Clinical Research

Glucose Variability And Mean Platelet Volume

Glikoz Değişkenliği Ve Ortalama Trombosit Hacmi

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ABSTRACT

Background: *Both glucose variability (GV) and increased mean platelet volume (MPV) have been linked to increased cardiovascular complications in patients with diabetes mellitus (DM). We investigated the relationship between these two variables in patients with type 2 DM.*

Materials and Methods: *A total of 100 patients (54 women, the mean age of 59.59±9.12 years) with type 2 DM were recruited in the study. All patients measured the blood glucose on successive two days at home by self-monitoring of blood glucose (SMBG). Seven points SBGM data were used for GV formulas. Intra-day GV with standard deviation (SD) and coefficient of variation (CV), day-to-day GV with mean of daily differences (MODD) was assessed. MPV values derived from automated cell counting on the third day when collecting the SMBG results. Also; total cholesterol, high and low-density cholesterols, triglyceride and hemoglobin A1C (HbA1C) were measured.*

Results: *There were no statistically significantly differences between the MPV values of patients with lower and upper quartiles for SD and CV (8.26±1.18 vs 8.15±1.26, p>0.05, 8.2±1.21 vs 8.39± 1.1, p>0.05, respectively), and also with the lower and upper quartiles for MODD (8.01±0.97 vs 8.39±1.3, p>0.05). No correlation found between MPV and HbA1c and lipid parameters. There were no significantly differences for MPV values between patients with coronary ischemia, diabetic retinopathy, neuropathy, nephropathy and those without these complications (8.20±1.12 vs 7.78±1.09, p>0.05; 8.25±1.18 vs 8.12±1.11, p>0.05; 8.23±1.08 vs 8.05±1.14, p>0.05; 7.99±1.25 vs 8.11±1.09, p>0.05; respectively).*

Conclusions: *Glucose variability does not affect the mean platelet volume.*

Keywords: *glucose variability; mean platelet volume; cardiovascular complications; platelet activity*

ÖZET

Amaç: *Hem glikoz değişkenliği (GD) hem de artmış ortalama trombosit hacmi (OTH) diyabetes mellitusu (DM) olan hastalarda artmış kardiyovesküler komplikasyonlarla ilişkilendirilmiştir. Biz tip 2 DM hastalarında bu iki değişken arasındaki ilişkiyi araştırdık.*

Materyal ve Metod: *54'ü kadın, ortalama yaşı 59,59 ±9.12 yıl olan toplam 100, tip 2 DM hastası çalışmaya alındı. Tüm hastaların takip eden 2 gün boyunca ve günde 7 kez SBGM ile kan şekerleri ölçüldü. Glikoz değişkenliğini ölçen formüllerde self blood glucose monitoring (SBGM) verileri kullanıldı. Gün içi glikoz değişkenliği standart sapma (SD) ve varyasyon katsayısı (CV), günler arası glikoz değişkenliği ise ortalama günlük farklar (MODD) formülleri ile değerlendirildi. Ortalama trombosit hacmi (MPV) SBGM ölçümlerinin tamamlandığı üçüncü günde alınan kanda bakılan tam kan sayımı sonuçlarından elde edildi. İlaveten hastaların total kolesterol, trigliserit, HDL ve LDL kolesterol değerleri ile HbA1c değerleri ölçüldü.*

Sonuçlar: *SD, CV ve MODD formüllerine göre en alt ve en üst glikoz değişkenlik çeyrek dilimlerinde yer alan hastaların MPV değerleri arasında istatistiki olarak anlamlı fark bulunmadı. (sırasıyla 8,26±1,18 ve 8,15±1,26; p>0,05; 8,2±1,21 ve 8,39± 1,1; p>0,05; 8,01±0,97 ve 8,39±1,3; p>0,05). MPV ile lipid parametreleri ve HbA1c değerleri arasında anlamlı korelasyon saptanmadı. Diyabetin makro ve mikrovasküler komplikasyonları (Koroner iskemisi, retinopati, nefropati ve nöropati) olan ve olmayan hastaların MPV değerleri arasında da anlamlı fark saptanmadı (Sırasıyla 8,20±1,12 ve 7,78±1,09; p>0,05; 8,25±1,18 ve 8,12±1,11; p>0,05; 8,23±1,08 ve 8,05±1,14; p>0,05; 7,99±1,25 ve 8,11±1,09; p>0,05).*

Sonuç: *Glikoz değişkenliği ortalama trombosit hacmini etkilememektedir.*

Anahtar Kelimeler: *glikoz değişkenliği, ortalama trombosit hacmi, kardiyovesküler komplikasyonlar, trombosit aktivitesi*

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INTRODUCTION

Glycemic variability (GV) means swings in blood glucose level and takes into account the intraday and day-to-day glycemic excursions including episodes of hyper and hypoglycemia.

