.20 \pm 0.045\%$ ($p = 0.020$); in mean platelet volume (MPV): 8.69 ± 1.288 fl vs 8.27 ± 1.244 fl ($p = 0.018$); and in platelet distribution width (PDW): 17.8 ± 1.06 fl vs 17.5 ± 0.87 fl ($p = 0.039$) in the DM and control groups, respectively. Values of MPV, PCT, and PDW were higher among patients with complications of T2DM ($p < 0.001$). In those with macrovascular disease, we observed a correlation between glycated hemoglobin (A1C) and MPV ($p = 0.015$) and PDW ($p = 0.009$) levels. Among patients with microvascular complications, there was a correlation between platelet count and MPV with A1C levels ($p < 0.001$). **Conclusion:** The study findings point to significant differences in platelet parameters in patients with T2DM, suggesting the presence of more reactive and aggregatable platelets in this group of individuals. These results suggest that platelet evaluation may be useful in the early detection of long-term complications in diabetic patients, considering that it is a simple and low-cost tool.

Key words: platelets; diabetes *mellitus*; hyperglycemia; mean platelet volume.

INTRODUCTION

Type 2 diabetes *mellitus* (T2DM) is a serious public health problem, considering its epidemic prevalence levels and high morbidity and mortality rate[1]. This type of diabetes that results from resistance to insulin action associated with a relative deficiency of this hormone, has an insidious development and is often diagnosed due to the presence of microvascular or macrovascular complications[2].

The development of long-term complications has a close relationship with endothelial dysfunction mainly caused by poor glycemic control, and is the leading cause of death and poor quality of life in this group of individuals[3]. The search for assessment tools to establish an early diagnosis of these complications is a challenge, but in recent years, several studies have highlighted the participation of platelets as one of the coagulation system elements involved in the genesis of these events[4-7].

In the process of atherogenesis, the activity of the platelets and their potential aggregation actively participate in the development of thrombi. Furthermore, the function of these cells seems to be related to their sizes. Some studies have shown that large platelets are most reactive and aggregatable, have high amounts of dense granules, and present increased thrombotic potential when compared with smaller and less active platelets[8-10]. Recent studies have shown significant increases in platelet parameters in diabetic subjects when compared with controls, particularly in mean platelet volume (MPV) and platelet distribution width (PDW). These studies suggest that platelets with altered morphology could be associated with increased risk of vascular complications

in diabetes[5-7, 11]. Hyperglycemia, in turn, contributes to increase in platelet reactivity by exerting direct effects on this cells and promoting glycosylation of platelet proteins[5, 6, 12, 13].

OBJECTIVE

The aim of this study is to evaluate the platelet parameters in patients with T2DM, in order to demonstrate a potential correlation between these indices and the microvascular and macrovascular complications of the disease.

MATERIALS AND METHODS

Selection of patients

This descriptive study includes analysis of platelet parameters and biochemical data of subjects seen at the Hospital of the Universidade Federal de Juiz de Fora (UFJF) from February 2013 to January 2014. The cohort study included two groups: patients with T2DM (DM group) and non-diabetic subjects as the control group.

To include patients in the DM group, we analyzed the electronic medical records of 420 outpatients seen at the Diabetes Clinic, of which 127 were selected and invited to participate in the study during their routine medical appointment. We included patients with T2DM regardless ethnicity and gender, aged between 30 and 60 years. In the control group, there were 152 individuals of both sexes and of any ethnicity, selected through analysis of electronic records to be age-matched to the DM group.

In both groups, we excluded subjects with anemia, leukopenia or leukocytosis, thrombocytopenia or thrombocytosis, hypertriglyceridemia, hypercreatininemia, human immunodeficiency virus (HIV) infection, hepatitis B, hepatitis C, systemic lupus erythematosus, thrombosis and/or hematologic disorders, as well as smokers and pregnant women. Subjects with fasting blood glucose levels ≥ 100 mg/dl or with a previous diagnosis of coronary artery disease were not included in the control group.

The study was approved by UFJF Hospital Institutional Ethics Committee, and registered under number 186,039. All participants filled out a free and informed consent form (FICF).

Medical history

After signing the FICF, we obtained from both groups the clinical history data by the analysis of medical records available in electronic files. These data included age, gender, duration of diabetes, medications in use, and previous diagnosis of microvascular (retinopathy or nephropathy) or macrovascular (coronary artery disease, stroke, and peripheral artery disease) complications.

