Original Investigation / *Özgün Araştırma*

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Early Inflammation Related to Pediatric Obesity

Pediyatrik Obezite İlişkili Erken Enflamasyon

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Abstract

Objective: Obesity is a serious health problem, has reached pandemic proportions and represents a major risk for several comorbidities. Some of the serum markers are considered to be associated with low-grade chronic inflammation. Neutrophil to lymphocyte ratio (NLR) is a new and cost-effective marker for the detection of subclinical inflammation that correlates with C-reactive protein (CRP) levels. The objectives of this study were to examine the relation between children's BMI and the biomarkers of early inflammatory predictors.

Material and Methods: The retrospective study included 176 children aged 5-18 years who applied to a primary care setting in Türkiye between January 2019 and March 2019. Participants with BMIs between 85-95 percentiles were defined as overweight and those over 95 percentiles as obese. For all groups, hemogram parameters, cell volumes, and ratios were evaluated and compared. In addition, NLR and PLR were compared.

Results: We found that neutrophil count and NLR were significantly different between the normal weight and overweight/obese groups (p= 0.001, p< 0.001 respectively) while hemoglobin, WBC, MPV, MCV, RDW, and PLR were similar in hemogram evaluation.

Conclusion: Obesity is associated with low-grade inflammation levels and is reaching alarming rates among both children and adults. Our study suggested that neutrophil counts and NLR were significantly higher in overweight/obese children. Obesity-related studies involving pediatric patients are crucial to developing appropriate methods for preventing the development of further complications in adulthood.

Keywords: Obesity, childhood, neutrophil to lymphocyte ratio, platelet to lymphocyte ratio

Öz

Giriş: Obezite, gerek çocuklarda gerekse erişkinlerde önemli bir sağlık problemi olmakla beraber sağlık sistemine önemli ölçüde yük oluşturmaktadır. Birçok serum belirtecinin düşük dereceli enflamasyon ile ilişkisi gösterilmiştir. Nötrofil-lenfosit oranı, subklinik enflamasyonda C-reaktif protein (CRP) düzeyleri ile korele, yeni keşfedilmiş ve maliyet etkin bir parametredir. Bu çalışmanın amacı, çocuklarda beden kitle indeksi ile erken enflamasyon belirteçleri arasındaki ilişkinin incelenmesidir.

Gereç ve Yöntemler: Retrospektif olarak planlanan çalışmaya, Ocak 2019-Mart 2019 tarihleri arasında birinci basamağa başvuran 5-18 yaş arası 176 çocuk dahil edilmiştir. Beden kitle indeksi 85-95 persentil olanlar "aşırı kilolu", 95 persentil üzeri olanlar "obez" olarak değerlendirilmiştir. Tüm gruplar için, hemogram parametreleri, hücre volümleri ve oranlar hesaplanmış ve karşılaştırılmıştır.

Bulgular: Nötrofil sayısı ve NLR düzeyi, normal ve aşırı kilolu/obez grup arasında anlamlı farklılık göstermiştir (sırasıyla p= 0.001, p< 0.001). Hemoglobin, WBC, MPV, MCV, RDW ve PLR düzeyleri arasında anlamlı fark saptanmadı.

Sonuç: Obezite, düşük dereceli sistemik enflamasyonla ilişkilidir ve hem çocuklarda hem erişkinlerde oranı giderek artmaktadır. Çalışmamız göstermiştir ki, nötrofil sayısı ve NLR düzeyleri obez ve aşırı kilolu çocuklarda daha yüksektir. Yetişkin dönemde gelişebilecek komplikasyonları önlemek için doğru ve uygun metodların geliştirilmesi açısından, pediyatrik obezite ile ilişkili çalışmalar kritik öneme sahiptir ve artırılmalıdır.

Anahtar Kelimeler: Obezite, çocukluk çağı, nötrofil lenfosit oranı, platelet lenfosit oranı

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Introduction

Obesity is a serious health problem, has reached pandemic proportions and represents a major risk for several comorbidities. In addition, it has been reported that pediatric obesity significantly increases the risk of obesity and its cardiovascular complications during childhood and adulthood. It is estimated that 20% of the world's adult population will be obese by 2030 (1). A meta-analysis in Türkiye has revealed that the prevalence of obesity increased from 0.6% to 7.3% between the periods 1990-1995 to 2011-2015 (2). Studies need to focus on childhood obesity to prevent complications and other chronic conditions in adulthood.

Obesity is not accepted as an imbalance of energy intake and expenditure anymore. Since the adipose tissue used to be considered a passive energy store, it is now considered a major endocrine organ (3,4).

Some serum markers are considered to be associated with low-grade chronic inflammation. Neutrophil to lymphocyte ratio (NLR) is a new and cost-effective marker for the detection of subclinical inflammation that correlates with C-reactive protein (CRP) levels. This marker is associated with multiple inflammatory conditions, cardiovascular diseases, and cancer. It has been shown that NLR and the degree of inflammation has a positive correlation (5-7). Platelet to lymphocyte ratio (PLR) is another biomarker, and these markers can be calculated based on a simple blood test (CBC) and has been proven to be useful in the diagnosis and monitoring of several systemic inflammatory conditions (8,9).

