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Evaluation of inflammation in obesity and chronic kidney disease with hemogram parameters

Obezite ve Kronik Böbrek Hastalığındaki İnflamasyonun Hemogram Parametreleri ile Değerlendirilmesi

Ilter Bozaci[1*], Erhan Tatar[2]

1.Department of Nephrology, Manisa City Hospital, Turkey
2.Department of Nephrology, University of Health Sciences Bozyaka Training and Research Hospital, Izmir, Turkey

ABSTRACT

Aim: Chronic inflammation is involved in the pathogenesis of both obesity and chronic kidney disease (CKD). We aimed to evaluate the parameters derived from complete blood count (CBC) as inflammatory markers in obese patients and obese CKD patients.
Methods: Individuals enrolled in the study were divided into three groups. Group-1 was composed of obese patients; group-2 was composed of obese CKD patients and group-3 was composed of healthy individuals as the control group. This study was conducted at a training and research hospital over 6 months period.
Results: Forty-one patients were in group-1; 41 patients were in group-2 and 22 individuals were in group-3. White blood cell count (WBC) was significantly higher in group-1 and group-2 compared with group-3 (7,5±1,4 x103/μL vs 8,4±2,4 x103/μL vs 6,5±1,3 x103/μL, respectively, p<0.001) and neutrophile to lymphocyte ratio (NLR) was significantly higher in group-1 and group-2 compared with group-3 (1,9±0,7 vs 2,5±1,5 vs 1,7±0,4, respectively, p<0.001). NLR and WBC was found positively correlated with systolic blood pressure, urea, creatinine, uric acid, whereas negatively correlated with estimated glomerular filtration rate.
Conclusions: It is important to determine significant results in CBC derived markers that are widely used in routine clinical practice as inflammatory markers.

Keywords: Inflammation, Renal Insufficiency, Blood cell count.

ÖZ

Amaç: Kronik inflamasyon hem obezitenin hem de kronik böbrek hastalığının patogenezi ile ilişkilidir. Çalışmamızda obez hastalarda ve obez kronik böbrek hastalarında inflamasyon belirteci olarak tam kan sayımı parametrelerinin değerlendirilmesini amaçladık.
Yöntemler: Çalışmada yer alan bireyler 3 ayrı gruba bölündü. Grup-1 obez hastalardan, grup-2 obez kronik böbrek hastalarından, grup-3 kontrol grubu olarak sağlıklı bireylerden oluşmakta idi. Çalışmamız, 6 aylık bir sürede bir eğitim ve araştırma hastanesinde gerçekleştirildi.
Bulgular: Kırkbir hasta grup-1'de; 41 hasta grup-2'de ve 22 sağlıklı birey grup-3'de yer aldı. Beyaz küre sayıları grup-3'e kıyasla grup-1 ve grup-2'de anlamlı düzeyde yüksek saptandı (7,5±1,4 x103/μL vs 8,4±2,4 x103/μL vs 6,5±1,3 x103/μL, sırasıyla, p<0.001) ve nötrofil lenfosit oranı grup-3'e kıyasla grup-1 ve grup-2'de anlamlı düzeyde yüksek saptandı (1,9±0,7 vs 2,5±1,5 vs 1,7±0,4, sırasıyla, p<0.001). Nötrofil lenfosit oranı ve beyaz küre sayısının, sistolik kan basıncı, ürik asit, üre ve kreatinin arasında pozitif; glomerüler filtrasyon hızı ile negatif korelasyon saptandı.
Sonuçlar: Rutin klinik pratikte sıkça kullanılan hemogramdan elde edilen parametrelerin inflamasyon belirteçleri olarak anlamlı sonuçlanması önemlidir.

Anahtar Kelimeler: İnflamasyon, Böbrek Yetmezliği, Kan Hücre Sayımı.

