

The relationship between childhood obesity with inflammatory mediators

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Abstract

Objectives: To determine the association of various obesity markers with systemic immune-inflammatory index.

Methods: The cross-sectional study was conducted at Marmara University, Istanbul, Turkey, from January 2018 to October 2018 and comprised children aged 6-16 years admitted to the outpatient clinic due to obesity. The patients were evaluated for height, weight, body mass index (BMI), fat percentage (F%), fat mass (FM) and fat-free mass (FFM). Waist circumference was measured and neutrophil, platelet and lymphocyte counts and neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and systemic immune-inflammation index (SII) were calculated on the basis of haemogram. Data was analysed using Number Cruncher Statistical System 2007.

Results: Of the 335 subjects, 203(60.6%) were girls and 132(39.4%) were boys. Univariate analysis of girls showed the effects of BMI, F%, FM, FFM and WC on NLR. FM remained a significant and independent risk factor for NLR ($p < 0.01$). The effects of BMI, F%, FFM and WC were not significant in multivariate model ($p > 0.05$). Univariate analysis of girls also showed the effects of BMI, F%, FM, FFM and WC measurements on SII. F% remained a significant and independent risk factor on SII ($p < 0.01$). The effects of BMI, fat mass, FFM and WC were not significant in multivariate model ($p > 0.05$).

Conclusion: In this study, the increase of SII, NLR and thrombocyte in terms of weight, BMI, fat percentage and fat mass supports the increase of inflammation due to the increase of fat in obesity. In terms of comorbidities in obesity, SII and NLR suggest that there may be inflammatory biomarkers which can be used in follow-up.

Keywords: Childhood obesity, Systemic immune inflammatory index, Neutrophil-to lymphocyte ratio, Fat mass.

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Introduction

Obesity is a common public health problem worldwide which affects all age groups in children and adults.^{1,2} It is a clinical condition characterised by chronic low level activation of innate immune system.³

As in adults, obesity in children has reached alarming dimensions all over the world. It has been shown that childhood obesity increases risks of hyper-insulinaemia and insulin resistance (IR) and increases cardiovascular risk factors such as hypertension (HTN). In addition, it has been shown that obesity that started in childhood increases the risk of developing chronic diseases, such as diabetes, HTN and cancer in later years.⁴⁻⁷

The standard body mass index (BMI) definition for children aged 2-20 years describes overweight as anyone falling between the 85th and 95th percentile for age and gender. BMI at or greater than 95th percentile for age and gender is called obesity.⁸

It has been known since the 1970s that inflammation plays an important role in obesity. Inflammation in

obesity is primarily caused by adipose tissue and inflammatory cytokines, such as tumour necrosis factor-alpha (TNF- α) and interleukin-6 (IL-6), which are secreted in large amounts by adipose tissue, are known to induce chronic inflammation.⁹ Recent studies have shown that peripheral blood cells, such as platelets, neutrophil, lymphocyte and monocyte counts, are associated with the progression of various types of tumours.¹⁰

Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR) are considered and used as biomarkers associated with immune response from neutrophil, lymphocyte, platelet and monocyte counts.¹¹⁻¹³ In addition, systemic immune inflammatory index (SII) (neutrophil $\times$ platelet / lymphocyte) derived from neutrophil, platelet and lymphocyte counts have shown that inflammation in the SII is a biomarker.¹⁴

Neutrophil, lymphocyte, platelet counts, NLR, PLR and SII have been shown to be related to BMI in adults.¹⁵ However, there is insufficient literature about the use of these markers in childhood obesity. The current study was planned to assess the relationship between weight, BMI, fat percentage (F%), fat mass (FM) and fat-free mass (FFM) with platelet count, mean platelet

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volume (MPV), NLR, PLR, and SII in obese paediatric patients.

Patients and Methods

The cross-sectional study was conducted at Marmara University, Istanbul, Turkey, from January 2018 to October 2018 After approval from the institutional ethics review board, children of either gender aged 6-16 years admitted to the outpatient clinic due to obesity were included. Children outside the 6-16 age bracket were excluded. Weight, BMI, F%, FM, FFM were determined with a bio-impedence device (TANITA BC-418MA) after measuring the height of the child on bare foot. Waist circumference (WC) was measured. NLR, PLR and SII were calculated from neutrophil, lymphocyte and platelet counts obtained from haemogram.

Data was analysed using Number Cruncher Statistical System (NCSS) 2007. Descriptive statistics mean, standard deviation, median, frequency, percentage, minimum-maximum range were used to evaluate data. Student-t test was used to compare the normal distribution of quantitative variables. Pearson correlation analysis was used to evaluate the relationship between quantitative variables. Linear regression backward analysis was used to determine the risk factors affecting NLR and SII. Statistical significance was set at $p < 0.05$.