Laboratory analysis

Venous blood samples were collected between 7 a.m. and 9 a.m. after a 12-hour fasting period in the Laboratory Professor Maurílio Baldi, UFJF. The following laboratory tests were performed: RBC count, hematocrit, hemoglobin, total WBC count, platelet count, MPV, PCT, PDW, fasting blood glucose, creatinine, total cholesterol, high density lipoprotein cholesterol (HDL-cholesterol), and triglycerides levels. In the DM group, glycated hemoglobin (A1C) levels were also measured.

Blood sample (approximate volume 4 ml) for complete blood count, platelet parameters, and A1C tests, was collected in vacuum tubes containing the anticoagulant ethylenediaminetetraacetic acid (K_3 EDTA). The samples were kept at room temperature and processed within two hours ater collection. For the biochemical tests, blood samples (5 ml) were collected in tubes without anticoagulant, and were centrifuged in LS-3 Plus (CELM) equipment for 5 minutes at 3,400 rpm for serum separation.

Hematological analysis

The complete blood count was determined in a Cell-Dyn®3700SL (Abbott Diagnostics) hematology analyzer, which uses electrical impedance/flow cytometry, light/laser scattering, and spectrophotometry method.

The following reference values were adopted for the erythrocyte count: 4.3 to 6.0 million/mm³ and 3.9 to 5.3 million/mm³; for hemoglobin: 13.5 to 17.8 g/dl and 12.0 to 16.0; for hematocrit: 41% to 54% and 36% to 48% for men and women, respectively; for total leukocyte count: 3,600 to 11,000/mm³; for platelet count 140,000 to 400,000/mm³; for MPV: 6.2 to 11.8 fl. For PCT and PDW there are no standardized reference values[14].

Biochemical analysis

Biochemical analyses were carried out in BT 3000 Plus equipment (Wiener Lab. Group), using diagnostic kits by Wiener Lab. Group. We used enzymatic methods to determine blood glucose levels, total cholesterol, HDL-cholesterol, and triglycerides levels; a kinetic method to determine creatinine levels, and an immunoturbidimetric inhibition assay to quantify A1C levels.

To analyze the biochemical parameters, namely, fasting glucose levels – 70 to 99 mg/dl; total cholesterol levels: 140 to 200 mg/dl; HDL-cholesterol levels: 40 to 60 mg/dl; triglycerides levels: 65 to 150 mg/dl; and creatinine levels: 0.7 to 1.4 mg/dl for men, and 0.6 to 1.1 mg/dl for women we adopted the reference values according to the kit manufacturer's specifications. For A1C, we used the reference value 4.8% to 5.9%. Friedewald[15] formula was used for estimation of LDL-cholesterol levels: LDL-chol = total-chol – HDL-chol – (TG/5).

Statistical analysis

The data were analyzed with the software for statistical analysis SPSS, version 15. We applied descriptive statistics and exploratory data analysis to obtain means and standard deviations. For the qualitative variables, the Chi-square test was performed and provided the number of patients for each gender in both groups. Analysis of variance (ANOVA) and independent t test were used to test the difference between means. To verify the association between fasting blood glucose and A1C levels with platelet parameters, we applied Pearson correlation, considering a statistically significant result when $p < 0.05$ and a strong correlation when $r > 0.60$. Furthermore, we used linear regression analysis to verify the clinical significance of glucose concentration and duration of diabetes between patients in the control group and DM group.

A total of 279 subjects were considered eligible, of which 79 were excluded due to abnormal laboratory results defined in the exclusion criteria. Among the 200 patients studied, 100 were included in the control group and 100 in the DM group. The mean duration of diabetes among the cases was 6.5 ± 3 years.

RESULTS

The groups were homogeneous regarding age and there was a female predominance in both groups, with sex ratio (male/female) of 0.4 in the DM group and 0.3 in the control group. The red blood cells and leukocyte count were within the reference values and showed no statistical difference between the groups. The biochemical and hematological findings in the studied groups are presented in **Table 1**.

Although the platelet counts were similar between the groups, there was an increase in PCT in the DM group: $0.214 \pm 0.0540\%$ and $0.198 \pm 0.0447\%$ ($p = 0.020$), in the DM and control groups, respectively.