Hemoglobin A1C (HbA1C) is the standard method used to measure of average glycemic control, but not the most complete expression of the degree of glycemia (1, 2). Diabetes Control and Complications Trial (DCCT) concluded that other features of diabetic glucose control, for example postprandial glycemic excursions, which are not reflected by HbA1C, may add to or modify the risk of complications(2). Standard HbA1C does not reflect the peaks and nadirs in blood glucose. GV has been linked to increased risk of diabetic vascular complications (3-5). Consequently, various indices of the GV derived from seven points self-monitoring of blood glucose (SMBG) and continuous glucose monitoring systems (CGMS) data have been developed.

The GV indices which is the most widely used are standard deviation (SD) of blood glucose, coefficient of variation (CV), M value (6), and continuous overall net glycemic action (CONGA-n) (7), mean of daily differences (MODD) (8), mean amplitude of glycemic excursions (MAGE) (9), lability index (10) and the average daily risk range (ADRR) (11).

On the other hand, altered platelet morphology and function have been reported in patients with diabetes mellitus (DM). Malachowska B et al reported that platelets in patients with type 1 DM showed morphological evidence of hyperreactivity increasing with poorer metabolic control (12).

Platelet size (mean platelet volume, MPV) is a marker of platelet function, large platelets being potentially more reactive. Larger platelets are younger, contain more dense granules, and undergo greater in vitro aggregation in response to agonists (13). The higher MPV was noted in patients with both type 1 and type 2 DM and these alterations is connected with metabolic control (14, 15). To the best of our knowledge, relationship between the MPV and GV has not been studied, although there are many studies concerning the link between type 2 DM and platelet morphology or function alteration. In this study, we investigated the relationship of the GV with MPV in type 2 DM patients.

METHODS

The study group was consisted of 100 patients with type 2 DM (54 women, mean age of 59.59 ± 9.12 years). Experimental protocol of this study was approved by local human ethics committee and informed consent was obtained from each subject. We collected sociodemographic and clinical data, including information on the duration of diabetes, the diabetes treatment and the presence of chronic diabetes-related complications. Seven points blood glucose measurement were asked from all participants per day (one measurement before each meal and one measurement 2 h after each meal, one measurement midnight) on successive two days by self-monitoring of blood glucose (SMBG) measurement. Intra-day GV by using SD and CV, day-to-day GV by using MODD was evaluated. CV is calculated from the formula of SD divided mean glucose X 100 and expressed as a percentage. The MODD index was estimated as the mean absolute values of differences between glucose values at the same time on two consecutive days and expressed as milligram/100 mL. MPV was used as an indicator of platelet activity.Venous blood samples were taken into ethylenediamine tetraacetic acid (EDTA) tubes for complete blood count by Abbott, Cell Dyne 3700 device on the third day when the two days SMBG measurements are completed. In addition, biochemical tests including total cholesterol, high- and low density cholesterols, triglyceride and HbA1C were done. HbA1C was measured by high performance liquid chromatography (HPLC) (Trinity Biotech Premier Hb9210), all other biochemical tests except LDL-cholesterol were measured with enzymatic method by autoanalyser (Abboth Architect C16000, USA). LDL-cholesterol was calculated using the Friedwald formula if triglyceride level is lower than 400 mg/dL.

Statistical analysis was conducted using IBM SPSS Statistics 22 (IBM SPSS, Türkiye) program. Distribution of parameters was tested by Shapiro Wilks test. Results were expressed as means ± standard deviation for the parameters showing normal distribution, median and ranges for the parameters showing abnormal distribution. The comparisons between groups in parameters showing normal distribution and the determination which group cause differences were made by using Oneway Anove and Turkey HDS tests, respectively. The comparisons of parameters that were not showing normal distribution were made by using Kruskal-Wallis test. The relationship between MPV and GV was investigated by comparing the upper and lower quartiles MPV values for SD,

CV and MODD and by Pearson's correlation analysis. Results were analyzed with 95% confidence interval and probability levels less than 0.05 were considered significant.

