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Components of the Complete Blood Count in Type 2 Diabetes Mellitus with Inadequate Glycemic Control

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Abstract

Objective: Inadequate control of glycemia in diabetic patients is the primary cause of both micro- and macrovascular complications. Several components of complete blood count were investigated and have found to be higher in diabetic patients. We aimed to evaluate white blood cell (WBC), neutrophil, lymphocyte and platelet counts and, red cell distribution width (RDW), mean platelet volume (MPV) and platelet distribution width (PDW) in type 2 diabetes mellitus (T2DM) patients with inappropriorate glycemic management (HbAlc >7%) despite using insulin therapy.

Methods: 135 type 2 diabetic patients with inappropriorate blood glucose management (HbAlc value >7 %) despite using insulin therapy for at least 3-month period (only insulin or insulin plus oral hypoglycemic agents) and 121 healthy subjects were included in the study. Demographic, anthropometric and laboratory data were recorded.

Results: WBC, neutrophil, lymphocyte and monocyte counts were higher in DM group (p<0.0001). WBC counts were positively correlated with diastolic blood pressure (DBP), body mass index (BMI), waist circumference (WC) and high-sensitive C- reactive protein (hsCRP), fasting plasma glucose (FPG), post-prandial glucose (PPG), HbA1c and triglyceride levels (p<0.05). Neutrophil counts were positively correlated with hsCRP, FPG, HbA1c, BMI, PPG, LDL-Cholesterol (LDL-C) and microalbumin levels (p<0.05). Lymphocyte counts were positively correlated with systolic blood pressure (SBP), DBP, BMI, WC and FPG, HbA1c, LDL-C and triglyceride levels (p<0.05). WBC, neutrophil and lymphocyte counts were negatively correlated with HDL-Cholesterol (HDL-C) levels (p<0.05). PDW was higher in DM group (16.65±0.59 to 16.51±0.51, p:0.043). PDW was positively correlated with age, DBP, FPG, PPG, HbA1c, LDL-C and triglyceride levels (p<0.05). Monocyte to HDL-C ratio was higher in DM group (13.50 ± 5.34 to 10.54 ± 4.29, p<0.0001).

Conclusions: In this study white blood cell, neutrophil and lymphocyte counts and PDW were higher in type 2 diabetic patients with inappropriorate glycemic management despite insulin therapy and they were correlated wıth cardio-metabolic risk factors. Leukocyte subtypes and PDW may be used as a marker for cardiovascular diseases in these patients.

Keywords: Type 2 diabetes mellitus, complete blood count indices, cardio-metabolic risk factors

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Yetersiz Glisemik Kontrolü Olan Tip 2 Diyabet Hastalarında Tam Kan Sayımı Parametreleri

Öz

Amaç: Diyabetik hastalarda yetersiz glisemik kontrol mikro- ve makrovasküler komplikasyonların gelişmesinde önemli bir risk faktörüdür. Çeşitli tam kan sayımı parametreleri diyabet hastalarında araştırılmış ve yüksek bulunmuştur. Bu çalışmada amacımız; lökosit, nötrofil, lenfosit sayıları ve red cell distribution width (RDW), mean platelet volume (MPV) and platelet distribution width (PDW) değerlerini insulin tedavisine rağmen yeterli glisemik kontrolün sağlanamadığı (HbAlc değeri >7%) tip 2 diyabetli hastalarda incelemektir.

Yöntemler: Çalışmaya en az 3 aydır insülin tedavisi almasına (sadece insülin ya da insülin+oral antidiyabetik ajan) rağmen yeterli glisemik kontrolün sağlanamadığı 135 tip 2 diyabet hastası ve 121 kontrol hastası alındı. Demografik, antropometrik ve laboratuvar verileri kaydedildi.

