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COULD INFLAMMATION RELATED HEMOGRAM PARAMETERS BE AN INDICATOR OF DIABETES MELLITUS?

İNFLAMASYONLA İLİŞKİLİ HEMOGRAM PARAMETRELERİ DİYABETES MELLİTUSUN BİR GÖSTERGESİ OLABİLİR Mİ?

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Abstract

Objective: Subclinical chronic inflammation plays an important role in the pathogenesis of type 2 diabetes mellitus (DM) and inflammation-related hemogram parameters have been proposed as an indicator of inflammation. In our study, we aimed to compare the hemogram parameters of normal oral glucose tolerance test (OGTT), prediabetes (preDM) and newly diagnosed type 2 DM patients.
Methods: Medical data of the patients who underwent 75 gr OGTT in the endocrinology outpatient clinic of our institution between february 2019 and december 2019 were obtained from the database and analyzed retrospectively. The test results were divided into 3 groups as normal OGTT, preDM and DM. Anthropometric measurements of patients, HbA1c and hemogram parameters were recorded.
Results: A total of 496 cases (246 normal OGTT, 105 patients with preDM and 145 patients with DM) were included in the study. Fasting plasma glucose (FPG) and HbA1c levels of men were higher than women (p<0.05). There was no significant difference between the three groups in terms of inflammation-related hemogram parameters. But, there was a positive correlation between FPG and MPV to platelet ratio (MPR) in diabetic patients (r=0.173; p=0.037).
Conclusion: Hemogram parameters associated with inflammation are easily calculated and cheap indices. However, they are not strong markers in new diagnosis, HbA1c ≤6.5% diabetic patients and prediabetic patients.

Keywords: *Diabetes mellitus, prediabetes, hemogram parameters, HbA1c, inflammation*

Öz

Amaç: Subklinik kronik inflamasyon tip 2 diabetes mellitus (DM) patogenezinde önemli bir rol oynar ve inflamasyonla ilişkili hemogram parametreleri inflamasyonun bir göstergesi olarak önerilmiştir. Çalışmamızda normal oral glukoz tolerans testi (OGTT), prediyabet (preDM) ve yeni tanı konmuş tip 2 DM hastalarının hemogram parametrelerini karşılaştırmayı amaçladık.
Yöntem: Şubat 2019-Aralık 2019 tarihleri arasında kurumumuzun endokrinoloji polikliniğinde 75 gr OGTT uygulanan hastaların tıbbi verileri veri tabanından elde edilmiş ve geriye dönük olarak analiz edilmiştir. Test sonuçları normal OGTT, preDM ve DM olarak 3 gruba ayrıldı. Hastaların antropometrik ölçümleri, HbA1c ve hemogram parametreleri kaydedildi.
Bulgular: Çalışmaya toplam 496 vaka (246 normal OGTT, 105 preDM'li hasta ve 145 DM'li hasta) dahil edildi. Erkeklerde açlık plazma glikozu (APG) ve HbA1c düzeyleri kadınlardan daha yüksekti (p<0,05). Üç grup arasında inflamasyonla ilişkili hemogram parametreleri açısından anlamlı fark yoktu. Ancak diyabetik hastalarda APG ile MPV/trombosit sayısı oranı (MPR) arasında pozitif korelasyon vardı (r= 0,173; p= 0,037).
Sonuç: İnflamasyon ile ilişkili hemogram parametreleri kolayca hesaplanabilir ve ucuz indekslerdir. Bununla birlikte, yeni tanı, HbA1c ≤% 6,5 diyabetik hastalar ve prediyabetik hastalar için güçlü belirteçler değildir.

Anahtar Kelimeler: *Diabetes mellitus, prediyabet, hemogram parametreleri, HbA1c, inflamasyon*

Introduction

Diabetes mellitus (DM) is a global health problem in which approximately 415 million people are affected. The count of patients with diabetes is expected to increase to 642 million by 2040. Approximately 90-95% of these cases constitute type 2 DM.[1] Subclinical chronic inflammation is a condition shown with inflammatory markers secreted from adipocytes in the natural course of diabetes.[2] Recent studies have shown that increased inflammation in diabetic patients leads to endothelial damage and the development of vascular complications[3]. Indices derived from routine hemogram testing such as red cell distribution width (RDW), mean platelet volume (MPV), neutrophil count / lymphocyte count ratio (NLR), platelet count/lymphocyte count ratio (PLR) are recommended as chronic inflammatory markers.[4,5] Hemogram parameters as new inflammatory markers attracted great interest from the researchers. Platelet volume, which is an indicator of the function and activation of platelets, is measured as MPV with hematological analyzers. The activity and aggregation capacity of platelets can be easily estimated with MPV. NLR is considered as a parameter giving information about systemic inflammatory status. Similarly, researchers consider that RDW increases due to secondary inflammatory response.[6,7]
According to these reports of previous studies, we assumed that inflammatory markers will increase in DM, as it is characterized by subclinical inflammation. We aimed to compare the hemogram parameters of newly diagnosed, type 2 diabetic patients with low HbA1c levels with non-diabetic and prediabetic patients.

