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Original Article

Efficacy of red cell distribution width and plateletcrit as predictors of subclinical inflammation in obesity

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Abstract

Aim: The present study aimed to investigate the relationship of the hematological predictors of inflammation in complete blood count with body mass index (BMI) and homeostatic model assessment for insulin resistance (HOMA-IR) values.

Material and Methods: The study included 354 subjects, who were admitted to the endocrinology outpatient clinic between January 2016 and March 2018. According to their BMI values, the subjects were divided into five groups as class III obesity, class II obesity, class I obesity, overweight, and normoweight. In addition, the subjects were divided into two groups as HOMA-IR <2.7 and HOMA-IR ≥2.7 to evaluate insulin resistance. Medical records of all the patients were reviewed and the data were collected retrospectively. As the predictors of subclinical inflammation, the mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT), red cell distribution width (RDW), neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR) were compared among the study groups.

Results: There were statistically significant differences among the BMI groups in terms of WBC, neutrophil count, lymphocyte count, RDW, platelet count, and PCT values. Hemoglobin, WBC, neutrophil count, lymphocyte count, RDW, platelet count, and PCT value were significantly higher in those having HOMA-IR value of ≥2.7. Multivariate linear regression analysis revealed significant correlations of BMI with RDW and PCT values, whereas HOMA-IR showed a correlation only with PCT value.

Conclusion: RDW and PCT are simple and low-cost markers that are able to predict the development of cardiovascular complications and other comorbidities in overweight and obese subjects.

Keywords: Obesity; homeostatic model assessment for insulin resistance; subclinical inflammation; red cell distribution width; plateletcrit.

INTRODUCTION

In the last decade, obesity has shown an increasing prevalence among both adults and children in many countries worldwide (1). Obese subjects pose a huge economic burden on healthcare system because of the obesity-associated complications such as type 2 diabetes, metabolic syndrome, malignancy, and cardiovascular diseases (1-3). It is known that adipose tissue secretes adipocytokines, which have autocrine, paracrine or endocrine functions and cause chronic low-degree inflammation, for the regulation of metabolic functions (4). These proinflammatory cytokines may lead to insulin resistance in the adipose tissue, skeletal muscle, and liver by impairing insulin signal transduction (3,4).

The mean platelet volume (MPV), platelet distribution width (PDW) and plateletcrit (PCT- the volume occupied by platelets in the blood as a percentage), which are among the thrombocyte indices used for assessing the activation and function of thrombocytes, play an important role in the pathophysiology of the diseases tend to cause inflammation (5,6). Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) have recently gained currency as practical methods providing valuable information in determining the risk and prognosis of systemic inflammatory diseases and cardiovascular diseases (7,8). Red cell distribution width (RDW), which is the heterogeneity measure of erythrocyte size in complete blood count, is accepted as the marker of inflammation and oxidative stress in numerous diseases such as hypertension, heart failure, coronary artery disease, and stroke (9).

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All these hematological inflammatory markers could be predictive for the development of metabolic syndrome, type 2 diabetes mellitus, malignancy, and cardiovascular and cerebrovascular diseases in overweight and obese subjects. The aim of the present study was to investigate the relationship of hematological inflammatory markers in the complete blood count with body mass index (BMI) and homeostatic model assessment for insulin resistance (HOMA-IR) values.

MATERIAL and METHODS

Hospital records of patients from June 2016 through March 2018 in the Endocrinology and Metabolism Disorders Clinic of Dumlupınar University Kütahya Evliya Çelebi Training and Research Hospital in Turkey were retrospectively reviewed. The patients were classified into five groups according to their BMI values, which were calculated using the formula "body weight (kg)/height2 (m2)", as class III obesity (BMI >40 kg/m2), class II obesity (35-39.9 kg/m2), class I obesity (30-34.9 kg/m2), overweight (25-29.9 kg/m2), and normoweight (18.5-24.9 kg/m2). Accordingly, a total of 354 patients consisting of 63 class III obese patients (46 females, 17 males, mean age 39±11.3 years), 63 class II obese patients (47 females, 16 males, mean age 38.5±10.8 years), 77 class I obese patients (54 females, 23 males, mean age 36.6±9.7 years), 77 overweight patients (47 females, 30 males, mean age 37.1±10.8 years), and 74 age- and gender-matched healthy normoweight subjects (48 females, 26 males, mean age 35.3±11.2 years) were enrolled into the study.