When we analyzed a possible correlation between fasting blood glucose levels and platelet parameters in the DM group, we observed a positive correlation with MPV ($p = 0.005$) and PDW ($p = 0.008$), indicating that patients with higher fasting blood glucose levels tended to present higher values of MPV and PDW. However, the correlation was weak ($r < 0.60$). In the control group, Pearson correlation was not significant (**Table 2**).

We also observed a positive and significant correlation between platelet parameters and A1C levels in the DM group, but a weak correlation for MPV, PCT, and PDW, suggesting that patients with higher A1C levels tend to have higher MPV, PCT, and PDW values (**Table 3**).

TABLE 1 – Biochemical and hematological analysis of the studied subjects

Parameters	DM Group ($n = 100$)	Control group ($n = 100$)	p value
Age (years)	52 ± 6.8	51 ± 6.8	0.184
Fasting blood glucose (mg/dl)	136 ± 46.6	92 ± 5.7	< 0.001
A1C (%)	8.1 ± 1.89	-	-
Total cholesterol (mg/dl)	187 ± 41.6	202 ± 37.6	0.006
HDL-cholesterol (mg/dl)	45 ± 9.9	48 ± 10.2	0.038
LDL-cholesterol (mg/dl)	119 ± 39.5	134 ± 34.8	0.007
Triglycerides (mg/dl)	112 ± 29.8	102 ± 33.9	0.037
Creatinine (mg/dl)	0.9 ± 0.19	0.9 ± 0.15	0.105
Erythrocyte count (million/mm³)	4.7 ± 0.39	4.7 ± 0.37	0.655
Hemoglobin (g/dl)	13.6 ± 1.07	13.8 ± 1.04	0.216
Hematocrit (%)	40 ± 3.1	41 ± 3.2	0.094
Total leukocyte count (/mm³)	7,403 ± 1,734.0	6,928 ± 1,759.2	0.056
Platelet count (/mm³)	246,910 ± 58,805.3	239,874 ± 59,223.1	0.400
MPV (fl)	8.69 ± 1.288	8.27 ± 1.244	0.018
PDW (fl)	17.8 ± 1.06	17.5 ± 0.87	0.039

Values are expressed as mean ± standard deviation.
DM: diabetes mellitus; A1C: glycated hemoglobin; HDL-cholesterol: high-density lipoprotein-cholesterol; LDL-cholesterol: low-density lipoprotein-cholesterol; MPV: mean platelet volume; PDW: platelet distribution width.

TABLE 2 – Pearson correlation for the association between platelet parameters and fasting blood glucose

Parameters	DM group ($n = 100$)		Control group ($n = 100$)	
	Correlation (r)	p value	Correlation (r)	p value
MPV	0.279	0.005	-0.032	0.755
PCT	0.196	0.051	0.018	0.858
PDW	0.262	0.008	-0.012	0.904

DM: diabetes mellitus; MPV: mean platelet volume; PCT: plateletcrit; PDW: platelet distribution width.

TABLE 3 – Pearson correlation for the association between platelet parameters and glycated hemoglobin in diabetic patients

Parameters	Correlation (r)	p value
MPV	0.393	< 0.001
PCT	0.331	0.001
PDW	0.361	< 0.001

MPV: mean platelet volume; PCT: plateletcrit; PDW: platelet distribution width.

Long-term complications of diabetes were present in 41% of patients with T2DM, and they are distributed as follows – atherosclerotic vascular disease (coronary artery disease/stroke): 12%, retinopathy: 11%, nephropathy: 9%, both macrovascular and microvascular complications: 8%, both nephropathy and retinopathy: 1%. When comparing platelet parameters in diabetics with and without complications, we found that patients with complications showed MPV, PCT, and PDW higher than patients without complications ($p < 0.001$). The results of the platelet parameters in diabetic patients are shown in **Table 4**.

Moreover, in patients with macrovascular complications, there was a statistically significant correlation between MPV and PDW with A1C levels ($p = 0.015$ and $p = 0.009$, respectively). For both parameters Pearson correlation coefficient was positive, indicating that among these patients, those with higher A1C levels tended to show higher values of MPV and PDW. Among patients with microvascular complications, we observed a statistically significant correlation between platelet count and MPV with A1C levels ($p < 0.001$) and, regarding MPV, Pearson correlation was strong positive. Platelet count had a strong negative Pearson correlation with A1C levels (**Table 5**). The linear regression analyzes were not significant.