Results

Of the 335 subjects, 203(60.6%) were girls and 132(39.4%)

Table-1: Distribution of anthropometric measurements according to gender.

		Gender	
		Girls (n=203)	Boys (n=132)
Height (cm)	Min-Max (Median)	113-178 (153)	116-185 (154)
	Mean $\pm$ SD	151,73 $\pm$ 12,92	153,97 $\pm$ 15,08
Weight (kg)	Min-Max(Median)	29,1-124,7 (63,7)	27,4-131,6 (65,95)
	Mean $\pm$ SD	66,31 $\pm$ 20,16	66,73 $\pm$ 19,56
BMI (kg/m ²)	Min-Max (Median)	20,35-44,55 (27,11)	19,44-38,45 (27,35)
	Mean $\pm$ SD	28,13 $\pm$ 5,04	27,52 $\pm$ 3,99
Fat %	Min-Max(Median)	19,1-56 (35,8)	19,5-48,5 (33,35)
	Mean $\pm$ SD	36,43 $\pm$ 5,79	33,75 $\pm$ 5,86
Fat Mass (kg)	Min-Max(Median)	7,8-64,1 (22,1)	7,7-55,9 (21,1)
	Mean $\pm$ SD	24,83 $\pm$ 11,18	22,67 $\pm$ 8,33
Fat Free Mass (kg)	Min-Max(Median)	18,8-66,7 (41,2)	19,7-81,2 (41,3)
	Mean $\pm$ SD	41,29 $\pm$ 10,09	44,05 $\pm$ 13,07
Waist circumference (cm)	Min-Max(Median)	61-119 (82)	63-112 (86)
	Mean $\pm$ SD	83,28 $\pm$ 10,97	86,08 $\pm$ 10,58

BMI: Body mass index; SD: Standard deviation.

were boys. Anthropometric measurements are shown according to gender in Table-1. The same was the case with distribution of haematological parameters as shown in Table-2. The BMI, fat percentage, fat mass, fat free mass and waist circumference measurements of the girls were found to be effective risk factors on NLR in univariate analysis.

Univariate analysis of girls showed the effects of BMI, F%, FM, FFM and WC on NLR (Table-3). FM remained a

Table-2: Distribution of haematological parameters according to gender.

		Gender		P Value P
		Girls (n=188)	Boys (n=108)	
Neutrophils	Min-Max(Median)	1,8-10,5 (4,4)	2-9,8 (4,2)	t:0,966
	Mean $\pm$ SD	4,63 $\pm$ 1,62	4,44 $\pm$ 1,55	a0,335
Lymphocytes	Min-MaX(Median)	1,1-7 (2,8)	1,4-7,9 (3)	t:-0,369
	Mean $\pm$ SD	2,96 $\pm$ 0,86	3,00 $\pm$ 0,81	a0,712
Platelets	Min-MaX (Median)	181-477 (309)	118-540 (299,5)	t:-0,969
	Mean $\pm$ SD	312,18 $\pm$ 60,7	320,65 $\pm$ 78,33	a0,334
MPV	Min-Max (Median)	6,7-11,7 (8,45)	6,1-11,5 (8,2)	t:2,507
	Mean $\pm$ SD	8,46 $\pm$ 0,87	8,2 $\pm$ 0,85	a0,013*
NLR	Min-Max (Median)	0,61-5,07 (1,55)	0,53-3,5 (1,44)	t:1,626
	Mean $\pm$ SD	1,67 $\pm$ 0,74	1,54 $\pm$ 0,59	a0,105
SII	Min-Max (Median)	148,28-1616,09 (483,82)	153,89-1419,42 (449,45)	t:0,734
	Mean $\pm$ SD	521,99 $\pm$ 254,00	499,79 $\pm$ 243,78	a0,463
PLR	Min-Max(Median)	41,29-190 (108,86)	53,64-200 (110,49)	t:0,068
	Mean $\pm$ SD	111,94 $\pm$ 31,69	111,68 $\pm$ 32,53	a0,946

^a Student-t Test. * $p < 0.05$. ** $p < 0.01$.

MPV: Mean platelet volume.

NLR: Neutrophil-to-lymphocyte ratio.

SII: Systemic immune inflammatory index.

PLR: Platelet-to-lymphocyte ratio.

Table-3: Relationship between girls' anthropometric properties and neutrophil-to-lymphocyte ratio (NLR).