Patients with thyroid dysfunction, diabetes mellitus, malignancy, and cardiovascular, cerebrovascular, hematological, or respiratory disorder; those with a history of drug use interfering with complete blood count parameters in the last three months; those undergoing any surgical intervention in the last six months; those with a history of acute infectious disease in the last one month; and pregnant women were excluded. The Institutional Ethics Committee of Dumlupınar University approved the study protocol.

Complete blood count, blood glucose, hemoglobin A1c (HbA1c), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), and insulin values measured after an overnight fasting of about 10-12 hours were recorded for all patients. Complete blood count was routinely performed in our laboratory by laser-based impedance measurement using an automated blood cell counter (Mindray BC-6800, Nanshan, Shenzhen, PR China). Hemoglobin, white blood cell (WBC)count, platelet count, neutrophil count, lymphocyte count, monocyte count, and RDW, MPV, PDW, PCT, NLR, and PLR values were calculated as the components of complete blood count. Fasting glucose level was assessed by glucose hexokinase method (Beckman Coulter Ireland Inc., Galway, Ireland). HbA1c values were determined using high-performance liquid chromatography (Tosoh Bioscience, South San Francisco, CA, USA). A automatic analyzer (Beckman Coulter AU 2700, Brea, CA, USA) measured TC, HDL-C, LDL-C, and TG. Serum insulin concentration was measured by ultrasensitive insulin assay, which is a simultaneous one-step immunoenzymatic ("sandwich") assay performed by the automated Access Immunoassay (Beckman Coulter DXI 600, Fullerton, CA, USA). HOMA-IR, value of insulin resistance, was calculated using the formula "fasting blood glucose (mg/dL) x fasting insulin (μIU/mL)/405"; the HOMA-IR value of ≥2.7 was considered to be an indicator of insulin resistance. Data were analyzed using the Predictive Analytics SoftWare (PASW) Statistics for Windows, Version 18.0(SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used for normality analysis of distribution of numerical data. Descriptive data were expressed as mean±standart deviation. Student's t-test was used for normally distributed data, while the Mann-Whitney U test was used for not normally distributed data. The difference between the groups was analyzed using a one-way ANOVA for each variable. Tukey's post hoc test was used to identify the significant difference between the groups. In addition, the chi-square test was used to compare the categorical data. The Pearson's correlation test was used for correlation analyses. Stepwise multivariate linear regression model, including significant variables in univariate analyses, was then used to determine which determinants independently explained a significant ($p<0.05$) fraction of the variance of the dependent variables. The data was analyzed at 95% confidence level and at a p value of less than 0.05 is considered significant.

RESULTS

In the present study, the data of 63 class III obese, 63 class II obese, 77 class I obese, and 77 overweight patients and 74 age- and gender-matched healthy normoweight subjects (354 cases) were compared. General characteristics of the patients and normoweight subjects are summarized in Table 1. There were no significant differences among the groups in terms of age, sex, smoking status, and total cholesterol values. As was expected, comparisons of the groups in terms of insulin, fasting blood glucose, HOMA-IR, HbA1c, and lipid parameters revealed statistically significant differences (Table 1).

The mean values of hemoglobin, WBC, neutrophil count, lymphocyte count, monocyte count, RDW, platelet count, MPV, PDW, PCT, NLR, and PLR are demonstrated in Table 2. When the groups were compared using the ANOVA test, statistically significant differenceswere determined in terms of hemoglobin, WBC, neutrophil count, lymphocyte count, RDW, platelet count, and PCT values ($p<0.001$ for each); however, monocyte count, MPV, PDW, NLR, and PLR showed no statistically significant differencesamong the groups (Table 2).