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*Corresponding Author: Ilter Bozaci, Adnan Menderes District 132. Street No:15, 45040 Sehzadeler, Manisa, Turkey, +902362292600, ilterbozaci@gmail.com

ORCID: 0000-0001-7535-9403

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INTRODUCTION

Inflammation is the basis for the pathogenesis of numerous diseases. Determination of the inflammatory state is essential in following the course of the disease, as well as in evaluating the response of treatment in inflammatory diseases. Unless properly regulated, inflammation and oxidative stress can cause devastating effects such as excessive cytokine production, increase in pro-inflammatory and oxidative stress mediators [1]. Obesity is defined as the positive energy balance resulting from the imbalance between energy intake and consumption [2]. Many pro-inflammatory and anti-inflammatory molecules, such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF- α), are known to be produced and released from adipose tissue [3]. Obesity has both direct and indirect effects on chronic kidney disease development. Compensatory hyperfiltration occurs in obese patients in order to meet the increased metabolic needs resulting from the increased body weight. In the long term, this condition results in CKD development via an increase in intraglomerular pressure and damage in the kidney structure. Moreover, inflammation and oxidative stress have been found to be associated with CKD progression in studies in the literature [4]. CBC testing is a widely used laboratory test in clinical practice and there are various clinical studies that demonstrate the association between inflammatory states in conditions such as infections, sepsis, tumoral and rheumatological diseases and parameters that derived from CBC testing, such as monocyte to lymphocyte ratio (MLR) neutrophile to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) [5-7]. In this study, we aimed to evaluate the parameters derived from CBC as inflammatory markers in obese patients and obese CKD patients.

MATERIAL and METHOD

Study Design

The study was approved by the institutional ethics committee on the date of March 21, 2018 with the approval number [8]. This study was conducted in the out-patient clinic of the department of nephrology at two training and research hospitals, over a 6 month period. Patients under 18 years old, those with acute infection, malignancy, congestive heart failure, chronic obstructive lung disease, diabetes mellitus and acute and or chronic liver disease, were excluded from the study. All of the patients included in the study signed informed consent. Individuals enrolled in the study were divided into three groups: Group-1 was composed of obese patients, Group-2 was composed of obese CKD patients and Group-3 was composed of healthy individuals, as the control group. Estimated glomerular filtration rate (eGFR) was calculated by the CKD Epidemiology Collaborative Study Equation [8]. Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline was used to determine the kidney function stage [9]. Body mass index (BMI) was calculated from the formula weight(kg)/height 2(m2). Obesity is defined as BMI greater or equal than 30 kg/m2 [10].

Laboratory Assessment

Laboratory results of patients, including glucose, urea, creatinine, eGFR, uric acid, albumin, ALT (alanine aminotransferase), AST (aspartate aminotransferase), cholesterol, low density lipoprotein (LDL) and CBC , were obtained from their most recent medical records. NLR, PLR and MLR were calculated by dividing neutrophil count to lymphocyte count, platelet count to lymphocyte count and monocyte count to lymphocyte count, respectively.

Statistical Analysis

Continuous parametric variables were represented as means ± standard deviation. Categorical variables were represented as percentages. The Chi-square and Fisher Exact test were used to compare categorical variables. Non-parametric continuous variables were represented as median with 25-75 interquartile range. Comparison of the means of numerical variables of more than two independent groups was made using the One-Way ANOVA test and the post-hoc Bonferroni test was used to determine if the groups were significantly associated. The relationship between NLR and WBC and other demographic and laboratory data was done using Pearson's correlation analysis. The SPSS 18.0 program (Chicago, IL USA) was used to perform all statistical analyses. In our study, $p < 0.05$ was considered significant.