Model	Unstandardised Coefficients		95,0% Confidence Interval for B	
	B	p	Lower Bound	Upper Bound
Fat Mass	0,014	0,002**	0,005	0,024
(Constant)	1,305	0,001**	1,054	1,555

Regression model for NLR;

NLR = 1,305 + 0,014 (Fat mass).

Table-4: Relation between girls' anthropometric properties and systemic immune-inflammation index (SII).

Model	Unstandardised Coefficients		95,0% Confidence Interval for B	
	B	p	Lower Bound	Upper Bound
Fat %	10,572	0,001**	4,672	16,472
(Constant)	133,111	0,228	-83,840	350,063

Regression model for SII;

SII = 133,111 + 10,572 (Fat percentage).

significant and an independent risk factor for NLR ($p < 0.01$). The effects of BMI, percentage%, FFM and WC were not significant in multivariate model ($p > 0.05$).

Univariate analysis of girls also showed the effects of BMI, F%, FM, FFM and WC measurements on SII (Table-4). F% remained a significant and independent risk factor on SII ($p < 0.01$). The effects of BMI, fat mass, FFM and WC were not significant in multivariate model ($p > 0.05$).

Discussion

Although there was a statistically significant relationship between F% and SII and between FM and NLR in obese girls, there was no significant relationship in obese boys.

We did not find a significant relationship between weight, BMI, percentage %, FM, FFM and PLR and MPV. Similarly, we did not detect any significant relationship between FFM and WC against SII, NLR, PLR, platelet, and MPV. These findings were true for both boys and girls.

SII is an easy to access parameter that has recently been introduced in obesity with respect to inflammation. In a study on adult obese individuals, SII increased with BMI.¹⁵ In our study of obese children, SII did not increase with BMI.

In studies conducted in non-obese adults, it was determined that SII did not change according to age and gender.¹⁶ The current study found that SII was elevated due to only F% in girls, but not in boys. It is likely that the use of these parameters may be important in terms of

comorbidities in obese girls only and fresh studies are needed on obese boys.

NLR has been used frequently as an easily accessible inflammatory marker in cardiovascular diseases in recent years.¹⁷ In addition, it has been shown that NLR has a prognostic significance in various malignancies.¹⁸ High NLR has been shown to be an independent predictor for type 2 diabetes in a study on morbid obese.¹⁹ In a study involving adult obese patients, no relationship was found between BMI and NLR. This suggests that the relationship between obesity and NLR may be related to FM and F% rather than BMI.²⁰

In the study of patients with metabolic syndrome, the finding that NLR increased in proportion to the weight of the fat supports studies that showed increased FM increasing comorbidities in obesity.^{21,22}

Similarly, in a study performed in girls, it was found that there was a direct relationship between human C-reactive protein (hCRP) and adipose tissue, which may increase the risk of cardiovascular disease in older ages.²³ Studies have shown that chronic inflammatory diseases, like chronic asthma, are more common in girls than in boys and studies continue to suggest that hormonal differences may be the cause.²⁴ The current study supports the finding that the inflammatory mechanisms in girls have increased. It also supports the notion that increased adipose tissue increases inflammatory mechanisms.²⁵

Inflammatory biomarkers, such as TNF- α , IL-6 and IL-8, have been shown on studies in childhood obesity and it is not always possible to reach these markers.²⁶ Although

new biomarkers, such as SII and NLR, are used in adult patients, it is seen that the data related to the studies is limited in children. In our study, data on these parameters were significant in obese children.

Studies have shown that platelet count and PLR were related to inflammation, especially as markers of systemic inflammation in cancer progression. Although the mechanism is not clear, platelets cause release of cytokines, such as vascular endothelial growth factor (VEGF) and transforming growth factor β (TGF- β) and, affect tumour angiogenesis, playing an important role in the activation of inflammatory diseases.^{27,28} The fact that the current study found an increase in the platelet count with F% seems to support findings regarding the relationship between obesity and inflammation.

In terms of limitations, the current study did not calculate the sample size.

Finding a meaningful relationship between PLR and F% indicates that more studies are needed in terms of the effect of this parameter on obesity. It is suggested that these parameters can be used as biomarkers in the follow-up of childhood obesity and in the prevention of obesity-related complications.

There was no association of FFM and WC with SII, NLR, PLR and platelets. It is also suggested that weight reduction methods should be applied to protect FFM and to decrease FM completely.

Conclusion

The increase of SII and NLR in terms of F% and FM indicates that the increase of inflammation was due to increase in fat tissue in obese girls, but not in boys. In terms of comorbidities in obesity, SII and NLR were found to be inflammatory biomarkers that may be used in follow-up.

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