All patients and normoweight subjects were divided into two groups as those having HOMA-IR value of <2.7 (n=208)

and those having HOMA-IR value of≥2.7 (n=146). Similar with the BMI groups, hemoglobin value, WBC, neutrophil count, lymphocyte count, RDW, platelet count, and PCT were significantly higher in those having HOMA-IR value of ≥2.7 group than those having HOMA-IR value of <2.7 (p=0.02, p<0.001, p=0.001, p<0.001, p=0.003, p<0.001, and p<0.001, respectively) (Table 3).

According to the Pearson's correlation analysis, RDW and PCT values showed strong positive correlation with both HOMA-IR and BMI (Table 4).

Multivariate linear regression analysis revealed statistically significant correlationsof BMI with RDW and PCT values; moreover, HOMA-IR also showed a significant positive correlation with PCT (Table 5).

Table 1. Demographic, clinical and laboratory characteristics of study participants

Variables	Normoweight (n: 74)	Overweight (n: 77)	Class I obesity (n: 77)	Class II obesity (n: 63)	Class III obesity (n: 63)	P-value
Female/male (n)	48/26	47/30	54/23	47/16	46/17	0.37
Smoker/nonsmoker (n)	14/60	16/61	11/66	11/52	10/53	0.51
Age (years)	35.3±11.2	37.1±10.8	36.6±9.7	38.5±10.8	39.5±11.3	0.16
BMI (kg/m2)	21.9±2.2	27.3±1.3	32.3±1.4	37.3±1.4	44.4±4	<0.001
İnsulin (uIU/mL)	6.6±3.4	9.0±5.4	12.4±5.8	13.5±8.4	14.5±7.1	<0.001
Glucose (mg/dl)	91.7±6.7	93.7±7.9	92.8±8.0	96.1±9.6	96.2±9.8	0.005
HOMA-IR	1.49±0.84	2.09±1.37	2.84±1.52	3.20±2.08	3.43±1.77	<0.001
HbA1c (%)	5.28±0.34	5.24±0.34	5.33±0.32	5.52±0.35	5.58±0.35	<0.001
LDL-C (mg/dl)	105.8±29.3	120.5±33.5	113.1±27.4	117.6±26.6	115.4±30.3	0.05
HDL-C (mg/dl)	54.7±11.0	46.8±10.8	47.4±11.1	46.8±9.5	47.4±10.5	<0.001
TC (mg/dl)	178.7±34.3	197.2±37.5	186.6±33.4	195.8±35.2	192.4±33.9	0.14
Triglyceride (mg/dl)	91.1±38.6	147.1±79.6	133.3±68.7	159.9±96.0	145.1±62.7	<0.001

BMI: Body mass index, HOMA-IR: Homeostatic Model of Assessment-Insulin Resistance, HbA1c: Hemoglobin A1c, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, TC: Total cholesterol
Data are shown as mean ± SD
P values were calculated by an ANOVA F-test

Table 2. Comparison of the hematological parameters in the groups

Variables	Normoweight (n: 74)	Overweight (n: 77)	Class I obesity (n: 77)	Class II obesity (n: 63)	Class III obesity (n: 63)	P-value
Hb (g/dL)	14.3 ±1.4	14.5±1.3	13.9±1.4	13.7±1.3	13.5±0.9	<0.001
WBC (103/mm3)	6.83±1.33	7.29±1.54	7.42±1.57	8.03±1.57	8.48±1.89	<0.001
NEUT (103/mm3)	3.87±1.01	4.13±1.10	4.29±1.23	4.57±1.04	4.93±1.39	<0.001
LYMPH (103/mm3)	2.23±0.66	2.52±0.67	2.43±0.56	2.68±0.70	2.82±0.88	<0.001
MON (103/mm3)	0.44±0.13	0.46±0.12	0.43±0.12	0.46±0.14	0.49±0.11	0.09
RDW (%)	13.38±0.92	13.43±1.00	13.70±1.16	13.77±1.08	14.13±1.23	<0.001
PLT (103/mm3)	245.5±45.4	265.8±53.8	273.8±55.6	284.7±56.5	286.7±56.1	<0.001
MPV (fL)	9.6±1.06	9.7±1.06	9.6±1.02	9.5±1.28	9.8±1.10	0.74
PDW (fL)	16.09±0.50	16.13±0.39	16.03±0.46	15.82±1.35	15.75±2.04	0.17
PCT (%)	0.233±0.03	0.255±0.04	0.262±0.04	0.268±0.04	0.279±0.05	<0.001
NLR	1.83±0.67	1.72±0.55	1.82±0.60	1.78±0.54	1.86±0.67	0.66
PLR	117.02±39.6	111.37±33.1	118.45±37.0	112.51±35.6	109.49±36.9	0.54