The objectives of this study were to investigate the relation between children's body mass index (BMI) and the biomarkers of early inflammatory predictors.

Materials and Methods

This retrospective study included 176 children aged 5-18 years and admitted to Kırıkkale Bağlarbaşı Family Health Center for routine follow-up according to "Infant, child and adolescent follow-up protocols" between January 2019 and March 2019. Body mass indices (BMIs) of the children were estimated based on BMI percentiles established by the Centers for Disease Control 2000 (CDC) for children and adolescents. BMI was calculated as weight in kilograms divided by height in meters squared. Participants with BMIs ≤84 percentiles were defined as healthy control, between 85-95 percentiles were defined as overweight and those over 95 percentiles as obese. Secondary obesity, infectious disease, receiving antimicrobial therapy, chronic illnesses, and obesity-related complications were excluded.

For all groups, hemogram parameters, cell volumes, and ratios were evaluated and compared. In addition, NLR and PLR were compared. NLR was calculated as neutrophil counts were divided by lymphocyte counts. PLR was calculated as platelet counts were divided by lymphocyte counts. This study was approved by Kırıkkale University Non-Invasive Research Ethics Committee (No: 2019.12.05; Date 08.01.2020).

Statistical Analysis

For all statistical analyses, IBM SPSS version 22 was used. Normality of the variables were checked with Kolmogorov-Smirnov test. Mean ± standard deviation was given for normally distributed values while median (minimum-maximum) was given for not normally distributed values. Categorical variables were expressed with numbers and percentages. Fisher's exact test was utilized for the comparison of categorical variables. For comparison of three groups' continuous variables with non-normal distribution, Kruskal Wallis H test was used. Then Mann-Whitney U test was performed to two groups with Bonferroni correction. One-Way ANOVA test was used for the comparison of normally distributed variables, then post-hoc test with Tukey was performed to two groups' comparisons. Relations in between data were analyzed with Pearson or Spearman correlation analysis according to distribution. $p< 0.05$ was considered significant for all tests.

Results

Median age of the study population was 12, and the dominant sex was male (53.5%). Median height was 153 centimeters while median weight was 47 kilograms. Between healthy control, overweight and obese individuals, age and sex distributions were similar. For these groups, the counts of neutrophil and platelet, plateletcrit (PCT), and NLR were significantly different while hemoglobin, white blood cell (WBC), mean platelet volume (MPV), mean erythrocyte volume (MCV), red cell distribution width (RDW), and PLR were similar in hemogram evaluation. NLR was significantly different between the groups. All comparisons are given in Table 1, and Table 2 showed two groups comparisons with post-hoc analyses if there was a significance in Table 1.

When the correlation between CBC parameters and BMI was evaluated, BMI was found to have a statistically significant positive linear correlation with neutrophil count, hematocrit (HCT) and mean corpuscular hemoglobin concentration (MCHC) ($p< 0.05$). An extremely significant positive linear correlation ($p< 0.01$) was found between BMI and NLR while there was a negative correlation between BMI and lymphocyte count ($p< 0.05$).

Discussion

The present study showed that overweight and obese children had higher inflammatory markers, especially NLR and neutrophil counts, than normal weighted children. Many studies revealed an association between obesity and inflam-

Table 1. The comparison of all groups

	Healthy control (n= 112) median (min-max)	Overweight (n= 31) median (min-max)	Obese (n= 33) median (min-max)	p
Age (years)	12 (5-17)	12 (5-17)	13 (6-17)	p= 0.49
Girls, n (%)	52 (46.3)	14 (45.2)	16 (48.5)	p= 0.87
Hemoglobin (g/dL)	13.4 (10.5-16.3)	13.4 (10.3-17.1)	13.5 (11.4-15.5)	p= 0.77
Neutrophil (10^3/mm^3)	3.36 (1.23-7.34)	3.68 (2.47-6.78)	4.07 (2.49-6.81)	p= 0.001
Lymphocyte (10^3/mm^3)	2.61 (0.97-4.94)	2.52 (1.42-4.44)	2.60 (1.57-4.59)	p= 0.49
Platelet (10^3/mm^3)	299 (166-507)	277 (183-464)	325 (155-494)	p= 0.04
Monocyte (10^3/mm^3)	0.42 (0.16-0.98)	0.47 (0.23-0.96)	0.45 (0.3-0.75)	p= 0.6
Eosinophil (10^3/mm^3)	0.14 (0.01-2.2)	0.13 (0.03-0.68)	0.14 (0.05-0.68)	p= 0.98
Basophil (10^3/mm^3)	0.20 (0.01-0.4)	0.03 (0.01-0.07)	0.20 (0.01-0.09)	p= 0.72
Red cell distribution width (%)	13.2 (11.8-17.9)	13.5 (12.4-15.9)	13.5 (12.6-28.8)	p= 0.19
Mean erythrocyte volume (fL)	84.5 (58-95.2)	84.8 (73-93)	83.9 (70.8-88.9)	p= 0.33
NLR*	1.2 (0.25-5.97)	1.54 (0.83- 3.17)	1.54 (0.68-3.19)	p< 0.001
PLR*	115.48 (43.12-338.38)	112.99 (68.02-199.3)	120,75 (64.05-223.1)	p= 0.42
	Healthy control (n= 112) mean ± sd	Overweight (n= 31) mean ± sd	Obese (n= 33) mean ± sd	
Mean platelet volume (fL)	10.24 ± 1.15	10.25 ± 1.17	10.32 ± 1.01	p= 0.94
White blood cell (10^9/mm^3)	6.83 ± 1.50	7.11 ± 1.37	7.52 ± 1.58	p= 0.063
Red blood cell (10^{12}/mm^3)	4.87 ± 0.42	4.79 ± 0.39	4.99 ± 0.40	p= 0.153
Plateletcrit (10^3/mm^3)	0.31 ± 0.06	0.28 ± 0.05	0.33 ± 0.06	p= 0.02

*NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio.

Table 2. Two-group comparisons

	NLR	PCT	PLR	Neutrophil
Healthy control-Overweight	p= 0.004	p= 0.129	p= 0.062	p= 0.033
Healthy control-Obese	p< 0.001	p= 0.273	p= 0.23	p= 0.001
Overweight-Obese	p= 0.39	p= 0.016	p= 0.013	p= 0.219

mation mostly in adults, but a great majority of studies did not exclude chronic diseases or conditions (10-14). A study performed with 223 participants in Türkiye by Furuncuoglu et al. has found an extremely significant positive linear correlation (p< 0.01) between BMI and WBC, neutrophil count, PCT, and platelet count (15). A study performed with 6766 patients from the dataset of NHANES (2005-2006, 2007-2008, 2009-2010) has been analyzed, and significant positive correlations have been found between waist circumference and neutrophil, lymphocyte, leukocyte, platelet levels and medium platelet volume (MPV) (16). Similar to these results, our study showed statistically significant differences between normal and overweight/obese groups in terms of neutrophil counts but PLT did not show any statistically significant difference in our study, and PCT was different only between overweighted and obese groups. Our study supported these studies with positive linear correlations between BMI and neutrophil counts.

In studies performed in the pediatric population, adipokines such as IL-6, TNF-alfa, leptin, and CRP have been the most preferred inflammatory markers to compare normal and obese/overweight children (17-21).

In a study performed by Aydin et al. with 187 children (130 obese individuals and 57 healthy controls) regarding blood parameters, the authors have found that lymphocyte and neutrophil counts and NLR were significantly higher in obese children (22). Similarly, our study also showed a significant increase in neutrophil counts and NLR among the overweight/obese group, but it failed to show significant differences in terms of lymphocyte count between the groups. Besides, our study showed a significant negative correlation between BMI and lymphocyte counts. Moreover, the previously mentioned study (22) has not identified any significant differences between obese and normal-weight children for PLR, as in our study.

Arslan and Makay have demonstrated that MPV levels were higher in obese adolescents with non-alcoholic fatty liver when compared to healthy controls (23); however, Kilciler et al. have reported that no significant difference was found between the patients with non-alcoholic fatty liver disease as for MPV levels (24). We did not find any significant difference between the groups for MPV levels.

It is understood that obesity is associated with low-grade inflammation and causes certain chronic conditions such as cardiovascular disease, type 2 diabetes mellitus, metabolic syndrome, and non-alcoholic steatohepatitis (10,25). This inflammation is due to the malfunction of immune-related activities in the adipose tissue, involving a transient infiltration of neutrophils within the abdominal fat and their binding to adipocytes (26).

A lot of chemical signals which play a role in multiple physiological processes in the entire body are produced by adipose cells. Inflammatory markers are associated with vascular atherosclerotic lesions, which are considered to be a part of insulin resistance by negatively influencing insulin sensitivity (27). Additionally, hypertrophic fat tissue produces reactive oxygen species which are an underlying cause of oxidative stress and pro-inflammatory cytokine release (28).

The adipose tissue contributes to the initiation and maintenance of systemic inflammation (29). Adipose tissue-related inflammation causes numerous immune responses, and macrophage involvement and mast cell polarization occur after neutrophil participation (30).

This study has several limitations. It is a retrospective analysis and evaluation of hemogram parameters. Other inflammatory markers were not assessed. Furthermore, the sample size was small. Further investigations are needed to evaluate the relation between inflammation and obesity in more detail.

Conclusion

Obesity is associated with systemic low-grade inflammation and is reaching alarming rates among both children and adults. Due to the high probability of obese children becoming obese adults, these individuals may have an even greater risk of developing health problems because of exposure to elevated inflammatory markers across their further life. Our study suggested that neutrophil count and NLR were significantly higher in overweight/obese children which cannot be explained by any chronic disease or other factors associated with inflammation. Obesity-related studies involving pediatric patients are crucial to developing appropriate methods for preventing the development of further complications in adulthood.

Ethics Committe Approval: This study was approved by Kırıkkale University Non-Invasive Research Ethics Committee (Decision no: 2019.12.05, Date: 08.01.2020).

Informed Consent: Patient consent was obtained.

Peer-review: Externally peer-reviewed.

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