Sonuçlar: Lökosit, nötrofil, lenfosit ve monosit sayıları diyabetli hastalarda daha yüksekti ($p<0.0001$). Lökosit sayıları diyastolik kan basıncı (DKB), vücut kitle indeksi (VKİ), bel çevresi (BÇ) ile hsCRP, açlık kan şekeri (AKŞ), tokluk kan şekeri (TKŞ), HbA1c, trigliserid düzeyleri ile pozitif korele idi ($p<0.05$). Nötrofil sayıları VKİ ile hsCRP, AKŞ, TKŞ, HbA1c, LDL-kolesterol (LDL-K) ve mikroalbumin düzeyleri ile pozitif korele idi ($p<0.05$). Lenfosit sayıları sistolik kan basıncı (SKB), DKB, VKİ, BÇ ile hsCRP, AKŞ, HbA1c, LDL-K ve trigliserid düzeyleri ile pozitif korrele idi ($p<0.05$). Lökosit, nötrofil ve lenfosit sayıları HDL-kolesterol (HDL-K) düzeyleri ile negatif korrele idi ($p<0.05$). PDW diyabetik hastalarda daha yüksekti (16.65±0.59 to 16.51±0.51, p:0.043). PDW yaş, DKB, AKŞ, TKŞ, HbA1c, LDL-K ve trigliserid düzeyleri ile pozitif korele idi ($p<0.05$). Monosit/HDL-K oranı diyabetik hastalarda daha yüksekti (13.50 ± 5.34 to 10.54 ± 4.29, $p<0.0001$).

Tartışma: Bu çalışmada lökosit, nötrofil ve lenfosit sayıları ile PDW yetersiz glisemik kontrollü diyabetik hastalarda yüksekti ve kardiyo-metabolik risk faktörleri ile korele idi. Bu bulgular, lökosit subtipleri ve PDW'nin kötü glisemik kontrollü tip 2 diyabetli hastalarda kardiovasküler hastalıklar için bir belirteç olabileceğini düşündürebilir.

Anahtar kelimeler: Tip 2 diyabetes mellitus, hemogram parametreleri, kardiyo-metabolik risk faktörleri

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a substantial public health issue in which incidence has been rising dramatically worldwide[1]. Inadequate control of glycemia in diabetic patients is the major key factor for the occurrence of both micro- and macrovascular complications[2]. Cardiovascular diseases (CVD) are the primary source of the mortality in diabetics however, microvascular complications are the primary cause of morbidity[3]. It is well-known that atherosclerosis is an inflammatory disease[4]. Almost all of the cellular ingredients of the blood such as white blood cells (WBC), red blood cells (RBC), and platelets have a role in the underlying pathogenesis of atherosclerosis[5]. Several complete blood count indices were investigated in patients with T2DM. DM can cause anemia of chronic disease, erythrocyte, leukocyte and platelet dysfunction[6–8]. White blood cell (WBC) count has an association with higher cardiovascular death in patients with T2DM[9]. Coronary artery disease patients have increased neutrophil counts[10]. Diabetic patients and especially those with poor glycemic control have higher red cell distribution width (RDW)[11]. Mean platelet volume (MPV) is higher in patients with T2DM[8,12]. Chen et al reported that platelet count and platelet distribution width (PDW) were not increased in T2DM[12]. The monocyte count to HDL-C ratio (MHR) is considered as a novel prognostic marker for CVD [13,14].

We aimed to evaluate the white blood cell, neutrophil, lymphocyte, monocyte and platelet counts and, RDW, MPV and PDW in T2DM patients with inappropriorate glycemic

management (HbAlc >7 %) despite using insulin therapy.

METHODS

We evaluated the hemogram indices in 135 type 2 diabetic patients with inappropriorate glycemic management (HbAlc >7 %) despite insulin therapy for at least 3-month period (only insulin or insulin plus oral hypoglycemic agents) and 121 healthy subjects followed by the endocrinology outpatient clinic of University of Health Sciences, Diskapi Yıldırım Beyazıt Training and Research Hospital in Turkey. Local ethical committee approval was obtained and all participant have given written informed consent before the study began. Patients with anemia, renal disease, cardiac failure, chronic liver disease, pregnancy, thyroid disease, infectious disease, autoimmune disease or blood disease were excluded.

Demographic info and medical history of all subjects such as diabetes duration, the treatment protocol was recorded. Anthropometric measurements including weight, height, waist circumference (WC), hip circumference (HC) and systolic and diastolic blood pressure (BP) were performed. Body mass index (BMI) was measured as dividing the weight by the height squared (kg/m^2).