RESULTS

There were no statistically significant differences the MPV values of patients with lower and upper quartiles for SD (Table 1) and CV (Table 2) (MPV values of patients for the lower and upper SD and CV quartile 8.26 ± 1.18 vs. 8.15 ± 1.26, P > 0.05, 8.2 ± 1.21 vs. 8.39 ± 1.1, P > 0.05, respectively), and also with the lower and upper quartiles for MODD (Table 3) (8.01 ± 0.97 vs. 8.39 ± 1.3, P > 0.05).

Table 1: *The results of lower and upper quartiles for SD.*

Parameter	25th percentile Mean±SD (Median)	75th percentile Mean±SD (Median)	*p*
HbA1c (%)	7.63 ± 0.56	8.07 ± 0.52	[1]0.028*
Total cholesterol (mg/dL)	214.12 ± 47.2	205.52 ± 51.4	[1]0.887
LDL-cholesterol (mg/dL)	131.56 ± 39.81	128.7 ± 44.46	[1]0.519
HDL-cholesterol (mg/dL)	45.16 ± 11.7 (40)	45.96 ± 11.08 (44)	[2]0.619
Triglyceride (mg/dL)	185.4 ± 127.45 (149)	152.44 ± 67.02 (153)	[2]0.858
MPV (fL)	8.26 ± 1.18	8.15 ± 1.26	[1]0.868

1: *One-Way ANOVA* ***2:*** *Kruskal Wallis Test* ****:*** *p<0.05*

Table 2: *The results of lower and upper quartiles for CV.*

Parameter	25th percentile Mean±SD (Median)	75th percentile Mean±SD (Median)	*p*
HbA1c (%)	7.68 ± 0.61	7.88 ± 0.57	[1]0.868
Total cholesterol (mg/dL)	218.85 ± 48.32	206.28 ± 50.44	[1]0.459
LDL-cholesterol (mg/dL)	138.35 ± 42.55	126.98 ± 48.25	[1]0.197
HDL-cholesterol (mg/dL)	43.44 ± 10.59 (40)	46.68 ± 10.21 (46)	[2]0.275
Triglyceride (mg/dL)	192.93 ± 102.78 (165)	154.2 ± 98.31 (131)	[2]0.235
MPV (fL)	8.2 ± 1.21	8.39 ± 1.1	[1]0.416

1: *One-Way ANOVA* ***2:*** *Kruskal Wallis Test*

Table 3: *The results of lower and upper quartiles for MODD.*

Parameter	25th percentile Mean±SD	75th percentile Mean±SD	*p*
HbA1c (%)	7.63 ± 0.53	8.11 ± 0.50	[1]0.012
Total cholesterol (mg/dL)	202.88 ± 43.72	209.64 ± 45.33	[1]0.805
LDL-cholesterol (mg/dL)	120.84 ± 40.84	129.29 ± 34.72	[1]0.739
HDL-cholesterol (mg/dL)	46.04 ± 10.65	45.92 ± 10.93	[1]0.969
Triglyceride (mg/dL)	158.44 ± 92.78	163.48 ± 100	[1]0.854
MPV (fL)	8.01 ± 0.97	8.39 ± 1.15	[1]0.375

1: *One-Way ANOVA*

No correlation was found between MPV and mean glucose, SD, CV, MODD, HbA1C and lipid parameters. There were no significant differences for the MPV values between in patients with coronary ischemia, diabetic retinopathy, neuropathy, nephropathy and those without these complications (8.20 ± 1.12 vs .7.78 ± 1.09, P> 0.05; 8.25 ± 1.18 vs. 8.12 ± 1.11, P> 0.05; 8.23 ± 1.08 vs. 8.05 ± 1.14, P > 0.05; 7.99 ± 1.25 vs. 8.11 ± 1.09, P> 0.05; respectively). Also, there were no significant differences for MPV values between patients with receiving oral antidiabetic drug and/or drugs alone and receiving insulin alone or combined with oral antidiabetics (7.96 ± 0.95 vs. 8.20 ± 1.18, P> 0.05; respectively).

