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Links between Inflammation and Insulin Resistance in Children with Morbid Obesity and Metabolic Syndrome

Mustafa M. Donma, Orkide Donma

Abstract**—**Obesity is a clinical state associated with low-grade inflammation. It is also a major risk factor for insulin resistance (IR). In its advanced stages, metabolic syndrome (MetS), a much more complicated disease which may lead to life-threatening problems, may develop. Obesity-mediated IR seems to correlate with the inflammation. Human studies performed particularly on pediatric population are scarce. The aim of this study is to detect possible associations between inflammation and IR in terms of some related ratios. 549 children were grouped according to their age- and sex-based body mass index (BMI) percentile tables of WHO. MetS components were determined. Informed consent and approval from the Ethics Committee for Clinical Investigations were obtained. The principles of the Declaration of Helsinki were followed. The exclusion criteria were infection, inflammation, chronic diseases and those under drug treatment. Anthropometric measurements were obtained. Complete blood cell, fasting blood glucose, insulin, and C-reactive protein (CRP) analyses were performed. Homeostasis model assessment of insulin resistance (HOMA-IR), systemic immune inflammation (SII) index, tense index, alanine aminotransferase to aspartate aminotransferase ratio (ALT/AST), neutrophils to lymphocyte (NLR), platelet to lymphocyte, and lymphocyte to monocyte ratios were calculated. Data were evaluated by statistical analyses. The degree for statistical significance was 0.05. Statistically significant differences were found among the BMI values of the groups ($p < 0.001$). Strong correlations were detected between the BMI and waist circumference (WC) values in all groups. Tense index values were also correlated with both BMI and WC values in all groups except overweight (OW) children. SII index values of children with normal BMI were significantly different from the values obtained in OW, obese, morbid obese and MetS groups. Among all the other lymphocyte ratios, NLR exhibited a similar profile. Both HOMA-IR and ALT/AST values displayed an increasing profile from N towards MetS3 group. BMI and WC values were correlated with HOMA-IR and ALT/AST. Both in morbid obese and MetS groups, significant correlations between CRP versus SII index as well as HOMA-IR versus ALT/AST were found. ALT/AST and HOMA-IR values were correlated with NLR in morbid obese group and with SII index in MetS group, ($p < 0.05$), respectively. In conclusion, these findings showed that some parameters may exhibit informative differences between the early and late stages of obesity. Important associations among HOMA-IR, ALT/AST, NLR and SII index have come to light in the morbid obese and MetS groups. This study introduced the SII index and NLR as important inflammatory markers for the discrimination of normal and obese children. Interesting links were observed between inflammation and IR in morbid obese children and those with MetS, both being late stages of obesity.

Keywords**—**Children, inflammation, insulin resistance, metabolic syndrome, obesity.

Mustafa M. Donma (Prof. Dr.) is with the Tekirdag Namik Kemal University, Faculty of Medicine, Department of Pediatrics, Tekirdag, Turkey (corresponding author to provide phone: 00-90-532-371-72-07; fax: 00-90-282—250-99-28; e-mail: mdonma@ gmail.com).

Orkide Donma (Prof. Dr.) is with the Istanbul University Cerrahpasa, Cerrahpasa Medical Faculty, Department of Medical Biochemistry, Istanbul, Turkey (e-mail: odonma@gmail.com).

I. Introduction

INFLAMMATION is a process contributing to the pathogenesis of many diseases including obesity, which is associated with a low grade inflammation. During the course of this clinical status, inflammation is commonly associated with IR. Within the scope of such a complicated network, complete blood cell count profile covering also hematological parameters should also be considered. Some of these red blood cell (RBC), leukocyte and/or platelet indices have already been introduced as inflammatory markers. It is also interesting to note that ratios derived from some enzymes -so far their relations were not clarified- were announced as the marker related to IR. Alanine transaminase to aspartate transaminase (ALT/AST) is one of them [1]-[5].

Mean platelet volume (MPV), an inflammatory marker is found higher in diabetes [6]. Neutrophils-to-lymphocyte ratio (NLR), as well as platelet-to-lymphocyte (PLR) ratio are introduced as two new inflammatory markers associated with disease activity in dermatomyositis [7].

Aside from CRP, the SII index based on peripheral lymphocyte, neutrophil and platelet counts has recently been reported to be associated with clinical outcome of several tumors [8]-[10]. Due to an existing and new hypothesis for a casual connection between obesity and cancer [11], this index is also being investigated in obesity [12].