RESULTS

Forty-one patients were in group-1, 41 patients were in group-2 and 22 individuals were in group-3. According to the KDIGO clinical practice guideline, 32 CKD patients (78%) in group-2 were in stage-3 and 9 CKD patients (22%) in group-2 were in stage-4. There was no statistically significant difference between groups in terms of age (44±9,8 years vs 46±5,5 years vs 42±9,5 years; p=0.432) and gender (73/27 F/M% vs 58/42 F/M% vs 59/41 F/M%; p=0.323), respectively. BMI was significantly higher in group-1 and group-2 compared with group-3 (36±3 kg/m2 vs 35±3 kg/m2 vs 27±5, respectively, p<0.001). Serum urea levels were significantly higher in group-2 compared with group-1 and group-3 (26±7 mg/dl vs 62±34 mg/dl vs 29±6 mg/dl, respectively, p<0.001). Serum creatinine levels were significantly higher in group-2 compared with group-1 and group-3 (0,9±0,1 mg/dl vs 1,8±0,5 mg/dl vs 0,9±0,2 mg/dl, respectively, p<0.001) and eGFR was significantly lower in group-2 compared with group-1 and group-3 (84±17 ml/min/1.73m2 vs 39±13 ml/min/1.73m2 vs 90±15 ml/min/1.73m2, respectively, p<0.001).

Serum uric acid levels were significantly higher in group-1 and group-2 compared with group-3 (5,5±1,5 mg/dl vs 7,7±1,7 mg/dl vs 4,6±0,9 mg/dl, respectively, p<0.001). Serum ALT levels were significantly higher in group-1 and group-2 compared with group-3 (26±12 IU/L vs 20±10 IU/L vs 19±6 IU/L, respectively, p<0.001) and serum AST levels were significantly higher in group-1 and group-2 compared with group-3 (24±8 IU/L vs 22±9 IU/L vs 19±5 IU/L, respectively, p<0.001), as well. Serum hemoglobin levels were significantly lower in group-2 compared with group-1 and group-3 (14±1,5 g/dL vs 13±1,8 g/dL vs 14±1,6 g/dL, respectively, p<0.001).

Systolic blood pressure (SBP) levels were significantly higher in group-1 and group-2 compared with group-3 (122±11mmHg vs 142±21 mmHg vs 122±10 mmHg, respectively, p<0.001); diastolic blood pressure (DBP) levels were significantly higher in group-1 and group-2 compared with group-3 (80±7mmHg vs 89±14 mmHg vs 78±9 mmHg, respectively, p<0.001) and mean blood pressure (MBP) levels were significantly higher in group-1 and group-2 compared with group-3 (99±8mmHg vs 114±15 mmHg vs 97±8 mmHg, respectively, p<0.001). Demographical data and laboratory results of groups are presented in Table.1.

Table.1 Demographical and Laboratory Results of groups 1, 2 and 3.

	Group-1 (n=41)	Group-2 (n=41)	Group-3 (n=22)	p
Age (years)	44±10	46±6	42±9	0.43
Gender F/M (%)	73/27	59/41	59/41	0.32
BMI (kg/m2)	36±3	35±3	27±5	0.00 **, ***
Glucose (mg/dl)	91±8	96±13	93±10	0.09
Urea (mg/dl)	26±7	62±34	29±6	0.00 *, ***
Creatinine (mg/dl)	0,9±0,1	1,8±0,5	0,9±0,2	0.00 *, ***
eGFR (ml/min/1.73m2)	84±17	39±13	90±15	0.00 *, ***
Uric Acid (mg/dl)	5,5±1,5	7,7±1,7	4,6±0,9	0.00 *, ***
Albumin (g/dl)	4,4±0,2	4,3±0,4	4,3±0,3	0.38
ALT (IU/L)	26±12	20±10	19±6	0.00 **, ***
AST (IU/L)	24±8	22±9	19±5	0.04 **, ***
Cholesterol (mg/dL)	213±36	222±61	201±47	0.28
LDL (mg/dL)	139±28	146±45	130±37	0.28
SBP (mmHg)	122±11	142±21	122±10	0.00 **, ***
DBP (mmHg)	80±7	89±14	78±9	0.00 **, ***
MBP (mmHg)	99±8	114±15	97±8	0.00 **, ***

Abbreviations: NLR: Neutrophil to Lymphocyte Ratio; PLR: Platelet to Lymphocyte Ratio; MLR: Monocyte to Lymphocyte Ratio; BMI: Body Mass Index; eGFR: estimated glomerular filtration ratio; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; LDL: Low density lipoprotein; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MBP: Mean blood pressure.