Methods

The present study was conducted in Endocrinology and Metabolism diseases clinic of Kocaeli University Hospital. It was approved by the local ethics committee (GOKAEK-2020/10.07). Medical data of all patients who underwent 75 gr oral glucose tolerance test (OGTT) in our endocrinology outpatient clinic between February 2019 and December 2019 were obtained from the database and analyzed retrospectively. Patients with active infectious diseases, active malignant tumors, using steroids and/or other immunosuppressive agent, hematological disease, chronic obstructive pulmonary disease or inflammatory conditions; such as rheumatoid arthritis, inflammatory bowel diseases, were excluded. After an overnight fasting, a standard 75 gr OGTT was performed to establish glucose tolerance status. An IV cannula was inserted for blood sampling. Blood samples for glucose concentrations were taken at 0, 60 and 120 min.Age, height, weight, waist circumference of the participants were recorded. The body mass index (BMI) was calculated by division of weight (kg) by the square of height (m).
Patients were divided into 3 groups according to OGTT results; normal OGTT, prediabetes (impaired glucose tolerance [IGT] and impaired fasting glucose [IFG]) and DM. Diabetes and prediabetes were diagnosed based on the World Health Organization consulting criteria[8] (i.e., DM was identified if the fasting plasma glucose [FPG] of ≥126 mg/dL and/or a 2-h post-glucose value of ≥200 mg/dL. IGT is defined as two-hour glucose levels of 140 to 199 mg/dL on the 75grOGTT and IFG is defined as glucose levels of 100 to 125 mg/dL in fasting patients.Normal OGTT was diagnosed if the 2-h post-glucose value was <140 mg/dL and FPG was <100 mg/dL).
The hemogram parameters and HbA1c values of these patients were obtained from database and recorded.White blood cell count (WBC), neutrophil count, lymphocyte count, hemoglobin (Hb), RDW, platelet count (PLT), and MPV values of the subjects were obtained from database and recorded. NLR, MLR, MPR, and RPR were calculated as division of neutrophil count by lymphocyte count, MPV by lymphocyte count, MPV by PLT, and RDW by PLT, respectively.
Statistical evaluation was done with IBM SPSS 20.0 (IBM Corp., Armonk, NY, USA) package program. The normal distribution compatibility test was evaluated with the Kolmogorov-Smirnov Test. Numerical variables that are not normally distributed are given as median (25th-75th percentile), categorical variables as frequency (%). For numerical variables that do not have a normal distribution, the differences between the groups were tested with Mann Whitney U test, Kruskal Wallis One Way Variance analysis and Dunn's multiple comparison test, and Monte Carlo chi-square test for categorical variables. The relationship between numerical variables was evaluated by Spearman / Pearson Correlation Analysis. For the testing of bidirectional hypotheses, $p<0.05$ was considered sufficient for statistical significance.

Results

A total of 496 subjects (246 normal OGTT, 105 patients with prediabetes (preDM) and 145 patients with DM) enrolled to the study (Table 1).

Table 1: Quantitative data of 75 gr OGTT results

		75 gr OGTT			Total
		Normal	preDM	DM	
Female	Count	190	71	80	341
	% rate	77.2%	67.6%	55.2%	68.8%
Male	Count	56	34	65	155
	% rate	22.8%	32.4%	44.8%	31.2%
Total	Count	246	105	145	496
	% rate	100.0%	100.0%	100.0%	100.0%

All patients median age, height, weight, waist circumference and body mass index (BMI) were 42 (32-53), 165 (160-172) cm, 84 (70-95) kg, 104 (96-114) cm, 29.6 (25.6-34.4) kg/m2, respectively. In the gender comparison, the age, weight and waist circumference of men were higher than women ($p<0.05$) whereas BMI was similar ($p>0.05$). Similarly, FPG and HbA1c were higher in men than in women ($p<0.05$). Demographic data of the patients are given in table 2.