BHb: Hemoglobin, WBC: White Blood Cells, NEUT: Neutrophils, LYMPH: Lymphocytes, MON: Monosit, RDW: Red cell Distribution, PLT: Platelets, MPV: Mean Platelet Volume, PDW: Platelet Distribution Width, PCT: Plateletcrit, NLR: Neutrophil Lymphocyt Ratio, PLR: Platelet Lymphocyt Ratio
Data are shown as mean ± SD
P values were calculated by an ANOVA F-test.

Table 3. Comparison of the hematological parameters in the HOMA-IR < 2.7 and HOMA-IR > 2.7 groups

Variables	HOMA-IR < 2.7 (N: 208)	HOMA-IR > 2.7 (N: 146)	P-value
Hb (g/dL)	14.2±1.43	13.8±1.29	0.02
WBC (103/mm3)	7.2±1.59	8.0±1.66	<0.001
NEUT (103/mm3)	4.15±1.18	4.60±1.20	0.001
LYMPH (103/mm3)	2.37±0.66	2.73±0.75	<0.001
MON (103/mm3)	0.45±0.13	0.46±0.11	0.21
RDW (%)	13.5±0.9	13.8±1.2	0.003
PLT (103/mm3)	258.8±48.1	287.1±60.6	<0.001
MPV (fL)	9.7±1.14	9.6±1.05	0.36
PDW (fL)	16.05±0.84	15.87±1.39	0.12
PCT (%)	0.249±0.04	0.272±0.05	<0.001
NLR	1.83±0.63	1.76±0.57	0.29
PLR	115.6±36.2	111.5±36.8	0.30

Data are shown as means ± SD
P values were calculated by student t-test.

Tablo 4. Pearson correlation analysis between hematological parameters and BMI and HOMA-IR

Variables	RDW		PCT	
	r	p	r	p
BMI	0.275	<0.001	0.301	<0.001
HOMA-IR	0.157	0.003	0.224	<0.001

BMI: Body mass index, HOMA-IR: Homeostatic Model of Assessment-Insulin Resistance

Table 5. Multivariate linear regression analysis of variable influencing PCT and RDW values in the groups

Variables	R2	β	95 % Confidence Interval	P value
	r	p	r	p
PCT				
BMI	0.100	0.317	0.01-0.02	<0.001
HOMA-IR	0.111	0.116	0.001-0.006	0.04
RDW				
BMI	0.066	0.256	0.02-0.04	<0.001

DISCUSSION

Today, it is well-known that obesity is an independent risk factor for type 2 diabetes mellitus, dyslipidemia, and cardiovascular diseases (1). Based on the earlier studies, it is obvious that obesity is associated with cellular stress and activation of inflammatory pathways (10). Low-grade inflammation in obesity results in increased plasma concentrations of tumor necrosis factor-α, interleukin-6, and other inflammatory markers (2,4,11). Moreover, analysis of this high-cost cytokines requires an expert team. For this reason, cost-effective and easily applicable parameters that are able to determine grade of inflammation in obesity are required. NLR, PLR, MPV, PDW, PCT, and RDW are simple hematological inflammatory markers that can be easily measured by routinely-used complete blood count devices and their clinical importance hasbeen better understood by means of the studies performed in the recent years (11,12). The present study determined that PCT and RDW were significantly correlated with BMI and HOMA-IR in the overweight and obese patients.