Notification: Statistically significant difference between Group-1 and Group-2 is defined with the marker *; statistically significant difference between Group-1 and Group-3 is defined with the marker **; statistically significant difference between Group-2 and Group-3 is defined with the marker *.**

WBC was significantly higher in group-1 and group-2 compared with group-3 (7,5±1,4 x103/µL vs 8,4±2,4 x103/µL vs 6,5±1,3 x103/µL, respectively, p<0.001) and NLR was significantly higher in group-1 and group-2 compared with group-3 (1,9±0,7 vs 2,5±1,5 vs 1,7±0,4, respectively, p<0.001). Inflammation markers derived from CBC, are presented in Table.2.

In the Pearson correlation analysis, NLR was positively correlated with SBP, DBP, MAP, urea, creatinine, uric acid and WBC, whereas negatively correlated with eGFR, ALT and hemoglobin. On the

other hand, WBC was found positively correlated with BMI, SBP, urea, creatinine, uric acid, AST, hemoglobin and NLR, whereas negatively correlated with eGFR. Pearson correlation analysis of NLR and WBC is presented in Table.3.

Table.2 Complete Blood Count Parameters in terms of inflammation markers.

	Group-1 (n=41)	Group-2 (n=41)	Group-3 (n=22)	p
White Blood Cell (x103/μL)	7,5±1,4	8,4±2,4	6,5±1,3	0.00 **, ***
Hemoglobin (g/dL)	14±1,5	13±1,8	14±1,6	0.01 *, ***
NLR	1,9±0,7	2,5±1,5	1,7±0,4	0.00 **, ***
PLR	125±50	135±43	111±29	0.06
MLR	0,23±0,1	0,23±0,1	0,19±0,01	0.14

Abbreviations: NLR: Neutrophil to Lymphocyte Ratio; PLR: Platelet to Lymphocyte Ratio; MLR: Monocyte to Lymphocyte Ratio
Notification: Statistically significant difference between Group-1 and Group-2 is defined with the marker *; statistically significant difference between Group-1 and Group-3 is defined with the marker **; statistically significant difference between Group-2 and Group-3 is defined with the marker *.**

Table.3 Pearson's Correlation Analysis of NLR and WBC

	NLR		WBC (x10³/μL)	
	Rh0	p	Rh0	p
BMI (kg/m2)	-	-	0.503	0.000
SBP (mmHg)	0.310	0.001	0.199	0.043
DBP (mmHg)	0.216	0.027	-	-
MBP (mmHg)	0.295	0.002	-	-
Urea (mg/dl)	0.484	0.000	0.311	0.001
Creatinine (mg/dl)	0.580	0.000	0.381	0.000
eGFR (ml/min/1.73m²)	-0.427	0.000	-0.293	0.003
Uric Acid (mg/dl)	-	-	0.220	0.025
Hemoglobin (g/dL)	-0.277	0.004	0.889	0.000
WBC (x103/μL)	0.456	0.000	-	-
NLR	-	-	-0.277	0.004

Abbreviations: NLR: Neutrophil to Lymphocyte Ratio; BMI: Body Mass Index; eGFR: estimated glomerular filtration ratio; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MBP: Mean blood pressure; WBC: White Blood Cell Count.

Notification: Only significant results are presented.

DISCUSSION

In the present study, we evaluated CBC derived parameters such as WBC, NLR, PLR and MLR as markers of inflammation in obese patients and obese CKD patients. Although a statistically significant difference was found only for NLR and WBC, all of the markers derived from CBC such as WBC, NLR, PLR and MLR were found higher in obese patients and obese CKD patients, compared with healthy individuals. It is essential to determine the significance of CBC derived markers that are widely used in routine clinical practice as inflammatory markers.