TABLE 4 – Platelet parameters in diabetic individuals with and without chronic complications

Parameters	Diabetics with complication ($n = 41$)	Diabetics without complication ($n = 59$)	p value
MPV (fl)	9.83 ± 0.998	7.90 ± 0.769	< 0.001
PCT (%)	0.25 ± 0.0351	0.19 ± 0.0389	< 0.001
PDW (fl)	18.30 ± 1.090	17.40 ± 0.870	< 0.001

MPV: mean platelet volume; PCT: plateletcrit; PDW: platelet distribution width.

TABLE 5 – Pearson's correlation and p values for the association between glycated hemoglobin levels and platelet parameters in diabetic patients with chronic complications

Parameters	Microvascular complications ($n = 21$)		Macrovascular complications ($n = 20$)	
	Correlation (r)	p value	Correlation (r)	p value
Platelet count	-0.710	< 0.001	-0.316	0.162
MPV	0.726	< 0.001	0.522	0.015
PCT	0.074	0.757	0.083	0.720
PDW	0.030	0.901	0.558	0.009

MPV: mean platelet volume; PCT: plateletcrit; PDW: platelet distribution width.

DISCUSSION

In this study, we observed an increase in PCT, MPV, and PDW, and a positive correlation between platelet parameters and fasting blood glucose, and A1C levels in patients with T2DM. In the presence of macrovascular complications, there was a significant correlation between A1C levels, MPV and PDW. Furthermore, a significant correlation between A1C, platelet count and MPV was found in the presence of microvascular complications, supporting the idea that the presence of more reactive and aggregatable platelets may be one of the factors involved in the development of diabetes complications.

In fact, several authors have described platelets changes associated with diabetes. Furthermore, the wide use of electronic counters in laboratories has allowed the quantification of platelet parameters[16-18], which may reflect the functionality of these cells. Among these parameters, MPV and PDW stand out due to their involvement in the development of thromboembolic complications[19].

In the present study, the analysis of hematological parameters showed that the mean platelet count was higher in the diabetic group than in the control group, although the difference was not statistically significant. This was similar to other studies[13, 16, 20] findings. However, Hekimsoy *et al*. (2004)[6] observed an increased number of platelets in a group of non-diabetic patients compared with diabetic patients, this fact can be explained by the presence of other factors that may have influenced the platelet count, such as the mean platelet survival, and the platelet production and turnover rate in T2DM.

Another aspect that deserves attention is the platelet size seems to be related to their function. Studies have shown that platelets with greater volume are more reactive and aggregatable, have a greater amount of dense granules, and present increased thrombotic potential when compared with

smaller and less active platelets[5, 6, 8-10, 13, 16-18, 21-24]. Hyperglycemia is also a factor that contributes to an increase in platelet reactivity, since it exerts direct effects on these cells and promotes glycosylation of platelet proteins[5, 6, 12, 13]. Therefore, large circulating platelets are reflected by increase in MPV, and the elevation of this parameter is considered an independent risk factor for thromboembolism, stroke and acute myocardial infarction[25-27]. In diabetic patients, a high MPV is an important finding and could predict an increased risk for thrombosis and chronic complications[13, 20, 23].

Several authors have suggested that patients with T2DM have increased MPV when compared with non-diabetic and, among the diabetics, those with vascular complications presented higher MPV values[5, 6, 17, 18, 23, 24, 28-31]. The present study showed higher MPV values for the diabetics and in those with complications, although no significant difference related to the type of chronic complication (microvascular or macrovascular). In a study by Zuberi et al. (2008)[20], MPV was significantly higher in diabetic patients with vascular complications than in diabetics without complications. However, Papanas et al. (2004)[28] found higher MPV values in diabetics with microvascular complications, and in the studies of Ates et al. (2009)[23] and Tuzcu et al. (2014)[31], the MPV was higher in patients with retinopathy. In contrast, Kodiatte et al. (2012)[13] found higher MPV values in patients with microvascular complications, although no significant difference was found. In the present study, both patients with microvascular and macrovascular complications showed positive association between of A1C levels and MPV, a finding that was also reported by other authors[13, 16, 17, 24].

Regarding PDW, the present study showed that diabetic patients had higher PDW when compared to those without diabetes, a finding that has also been described by Dalamaga et al. (2010)[17]. The activated platelets differ in size from non-activated ones mainly due to a change from a discoid to a spherical shape and pseudopodia formation, leading to a change in the PDW, as observed by Vagdatli et al. (2010)[32]. In addition, significant differences were found in PDW parameter in diabetic patients with complications when compared with diabetics without complications, corroborating the results of Jindal et al. (2011)[5]. These findings can be attributed to the accelerated production of platelets in patients with T2DM. Thus, qualitative changes such as different sizes of platelets can be found. Consequently, the base of the histogram plotting the platelet distribution is enlarged, increasing the PDW[32].