Complete blood count indices, fasting and postprandial plasma glucose, urea, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol, triglyceride, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein (HDL) cholesterol, high-sensitivity C-reactive protein (hs-CRP), thyroid stimulating hormone (TSH), insulin, HbA1c, urinary micro-albumin, 25 (OH) vitamin D levels were all recorded.

Statistical Analysis

JMP 11.0.0 software (SAS Institute, Cary, NC) was used for statistical analysis. Variables are shown as mean±standard deviation (SD) or percentage (%). Kolmogorov-Smirnov and Shapiro-Wilk W test was used for determination of normality. Student's t-test was performed to compare differences between two independent groups. The Chi-square test or Fisher's exact test was used to compare categorical variables. Statistical significance was defined as a $p< 0.05$.

RESULTS

135 type 2 diabetic patients and 121 controls were included in the study. Gender, age and, TSH, creatinine, LDL-cholesterol, total cholesterol levels were similar between groups ($p>0.05$). SBP, DBP, WC and FPG, PPG, HbA1c, TG levels were higher in DM group ($p<0.0001$). BMI and hs-CRP levels were higher in DM group ($p<0.05$) (Table 1).

WBC, neutrophil, and lymphocyte counts were higher in DM group ($p<0.0001$). Hemoglobin levels and platelet counts, RDW and MPV were similar between groups ($p>0.05$) (Table 2).

Correlations of CBC indices with various cardio-metabolic risk factors were shown in Table 3.

Monocyte to HDL-C ratio was higher in DM group ($p<0.0001$). Monocyte counts were not correlated with age, DBP, BMI, WC and hsCRP, FPG, HbA1c, PPG, LDL-C, HDL-C, triglyceride and microalbumin levels ($p<0.05$). MHR were not correlated with age, DBP, BMI, WC and hsCRP, FPG, HbA1c, PPG, LDL-C and microalbumin levels ($p<0.05$). MHR were positively correlated with triglyceride levels ($p<0.05$). MHR were negatively correlated with HDL-C levels ($p<0.05$).

Table 1: Demographic and clinical characteristics of patients

	DM (n:135)		Control (n:121)		
	Mean or n	**SD or %**	**Mean or n**	**SD or %**	***p***
Age (yrs)	52.70	6.8	49.4	7.9	0.063
Sex (Female)	90	67	87	72	0.365
SBP (mmHg)	129.50	15.45	114.36	13.58	**<.0001**
DBP (mmHg)	80.50	9.94	71.18	9.06	**<.0001**
BMI (kg/m^2)	32.42	12.27	27.95	4.73	**0.0002**
WC (cm)	102.34	13.04	93.05	11.27	**<.0001**
Duration of Diabetes (yrs)	12.12	7.10	.	.	
Total Insulin Dose (u)	54.72	30.22	.	.	
TSH (uIU/mL)	2.04	1.77	1.91	1.30	0.505
hs-CRP	7.95	8.75	3.73	10.50	**0.003**
FPG (mg/dL)	218.99	82.52	94.93	10.86	**<.0001**
PPG (mg/dL)	306.97	82.83	109.25	23.12	**<.0001**
Creatinin (mg/dL)	0.88	0.18	0.86	0.14	0.277
HbA1c (%)	9.98	1.78	5.54	0.35	**<.0001**
LDL-C (mg/dL)	142.74	34.15	141.49	37.59	0.789
HDL-C (mg/dL)	43.35	9.60	49.51	10.20	**<.0001**
Total-C (mg/dL)	194.70	43.02	199.70	44.79	0.398
TG (mg/dL)	215.29	153.28	135.96	76.73	**<.0001**