So far, the relationship between lipid and hematological profiles with adiposity in obese adolescents were investigated [3]. Controversial results were reported. A positive correlation between WC and RBCs as well as hemoglobin was detected, while hemoglobin was negatively correlated to the sum of skinfold.

The aim of this study is to exhibit an integrative picture of some inflammatory parameters as well as some classical and recently introduced IR indices during the various stages of pediatric obesity and in children with MetS.

II. Patients and Methods

A. Patients

A total of 549 children, whose ages were between six and

17.5 years were included into the scope of this study. Patients and controls who consulted to Department of Pediatrics in Faculty of Medicine Hospital at Namik Kemal University (Tekirdag, Turkey) participated. The study population consisted of 109 children with normal body mass index (N-BMI) as well as 40 OW, 100 obese (OB), 166 morbid obese (MO) children. One hundred and thirty-four children with MetS were also evaluated. Of them, 110 were children with two major MetS components, 24 were children with three major MetS components.

B. Anthropometric Measurements

Anthropometric measurements of each child were taken following the detailed history and physical examination. Blood pressure (BP) values were recorded. BMI values were calculated. WHO BMI percentile curves based upon age and sex of the individuals created for 5-19 year-aged children and adolescents [13], were used as the values for determining the obesity criteria. The control group was composed of friends of patients, who were age and sex-matched. Patients and controls were included in the study simultaneously. Written informed consent forms from the parents of the participants and approval document from the Institutional Ethical Committee for Clinical Investigations were obtained. This work complies with the principles of the Declaration of Helsinki. The exclusion criteria were infection, inflammation, chronic diseases and those under the drug treatment.

C. Methods

Blood samples were obtained after 12-16 hours of overnight fasting. Basic hematological parameters were determined by the automatic hematology analyzer; Pentra DX-Nexus (Horiba Medical ABX SAS, Japan). Fasting blood glucose, insulin and CRP levels were measured by spectrophotometric hexokinase assay, ECLIA (electro-chemiluminescence immunoassay), and an immunological test system in a Roche COBAS C-501 chemistry analyzer, respectively.

D. Ratios

HOMA-IR index was calculated using fasting plasma glucose and insulin values [HOMA-IR= fasting glucose (mg/dL)* fasting insulin (μIU/ml)/ 22.5*0.0555)] [14], [15]. SII index was derived from the following formula: platelet count *(lymphocyte count/neutrophil count). Tense index was obtained by using the formula; (systolic BP + diastolic BP)/200 [16]. ALT/AST, NLR, PLR, lymphocyte to monocyte ratio (LMR) were calculated.

E. Statistical Analysis

The statistical analyses were performed using SPSS version 16 (SPSS inc. Chicago, IL, USA). Descriptive statistics were performed. Data were presented as mean ± standard deviation (SD) and median where it is appropriate. Kolmogorov-Smirnov test was used to determine whether data shows normal distribution or not. Both parametric and non-parametric tests were applied. One-way analysis of variance (ANOVA) and post hoc Tukey HSD tests were used to compare variables between groups. Some parameters that do not exhibit normal distribution were evaluated by Kruskal Wallis, Mann-Whitney U and Wilcoxon tests. Correlation analyses were performed using Pearson's or Spearman's rho analysis based upon the nature of the data distribution. Differences were considered statistically significant at a p level of ≤0.05.

III. Results

Ages of the participants were 12.1±2.8, 10.9±2.8, 9.8±2.7, 11.9±2.3, 10.9±3.0, 9.1±2.2 years in MetS3, MetS2, MO, OB, OW and N groups, respectively. Differences between the OW group and the other groups were statistically insignificant. WC, BMI and tense index values were determined. The values for these three parameters used for obesity evaluation were tabulated in Table I.

TABLE I
WC, BMI, Tense Index Values of the Groups (Mean±SD)

Groups	WC (cm)	BMI (kg/m^2)	Tense Index
N	55.3 ± 5.9	15.7 ± 1.1	0.86 ± 0.07
OW	71.7 ± 10.4	21.1 ± 2.7	0.89 ± 0.11
OB	81.8 ± 9.3	24.7 ± 2.7	0.92 ± 0.08
MO	85.5 ± 11.6	27.1 ± 3.8	0.93 ± 0.1
MetS2	89.8 ± 14.9	28.7 ± 5.3	0.96 ± 0.11
MetS3	95.1 ± 13.9	30.4 ± 5.4	1.02 ± 0.12

N- normal BMI.