Moreover, a positive correlation was found between fasting blood glucose levels and PDW in diabetic patients and, in those with macrovascular complications, positive correlation between A1C and PDW was found. When this group was analyzed for A1C, there was a also positive correlation for MPV and PCT. Changes in PDW and MPV may be related to poor glycemic control, possibly due to the osmotic effect resulting from increased glucose levels and some of its metabolites in blood[17].

There are a few reports in the literature on PCT, and in the present study, we found higher levels in diabetic subjects. Moreover, this parameter was significantly higher in the presence chronic complications. Considering that the platelet mass or PCT must be constant, as the platelet volume increases, the platelet count tends to decrease to maintain a normal PCT. Since in diabetic patients the platelets are larger and more reactive, the platelet mass increases, thereby increasing the PCT[33, 34].

Another important aspect is related to dyslipidemia that is considered to be an important risk factor for atherosclerosis in diabetic patients[3, 30]. In the present study, diabetic patients had higher levels of triglycerides and lower levels of HDL-cholesterol, this finding was also reported in the study by Abali et al. (2014)[30]. However, the DM group showed lower total cholesterol levels when compared to the control group, a finding that may be attributed to the use of statins by a large number of diabetics.

Due to ethical issues, medications commonly used by diabetics were kept, which was a limitation of the present study. On the other hand, this fact has contributed to an assessment of these individuals in a real scenario. In addition, other factors such as physical activity, diet, and family history may have influenced the results.

CONCLUSION

In conclusion, the present study points to significant differences in platelet parameters in patients with T2DM, especially those with vascular complications, when compared to non-diabetic individuals. Once the platelet parameters analysis is a simple and cost-effective diagnostic tool, it could be a useful prognostic marker for chronic complications of diabetes. Therefore, it contributes to the early detection of these complications, as well as to a potential reduction in morbidity and mortality in this group of individuals.

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RESUMO

Introdução: O desenvolvimento das complicações crônicas relacionadas com diabetes mellitus *representa a principal causa de mortalidade nesse grupo de indivíduos. Estudos recentes sugerem que plaquetas com morfologia alterada poderiam estar associadas ao aumento do risco de complicações vasculares no diabetes.* **Objetivo:** *Avaliar os índices plaquetários em diabéticos, correlacionando-os com as complicações micro e macrovasculares da doença.* **Materiais e métodos:** *Foi realizada a análise de índices plaquetários e dados bioquímicos de pacientes atendidos nos ambulatórios de um hospital universitário. Foram incluídos indivíduos com idade entre 30 e 60 anos, sendo 100 diabéticos (grupo DM) e 100 não diabéticos (grupo-controle).* **Resultados:** *Observou-se elevação do plaquetócrito: 0,21 ± 0,054% versus 0,20 ± 0,045% (p = 0,020); do volume plaquetário médio (VPM): 8,69 ± 1,288 fl versus 8,27 ± 1,244 fl (p = 0,018); e da distribuição de plaquetas (PDW): 17,8 ± 1,06 fl versus 17,5 ± 0,87 fl (p = 0,039), nos grupos DM e controle, respectivamente. Os valores de VPM, plaquetócrito e PDW apresentaram-se mais elevados entre os indivíduos com complicações do diabetes* mellitus *tipo 2 (DM2) (p < 0,001). Naqueles com complicações macrovasculares, observou-se correlação entre os níveis de hemoglobina glicada (A1C) e VPM (p = 0,015) e PDW (p = 0,009). Entre os pacientes com complicações microvasculares, observou-se correlação entre a plaquetometria e o VPM com os níveis de A1C (p < 0,001).* **Conclusão:** *Os dados do presente estudo apontam para diferenças significativas nos índices plaquetários em pacientes com DM2, sugerindo presença de plaquetas mais reativas e agregáveis nesse grupo de indivíduos. Tais resultados sugerem que a avaliação plaquetária pode ser útil na detecção precoce de complicações crônicas em diabéticos, sobretudo por ser ferramenta de fácil obtenção e baixo custo.*

Unitermos: plaquetas; diabetes mellitus*; hiperglicemia; volume plaquetário médio.*

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