Table 2: Comparison of CBC indices between groups

	DM (n:135)		Control (n:121)		
	Mean or n	**SD or %**	**Mean or n**	**SD or %**	***p***
WBC (x10^9/µl)	8629.00	1985.00	7229.00	1713.00	**<.0001**
Neutrophil (x10^9/µl)	5118.33	1548.34	4257.84	1393.01	**<.0001**
Lymphocyte (x10^9/µl)	2708.89	934.55	2253.65	594.20	**<.0001**
Neutrophil/ Lymphocyte	2.09	1.06	1.98	0.75	0.353
Hemoglobin (g/dL)	13.91	1.42	14.06	1.53	0.429
RDW (%)	13.97	1.41	13.86	1.18	0.495
Platelet count (x10^3/µl)	265.84	68.23	258.93	56.38	0.395
Mean Platelet Volume (fL)	8.98	1.20	8.93	0.97	0.723
PDW (%)	16.65	0.59	16.51	0.51	**0.043**
Monocyte count (x10^9/µl)	550.00	162.66	496.75	152.71	**0.009**
Monocyte/HDL-C ratio	13.50	5.34	10.54	4.29	**<.0001**

Table 3: Correlations of CBC indices with various variables

	WBC count		Neutrophil count		Lymphocyte count		PDW		MPV	
	r^2	p	r^2	p	r^2	p	r^2	p	r^2	p
Age	0.070	0.280	0.030	0.641	0.108	0.095	0.135	**0.037**	-0.123	0.061
SBP	0.111	0.097	0.073	0.276	0.135	**0.044**	0.092	0.171	-0.012	0.854
DBP	0.135	**0.043**	0.096	0.151	0.136	**0.041**	0.134	**0.044**	0.074	0.272
BMI	0.196	**0.003**	0.149	**0.024**	0.245	**0.0002**	0.028	0.680	0.120	0.070
WC	0.169	**0.011**	0.118	0.079	0.205	**0.002**	0.103	0.127	0.187	0.005
Duration of DM	-0.076	0.405	-0.075	0.407	-0.075	0.407	-0.082	0.363	-0.119	0.189
Total insulin dose	0.061	0.516	-0.003	0.977	0.147	0.119	0.046	0.628	0.041	0.670
hs-CRP	0.348	**<.0001**	0.364	**<.0001**	0.135	0.067	0.136	0.065	0.110	0.137
FPG	0.285	**<.0001**	0.271	**<.0001**	0.228	**0.0004**	0.139	**0.034**	0.037	0.575
PPG	0.322	**0.0008**	0.321	**0.0008**	0.180	0.065	0.241	**0.013**	0.138	0.160
HbA1c	0.357	**<.0001**	0.327	**<.0001**	0.264	**0.0001**	0.181	**0.009**	0.077	0.272
LDL-C	-0.028	0.671	-0.133	**0.045**	0.198	**0.003**	0.158	**0.018**	0.030	0.651
HDL-C	-0.235	**0.0006**	-0.193	**0.005**	-0.150	**0.029**	-0.022	0.747	0.070	0.312
Triglyceride	0.216	**0.001**	0.117	0.078	0.290	**<.0001**	0.201	**0.002**	0.007	0.922
Microalbumin	0.074	0.430	0.196	**0.036**	-0.161	0.086	-0.001	0.995	0.132	0.162

DISCUSSION

In the present study, we found that white blood cell, neutrophil and lymphocyte counts and PDW were higher in type 2 diabetic patients with inappropriorate glycemic management despite insulin therapy, however, RDW and MPV were similar between groups. Additionally, white blood cell, neutrophil and lymphocyte counts and PDW were correlated with many of the cardio-metabolic risk factors.

Inflammation is known to be a component of diabetes mellitus[15]. Various inflammatory biomarkers such as CRP and IL-6 have shown to predict the future diabetes risk[16]. Almost all of the cellular components in the blood, including WBC, RBC, and platelets have a role in the underlying pathogenesis of atherosclerosis which is known to be an inflammatory process. WBC count may be used as a predictor of future coronary events[5]. Epidemiological studies have shown that WBC as an indicator of inflammation could predict diabetes risk[17,18]. A meta-analysis showed that increased WBC corresponds to higher risk of T2DM[7]. Nada et al found that higher WBC counts in patients with uncontrolled glycemia (HbA1c >7%) than those with good glycemic control (HbA1c ≤7)[11]. In our study, WBC counts were higher in diabetic patients and it was correlated with several cardio-metabolic risk factors including hsCRP, FPG, HbA1c, DBP, BMI, WC, PPG, triglyceride, HDL-C.