Table 2: General characteristics of the study population

			FPG (mg/dl)	HbA1c (%)	Age	Height (cm)	Weight (kg)	BMI (kg/m^2)	Waist circumference (cm)
Normal OGTT	**Median**		87	5.4	37	165	75	27.5	100
	Percentiles	**25**	82	5.2	26	160	64	24.2	90
		75	93	5.6	46	170	94	33.3	110
PreDM	**Median**		101	5.8	45	165	86	30.0	107
	Percentiles	**25**	93	5.5	37	160	73	26.3	99
		75	107	6.0	55	171	96	35.5	116
DM	**Median**		106	6.0	48	165	88	31.2	110
	Percentiles	**25**	96	5.7	38	160	76	28.1	100
		75	117	6.5	58	172	98	34.7	118

There was no significant difference between the groups in terms of hemogram parameters (Table 3). In gender comparison; RDW and PLT were higher in female and RPR

and MPR were higher in male. Other hemogram parameters were similar in both genders. Age (p<0.05), weight (p<0.05), waist circumference (p<0.05) and BMI (p<0.05) were higher among subjects with prediabetes and diabetes compared to normal individuals. However, there was no difference in prediabetic and diabetic patients in these parameters. As expected FPG and HbA1c were higher in prediabetes and diabetes group compared to the control group.

Table 3: Laboratory data of the study population

	Normal OGTT	PreDM	DM	*p* value
FPG (mg/dL)	87 (82-93)	101 (93-107)	106 (96-117)	<0.001
HbA1c (%)	5.4 (5.2-5.6)	5.8 (5.5-6)	6 (5.7-6.5)	<0.001
WBC (x10^3/µL)	7.16 (5.99-8.44)	6.86 (5.69-8.62)	7.40 (6.40-8.90)	0.057
Neutrophil (x10^3/µL)	4 (3.14-4.97)	3.94 (3.14-4.95)	4.34 (3.40-5.36)	0.095
Lymphocyte (x10^3/µL)	2.33 (1.81-2.78)	2.12 (1.68-2.62)	2.35 (1.89-2.78)	0.142
RDW (%)	13.55 (13.08-14.40)	13.69 (13.13-14.79)	13.75 (13.18-14.74)	0.112
PLT (x10^3/µL)	253 (216-289)	263 (217-305)	248 (211-291)	0.274
MPV (fL)	8.97 (8.30-9.71)	8.85 (8.26-9.56)	8.80 (8.27-9.48)	0.255
NLR	1.76 (1.30-2.17)	1.85 (1.46-2.40)	1.82 (1.47-2.36)	0.150
RPR	0.055 (0.045-0.064)	0.054 (0.045-0.064)	0.056 (0.048-0.066)	0.479
MPR	0.036 (0.029-0.043)	0.033 (0.027-0.043)	0.035 (0.029-0.043)	0.530
MLR	3.86 (3.19-5.11)	4.10 (3.22-4.93)	3.80 (3.14-4.72)	0.219

Table 4 presents the results of pearson correlation analysis. In the normal OGTT group, there was a positive correlation between FPG and RDW (r=0.176; p=0.006), while no correlation was observed in other groups. There was a positive correlation between FPG and MPR in diabetic patients (r=0.173; p=0.037).

Tablo 4:Correlation results of FPG and HbA1c with hemogram parameters

		Normal OGTT	PreDM	DM
WBC	FPG	0.020 (0.754)	0.024 (0.808)	-0.085 (0.310)
	HbA1c	-0.028 (0.664)	0.221 (0.023)a	0.036 (0.666)
Neutrophil	FPG	0.013 (0.837)	0.012 (0.904)	-0.110 (0.187)
	HbA1c	-0.115 (0.072)	0.177 (0.071)	-0.017 (0.843)
Lymphocyte	FPG	0.058 (0.363)	0.044 (0.656)	0.051 (0.546)
	HbA1c	0.173 (0.007)a	0.215 (0.028)a	0.117 (0.161)
RDW	FPG	0.176 (0.006)**	-0.024 (0.808)	-0.019 (0.824)
	HbA1c	0.191 (0.003)a	0.091 (0.357)	0.186 (0.025)a
PLT	FPG	0.066 (0.303)	0.002 (0.983)	-0.180 (0.031)*
	HbA1c	0.161 (0.011)a	0.114 (0.248)	0.030 (0.724)
MPV	FPG	0.057 (0.377)	0.65 (0.511)	0.036 (0.665)
	HbA1c	-0.037 (0.568)	0.096 (0.330)	-0.119 (0.153)
NLR	FPG	-0.042 (0.518)	-0.034 (0.728)	-0.142 (0.088)
	HbA1c	-0.203 (0.001)a	-0.030 (0.761)	-0.111 (0.186)
RPR	FPG	-0.016 (0.803)	0.004 (0.968)	0.140 (0.094)
	HbA1c	-0.090 (0.163)	-0.093 (0.345)	-0.001 (0.991)
MPR	FPG	-0.034 (0.601)	0.055 (0.579)	0.173 (0.037)*
	HbA1c	-0.143 (0.056)	0.006 (0.956)	-0.070 (0.400)
MLR	FPG	-0.040 (0.531)	0.012 (0.903)	-0.045 (0.588)
	HbA1c	-0.183 (0.004)a	-0.191 (0.51)	-0.175 (0.035)a