DISCUSSION

We thought it might be a relationship between the GV and MPV, two variables contributing to cardiovascular complications of diabetes mellitus, and tested this hypothesis. The results of this study which the GV was evaluated by formula derived from seven points SBGM data and the MPV was used as an indicator of platelet activity showed no association between the MPV and GV indices, although the patients in the upper quartile for CV and MODD tend to have higher mean MPV values.

In recent years, a growing body of evidence suggests that glycemic instability may contribute to the development of diabetes complications (3). It has been suggested that postprandial hyperglycemia and glycemic variability, even in patients with well-controlled diabetes, may

be independent risk factors for macrovascular complications in patients with DM (16, 17).

Pathophysiologically, an acute increase in blood glucose can produce significant alterations in normal homeostasis, such as endothelial dysfunction and inflammation (18). Oxidative stress has been suggested as the key link between hyperglycemia and diabetic complications (19). Studies have suggested that intermittent hyperglycemia rather than chronic hyperglycemia exaggerates the production of reactive oxygen species (20, 21). Also, evidence have shown that the DM is affected the platelet morphology and function. The main abnormality observed in diabetic platelets is their hypersensitivity to agonists. It has been shown that the platelets obtained from patients suffering from DM expressed augmented adhesiveness and aggregation both spontaneous and in response the stimulating agents (15, 22). Increased platelet activity is associated with an elevated frequency of vascular complications in adult patients with type 2 DM (23). On the other hand, the MPV is thought to be an indirect indicator of platelet activity. Larger platelets are younger, contain more dense granules and produce more thromboxane A2 (24). It has also been suggested that increased MPV is a possible mechanism of increased cardiovascular risk in patients with postprandial hyperglycemia (25). It has been reported that the MPV is associated with higher HbA1C (26), retinopathy (27) and oral hypoglycemic therapy in patients with DM (28).

Taking into consideration the relationship of the GV and MPV with vascular complications of DM and reports showing effects on MPV of DM, it is expected to be a relationship between the GV and MPV. This relationship was the basis of the hypothesis that we put forward, but our results did not support this idea. It may be different explanations of this result.

The first possibility is that the result can be a reality rather than a surprise, so our hypothesis may be wrong. GV takes into account the intraday and day-to-day glycemic excursions including episodes of hyper and hypoglycemia. Blood glucose can be varied nadir to peak or peak to nadir directions. Therefore, theoretically, if platelet changes including MPV seen in patients with DM are result of higher blood glucose, the GV occurring the blood glucose changes from peak to nadir directions cannot produce any effect on the MPV. So what, we found that the patients in 75th percent of SD and MODD have also higher HbA1c. This result shows that the patients with apparent intraday and day to day GV have also exposure to higher glucose load. It means that the GV found in this study is not only associated with frequent episodes of hypoglycemia. Large prospective clinical studies have shown a strong relationship between time-averaged mean levels of glycemia as measured by HbA1c and diabetes complications (29-31). Thus, our hypothesis cannot be said to be wrong.

The second possibility, inconsistent results with hypothesis may be related to the methodology of the study. First, numerous formulas are used to evaluate the GV and do not have a consensus on about which formula is more effective. Some formulas such as SD, CV, MODD and ADRR derived from glucose values measured by SMBG are used widely in clinical practice to assess the GV and variability risk. SBGM data are insufficient to detect all isolated upward and downward acute glucose fluctuations. A CGMS is the most reliable and precise method to evaluate GV and postprandial hyperglycemia; however, it is not easily accessible in general practice.

Therefore, before the rejection of the hypothesis that we put forward, we think that the relationship between the GV and MPV should be investigate by using formulas derived CGMS data. Secondly, many variables affect the MPV and the patients included in this study are heterogeneous for comorbidity, duration of DM and given therapeutic regime. Therefore, we believe that this hypothesis should be test in more homogenous groups of patients in which the inclusion criteria are more clearly identified.

If the results of this study validate with other studies, we can conclude that GV leads to increased cardiovascular risk by other mechanisms than platelet activity. Thus, we can focus directly on reduction of GV rather than platelets.

Conclusion: The results of this study show that the GV does not affect the platelet activity.

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