Neutrophils also are suggested to be a marker of inflammation, which is closely related to the formation and rupture of atherosclerotic plaque. The neutrophil-platelet interaction may have a role in acute coronary syndrome[19,20]. Increased neutrophil count have an association with higher cardiovascular disease risk[21]. A meta-analysis demonstrated a relation between cardiovascular disease and neutrophil counts[10]. A large, population-based cohort study among 775,231 individuals showed that neutrophil counts were strongly associated with many

cardiac and vascular disorders[22]. In our study, neutrophil counts were higher diabetic patients and it was correlated with several cardio-metabolic risk factors including hsCRP, FPG, HbA1c, BMI, PPG, LDL-C, HDL-C and microalbumin levels.

Neutrophil-to-lymphocyte ratio (NLR) was postulated as a novel predictor of cardiovascular disease. NLR is higher in T2DM patients and it was independently correspond to the presence of coronary artery disease[23]. Yilmaz et al showed that NLR was higher in individuals with morbid obesity and could be an independent variable for predicting the development of T2DM[24]. Neutrophil and lymphocyte counts were higher in our diabetic patients, however, NLR was not.

Platelets are known to have a key role in atherosclerosis and arterial thrombosis[25]. MPV is accepted as a marker of platelet function and activation. DM is a "prothrombotic state" as a result of sustained hyperglycemia, dyslipidemia, and insulin resistance leading to endothelial damage. Diabetic patients have altered platelet morphology and function that may lead to this "prothrombotic state"[26]. Type 2 diabetic patients have shown to have higher MPV[8,27,28]. Buch et al have demonstrated that MPV and platelet distribution width could be a predictor of diabetic vascular complications[29]. Chen et al reported that MPV was increased in diabetics, however, platelet count and PDW were not[12]. In our study, platelet count and MPV were similar between groups and these indices were not correlated with cardio-metabolic risk factors. PDW was higher in diabetic patients and it was correlated with the many of the cardio-metabolic risk factors.

Elevated RDW has related to the cardiovascular mortality in the general population and various high-risk populations[30–32]. Nada et al showed that diabetic patients and especially those with poor glycemic control have higher RDW[11]. In our study, RDW was similar between groups and it was not correlated with cardio-metabolic risk factors.

Macrophages and monocytes possess a major role in the secretion of pro-inflammatory cytokines and involve to all stages of inflammation[33]. Monocyte activation has a key role in the beginning of atherosclerosis and monocyte count has been found to predict the future risk for the coronary events[34,35]. HDL-C carries out anti-inflammatory, antioxidant, and antithrombotic effects by various pathways, including promoting the efflux of cholesterol from macrophages, inhibiting expression of endothelial adhesion proteins, and encouraging reverse transport of oxidized molecules[36]. HDL-cholesterol decreases the inflammation by inhibition of monocyte activation and interruption of monocytes to macrophages differentiation[37]. MHR was postulated as a novel prognostic indicator of cardiovascular diseases[13,14]. In our study, we found that MHR was higher in diabetic group however, it was not associated with cardio-metabolic risk factors.

CBC indices might be suggested as a practical and an inexpensive way of evaluating cardiovascular risk in diabetic patients. White blood cell, neutrophil and lymphocyte counts were higher in our diabetic patients and besides that, they were correlated with many of the cardio-metabolic risk factors. Additionally, leukocyte subtypes and PDW was strongly associated with Hba1c levels. The results of our study may strengthen the notion that the diabetes mellitus is an inflammatory disorder. However, further studies are required to enlighten whether these findings are the result of the disease or could have a causality relationship.

In conclusion, white blood cell, neutrophil and lymphocyte counts and PDW were higher in type 2 diabetic patients with inappropriorate glycemic management despite insulin therapy however, RDW and MPV were not. MHR was

increased in these patients; however, it was not associated with cardio-metabolic risk factors. These findings might raise the idea that leukocyte subtypes and PDW could be used as a marker for poor glycemic control in T2DM.

Declaration of Conflicting Interests: The authors declare that they have no conflict of interest.

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