Discussion

In this study, patients were divided into three groups as normal OGTT, preDM and DM according to 75 gr OGTT result and hemogram parameters were compared between these three groups. A point to be considered in this study was HbA1c levels of diabetic patients ≤6.5%. There was no significant difference between the three groups in terms of hemogram parameters that may be associated with inflammation. There was a positive correlation between FPG and MPR in the diabetic population. Elevated MPR in patients with DM may be a reflection of the underlying inflammatory burden of the disease.

Numerous preclinical and clinical studies have shown that low-grade inflammation is effective in type 2 DM pathogenesis. In islets, activation of the immune system contributes to the reduction of β-cell mass and function. This activation is characterized by increased innate immune cells and proinflammatory cytokines.[9] The relationship between DM and inflammation has been investigated by many studies in the literature. In one study, IL-6 and CRP were higher in the diabetic population than the control group, and increased CRP and IL6 levels predicted the development of type 2 DM.[10] In another study of type 2 DM, chronic inflammation has been shown to be associated with increased mortality.[11]

In the literature, the correlation between inflammation-related hemogram parameters in the diabetic population compared to the control group is controversial. In a study of 265 diabetic patients with an average diabetes duration of 14.5±5.7 years, the MPV was higher in the diabetic population compared to the control group. However, in this study, there was no correlation between MPV with HbA1c levels.[12] On the other hand, Aktas et al showed a correlation between MPV and HbA1c[13]; Ulutas et al. found that the duration of diabetes was directly related to increased MPV.[14] In our study, no difference in MPV was observed in prediabetics and diabetics compared to the control group. We think that this difference was not detected because the patients we included in the study were newly diagnosed type 2 DM patients and had low HbA1c values. This suggests that inflammation in the early stages of diabetes may be at a subclinical level.

NLR is an indicator of systemic inflammation and an increased risk indicator for cardiovascular events. Also, increased NLR is thought to be associated with type 2 diabetes mellitus. A 2014 study found that NLR was higher in poorly controlled diabetics than in well-controlled diabetics.[15] In another study, NLR was found to be significantly higher in type 2 DM compared to healthy controls. It was also found that NLR correlated with FPG and HbA1c.[16] In a study in which 60 diabetic patients were evaluated, a significant correlation was found between NLR level and nephropathy and neuropathy complications6. In our study, no difference was observed between NLR between all three groups. It is known that the risk of cardiovascular disease increases at the first diagnosis of diabetes and even during prediabetes period.[17] However, this increase in risk is likely to be determined by NLR during overt diabetes. Because of our study consisted of prediabetic and early stage diabetic patients, there was no difference in NLR.

MPR has been recently shown as a new inflammatory predictor, and it has been found to be increased in hemodialysis patients[18] and sepsis.[19] In a study with diabetic patients, significantly higher MPR was detected in the diabetic population compared to healthy volunteers. In addition, there was a significant and positive correlation between MPR with FPG and HbA1c.[20] In our study, no significant difference was observed between the three groups in terms of MPR. However, a positive correlation was observed between FPG and MPR in the diabetic group. Studies have reported that NLR and MPV increase with aging in the healthy population.[21,22] If we look at similar

studies in the literature, it is seen that these studies consist of patients with high HbA1c levels and long diabetes duration. Unlike the literature, the patient population included in our study consists of younger, HbA1c ≤6.5% patients with new diagnosis diabetic patients.

Although inflammation-related hemogram parameters are proven markers in the literature, it can be said that they are not sufficient to show risk in early diabetes or prediabetes. These markers will be more suitable for use in overt diabetic individuals.

It may be due to these reasons that we get different results from the literature. As the age of diabetes increases and diabetes regulation deteriorates, inflammation-related hemogram markers appear to be detectable.

Limitations of our report are retrospective design and relatively small study population.

Conclusion

In conclusion, inflammation-related hemogram parameters may not be a strong enough marker to demonstrate impaired glucose metabolism and diabetes control level in prediabetic patients and early diabetes.

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Conflict of Interest

The authors have no conflicts of interest to disclose.

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Author Contributions

MS, AS: Design; MS, AS, BÇ: Project development; YÇ, YD: Data collection; MS, ZC: Analysis; MS, EG: Literature search; MS, AS: Manuscript writing; BÇ, ZC: Critical review

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