High NLR and PLR indices are associated with poor prognosis particularly in systemic inflammation, cardiovascular diseases, and malignant diseases (13,15). Studies conducted in overweight and obese patients have reported conflicting outcomes. While limited number of

studies has suggested a significant relationship between these parameters and obesity (16,17). İn the literature, there are many studies failing to determine such a significant relationship (17-20). In the present study, no significant relationship of these two parameters with BMI and HOMA-IR values was also determined. Therefore, it can be concluded that NLR and PLR are not efficient hematological markers for prediction of subclinical inflammation in obesity or insulin resistance.

Thrombocytes are not only involved in hemostasis but also regulate inflammatory processes. Secretion of inflammatory mediators is followed by enhanced thrombocyte activation. Change in production, activation, and function of thrombocytes results in change in thrombocyte indices such as MPV, PDW, and PCT (5,21,22). It has been reported that PCT in particular can be used as a prognostic biomarker for assessing the risk of acute coronary syndrome in cardiovascular diseases (23). Different results have been obtained in studies investigating the relationship of obesity with MPV and PDW. While some studies have determined a significant relationship and a positive correlation, the literature comprises also studies that have failed to determine such significant relationship (18,20,24,25). Moreover, studies have also demonstrated decreased MPV values in correlation with diet-associated weight loss or weight loss after bariatric surgery (26,27). In the present study, MPV and PDW values showed no statistically significant differences among the BMI groups or between the HOMA-IR groups.

Furuncuoğlu et al. evaluated the effects of hematological markers on obesity in the patients (n=223) grouped according to their BMI values and they found the PCT value to be 0.21±0.04 in the healthy group, 0.25±0.07 in the overweight group, 0.27±0.07 in the obese group, and 0.26±0.05 in the morbid obese group (p<0.001) (20). In the present study with higher patient number, likewise, PCT was 0.233±0.03 in the normoweight subjects, 0.255±0.05 in the overweight patients, 0.262±0.04 in the class I obese patients, 0.268±0.04 in the class II obese patients, and 0.279±0.05 in the morbid obese patients (p<0.001). In addition, when the study participants were grouped according to the presence of insulin resistance, PCT value was significantly higher in the HOMA-IR ≥2.7 group (p<0.001). PCT also showed significantly positive correlations with BMI and HOMA-IR both in correlation analysis and in linear regression analysis.

Red cell distribution width, which is considered as an inflammatory marker in numerous diseases, is a hematological parameter associated with both anemia and inflammatory conditions and indicates differences in the size of red blood cells. Moreover, the relation of increased RDW value with poor prognosis in cardiovascular diseases has also been reported (28). Fujita et al. conducted a study in the adolescents and found the RDW value to be significantly higher in the overweight adolescent group (13.39±10) as compared with the normal-weight adolescent group (13.07±0.09; p=0.015) (29). In another study conducted in children, RDW value was found to be significantly higher in the overweight children than in the normal-weight children (30). In many studies carried out in adult age group, not only RDW but also other inflammatory parameters, such as C-reactive protein and fibrinogen, were found to be significantly higher in obese group (28-32). In the present study, the mean RDW was 13.38±0.92 in the normoweight subjects, 13.43±1.00 in the overweight patients, 13.70±1.16 in the class I obese patients, 13.77±1.08 in the class II obese patients, and 14.13±1.23 in the class III obese patients (p<0.001). When the study participants were categorized according to the insulin resistance, RDW was determined to be significantly higher in the HOMA-IR ≥2.7 group (p=0.003). Both the correlation analysis and the linear regression analysis revealed positive correlation of RDW with BMI and HOMA-IR.

The major limitation of the present study is its retrospective design using the data from a single center. Another limitation is the lack of comparison of hematological parameters with high-sensitive C-reactive protein and other inflammatory markers, which would predict the subclinical inflammation in overweight and obese subjects, as they are not routinely studied.

CONCLUSION

Among the hematological inflammatory markers, RDW and PCT increase with increasing BMI and insulin resistance. RDW and PCT are simple and low-cost markers that are able to predict development of cardiovascular complications and other comorbidities in overweight and obese individuals. It can be suggested that instead of high-cost and not easily applicable proinflammatory cytokines, popularizing the use of these simple hematological markers would be more beneficial during routine outpatient controls of obese patients.

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