Obesity can result in a pro-inflammatory state via both increasing levels of pro-inflammatory cytokines and diminishing levels of anti-inflammatory cytokines and in the literature, obesity was found associated with chronic inflammation [11]. On the other hand, the absence of CKD in most obese patients indicates that weight gain alone does not lead to CKD development. Obesity is thought to contribute to the underlying inflammatory process in chronic kidney disease and as a result, increased oxidative stress and inflammatory process further increase the risk of CKD [12]. In our study, consistent with the findings in the literature, we found higher levels of CBC derived inflammatory markers such as WBC, NLR, PLR, MLR, and lower levels of eGFR in obese patients and obese CKD patients, compared with healthy individuals. The lack of statistically significance between groups in terms of MLR and PLR may be due to the insufficient number of patients in the study.

Plasma uric acid levels are increased in CKD due to a decrease in eGFR. In addition to CKD, an increase in serum uric acid levels is associated with many conditions, including obesity [13]. Although the underlying mechanism of uric acid increase in obesity has not been precisely identified, hyperuricemia may occur via an increased urate production, decreased renal clearance and reduced renal excretion [14]. The association between hyperuricemia and CKD progression still remains controversial. Jurascheck et al. found that hyperuricemia is more frequent in patients with reduced eGFR [15]. Russo et al. similarly reported hyperuricemia associated with CKD progression [16]. On the other hand, in some studies, such as the study conducted by Nakayama et al., the association between hyperuricemia and CKD progression could not be clearly demonstrated [17]. Sum of all, although some conflicting results exist about the relationship between hyperuricemia and CKD development and progression, data from comprehensive range studies support the relationship between them [18,19]. In

addition, in another study, uric acid was found to induce inflammation and to be associated with inflammatory markers [20]. In our study, similarly, we found the highest uric acid levels in obese CKD patients, followed by the obese patients and the healthy control group, respectively. A positive correlation was also found between uric acid and WBC as an inflammatory marker derived from CBC. It can also be speculated from our results that the underlying inflammation in obesity and CKD, might have contributed to the elevation in uric acid levels in the patient groups.

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in adults, whose prevalence between diabetic and obese individuals is around 80% compared to 30-50% of the general population and mildly elevated aminotransferase (ALT and AST) levels are the most common laboratory findings of NAFLD [21]. In our study, according to the literature results, we found mildly elevated aminotransferase levels both in obese patients and obese CKD patients.

It is a well-known fact that obesity is associated with higher blood pressure levels [22]. The role of inflammation in the pathophysiology of hypertension is suggested from the findings in the literature [23]. In our study, we found the highest blood pressure levels in obese CKD patients, followed by obese patients. In addition, we found a positive correlation between inflammation markers and blood pressure levels. Our results may suggest the association between inflammation and hypertension, both in obese patients and obese CKD patients.

CONCLUSION

Obesity and CKD are both chronic conditions that share common pathophysiological mechanisms, including inflammation. Although many inflammatory markers had been defined, simple and accessible examinations such as CBC derived markers stand out with their widespread use and easy accessibility, in monitoring both the disease course and the effectiveness of treatment strategies.

LIMITATIONS

First, the total number of individuals enrolled in the study was small. Second, although the central aim of the study was to evaluate CBC-derived markers, we also aimed to compare other commonly used inflammatory markers, such as c-reactive protein (CRP), between groups. However, we could not evaluate other markers as a result of technical problems developed during the study.

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Author / ORCID	Authorship Contrubition
İlter Bozacı 0000-0001-7535-9403	Concept, design, materials, data collection, interpretation,literature search, manuscript writing, final approval
Erhan Tatar 0000-0002-5068-4231	Concept, design, literature search, data collection, critical review