Statistically significant differences were obtained among WC values of all groups except OB-MO. On the other hand, BMI values differed significantly among N, OW, OB, MO, MetS2 and MetS3 (p=0.001). There were statistically significant differences between BMI values of the groups (p = 0.001).

Strong correlations were detected between BMI and WC in all groups. Tense index values were also correlated with both BMI and WC values in all groups except OW children.

Parameters, ratios and indices concerning IR and inflammation in MetS, MO, OB, OW and N children were summarized in Tables II and III.

Statistically significant differences were observed for HOMA-IR between the groups except OW-MO, OW-OB, OB-MO and OB-MetS2. ALT/AST ratios were significantly different among the groups except OW-OB, MO-MetS3 and MetS2-MetS3.

No significant difference among the groups was detected for CRP values (p=0.106). On the contrary, SII index values in N group significantly differed from the values obtained for this parameter in OW, OB, MO and MetS groups.

TABLE II
Parameters, Ratios and Indices Concerning IR (Median)

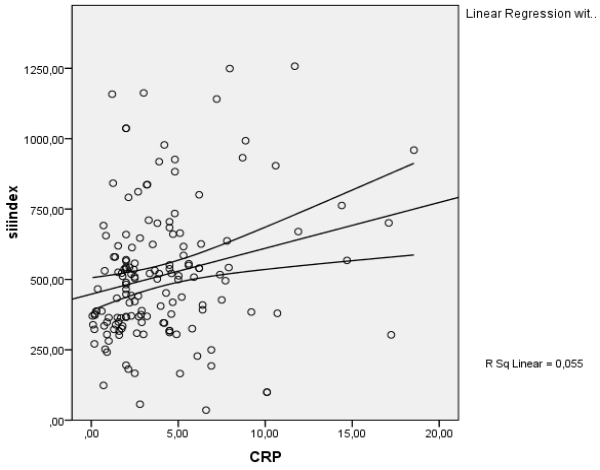
Groups	HOMA-IR	ALT/AST
N	0.45	0.50
OW	2.11	0.68
OB	2.37	0.74
MO	2.22	0.80
MetS2	3.2	0.92
MetS3	5.0	0.90

N- normal BMI, ALT/AST – alanine transaminase-to-aspartate transaminase.

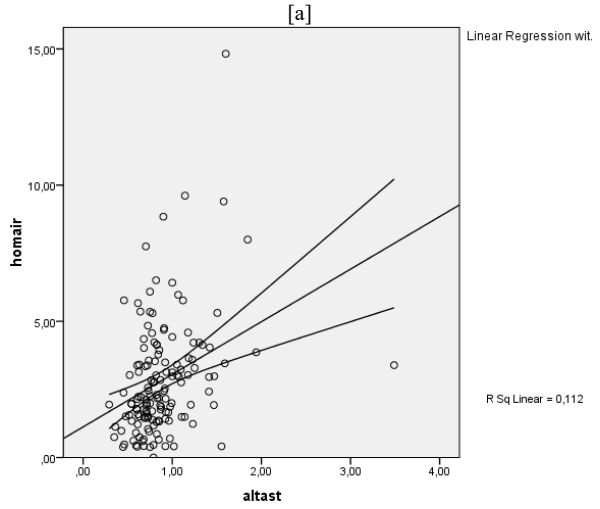
TABLE III
PARAMETERS, RATIOS AND INDICES CONCERNING INFLAMMATION (MEDIAN)

Groups	CRP	SIII	NLR	PLR	LMR	MPV
N	2.0	382	1.17	7.83	4.68	7.9
OW	1.7	528	1.58	10.19	4.21	8.1
OB	2.0	470	1.41	8.84	4.54	8.2
MO	2.9	503	1.38	9.31	4.54	8.1
MetS2	3.3	460	1.40	9.10	4.40	8.3
MetS3	2.9	440	1.38	8.68	4.55	8.6

N- normal BMI, LMR – lymphocyte-to-monocyte ratio.



[a]



[b]

Fig. 1 Scatter plots of patient individual measurements for SII index versus CRP (a) and HOMA-IR versus ALT/AST (b) in MO children. Positive correlations are observed. Linear regression lines are displayed

The values obtained for MPV were almost the same, being around 8.0 in all groups.

Lymphocyte ratios; NLR, PLR and LMR, did not give superior results. In terms of LMR, no significant difference was observed among the groups. Similar results were obtained for the remaining two ratios. NLR in N group differed from those calculated for OW, OB, MO, MetS2 and MetS3. The only difference for PLR values was the insignificance between N and MetS3 groups.

In all groups, BMI as well as WC were correlated with HOMA-IR and ALT/AST.

CRP values were correlated with SII index in MO and MetS groups. In these groups, HOMA-IR and ALT/AST were also correlated (Figs. 1 (a) and (b)).

IV. DISCUSSION

Correlation between BMI and WC observed in all groups is an expected finding. Tense index was found to be correlated with both WC and BMI in all groups except OW group. Actually, BP values did not alter during OW state. This is in accordance with the finding of this study showing that BP values did not change in this group. In OW group, WC as well as BMI values increase, however, BP values remain around normal.

Considering lymphocyte ratios, it has been concluded that LMR is not a valuable ratio for the evaluation of obesity stages. The most valuable ratio among all of three ratios came out as NLR, which exhibits a pattern quite similar to that of the SII index.

Both HOMA-IR and ALT/AST values exhibited increasing trend starting from N towards MetS3 group. However, ALT/AST was of a much more expected profile.

Both CRP and SII index were not correlated in the N group. Existence of the correlations between the CRP and SII index in the MO as well as MetS groups and lack of such associations in the other groups is an important finding. Of them, SII index is a marker used during the evaluation of several cancers. It serves as the hallmark for cancer development. CRP is also a parameter associated with cancers. Therefore, correlations observed between these two cancer-related inflammatory markers in MO and MetS groups is a very informative finding concerning the relationship between obesity and cancer.

IR became evident in MO and MetS groups, with the evidence of correlation between HOMA-IR and ALT/AST. None of the other groups displayed such a correlation. The existence of the correlations between HOMA-IR and ALT/AST as well as CRP and SII index only in the late stages of obesity is one of the striking outcomes of this study.

Recently, the possible links between inflammation and obesity-associated IR have drawn great attention. There are controversial views on the matter [17]-[21].

In our study, important links between inflammation and IR emerged both in MO and MetS groups. A statistically significant correlation was found between ALT/AST and NLR ($r= 0.165$; $p\leq0.05$). Another type of such a link was also observed in MetS group between HOMA-IR and SII index ($r= 0.259$; $p\leq0.05$) (Figs. 2 and 3).

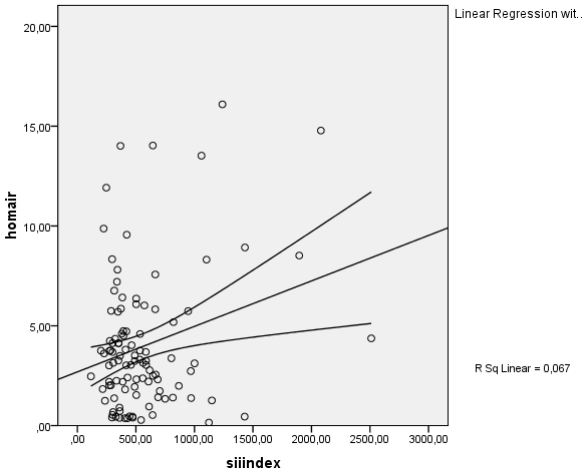


Fig. 2 Scatter plot for HOMA-IR and SII index with a linear regression fit line in MetS children.

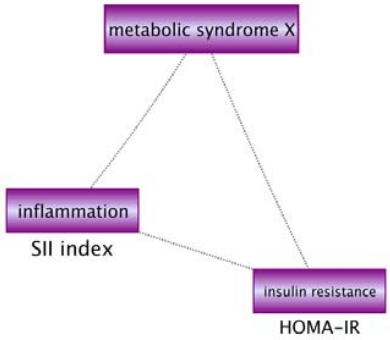


Fig. 3 The association between inflammation-IR in MetS

In conclusion, these findings highlighted the distinct aspects of metabolic profile in children with morbid obesity and MetS. The behavior of some well-known parameters shows completely different patterns in advanced obesity in comparison with those detected in some milder stages of obesity. This study pointed out that SII index and NLR may be important inflammatory parameters to discriminate children with normal BMI from obesity groups including OW, OB, MO, MetS2 and MetS3. Important links between inflammation and IR come into stage in the form of the association between ALT/AST and NLR in the MO group and as the correlation between HOMA-IR and SII index in the MetS group, both being late stages of obesity.

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