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Relationship between Iron-Related Parameters and Soluble Tumor Necrosis Factor-Like Weak Inducer of Apoptosis in Obese Children

Mustafa M. Donma, Orkide Donma, Savas Guzel

***Abstract*—**Iron is physiologically essential. However, it also participates in the catalysis of free radical formation reactions. Its deficiency is associated with amplified health risks. This trace element establishes some links with another physiological process related to cell death, apoptosis. Both iron deficiency and iron overload are closely associated with apoptosis. Soluble tumor necrosis factor-like weak inducer of apoptosis (sTWEAK) has the ability to trigger apoptosis and plays a dual role in the physiological versus pathological inflammatory responses of tissues. The aim of this study was to investigate the status of these parameters as well as the associations among them in children with obesity, a low-grade inflammatory state. The study was performed on groups of children with normal body mass index (N-BMI) and obesity. 43 children were included in each group. Based upon age- and sex-adjusted BMI percentile tables prepared by the World Health Organization, children whose values varied between 85 and 15 were included in N-BMI group. Children, whose BMI percentile values were between 99 and 95, comprised obese (OB) group. Institutional ethical committee approval and informed consent forms were taken prior to the study. Anthropometric measurements (weight, height, waist circumference, hip circumference, head circumference, neck circumference) and blood pressure values (systolic blood pressure and diastolic blood pressure) were recorded. Routine biochemical analyses, including serum iron, total iron binding capacity (TIBC), transferrin saturation percent (Tf Sat %) and ferritin, were performed. sTWEAK levels were determined by enzyme-linked immunosorbent assay. study data were evaluated using appropriate statistical tests performed by the statistical program SPSS. Serum iron levels were 91 ± 34 mcrg/dl and 75 ± 31 mcrg/dl in N-BMI and OB children, respectively. The corresponding values for TIBC, Tf Sat %, ferritin were 265 mcrg/dl vs. 299 mcrg/dl, 37.2 ± 19.1% vs. 26.7 ± 14.6%, and 41 ± 25 ng/ml *vs* 44 ± 26 ng/ml. In N-BMI and OB groups, sTWEAK concentrations were measured as 351 ng/L and 325 ng/L, respectively ($p > 0.05$). Correlation analysis revealed significant associations between sTWEAK levels and iron related parameters ($p < 0.05$) except ferritin. In conclusion, iron contributes to apoptosis. Children with iron deficiency have decreased apoptosis rate in comparison with that of healthy children. sTWEAK is an inducer of apoptosis. OB children had lower levels of both iron and sTWEAK. Low levels of sTWEAK are associated with several types of cancers and poor survival. Although iron deficiency state was not observed in this study, the correlations detected between decreased sTWEAK and decreased iron as well as Tf Sat % values were valuable findings, which point out decreased apoptosis. This may induce a proinflammatory state, potentially leading to malignancies in the future lives of OB children.

***Keywords*—**Apoptosis, children, iron-related parameters, obesity, soluble tumor necrosis factor-like weak inducer of apoptosis.

I. Introduction

IRON is the most abundant trace element in the body. It is physiologically essential however it also participates in reactions to produce free radical species, which can damage cellular constituents. It plays a pivotal role in hematopoiesis. In addition to its role in hemoglobin production, it is involved in structures of many vital proteins such as myoglobin, transferrin, ferritin, cytochromes. Iron deficiency is the most common cause of anemia [1], [2].

Iron deficiency is associated with obesity. Obesity may disrupt iron homeostasis, resulting in iron deficiency anemia [3]-[8]. Iron maintains metabolic homeostasis and genome stability. Iron deficiency can increase the risk of cancer [9]. A very recent study has drawn attention to the high prevalence of iron deficiency in patients with cancer [10]. Growing evidence supports associations between childhood or adolescent obesity and increased risk of several types of cancers [11], [12].

Apoptosis is a process, which is affected by iron deficiency as well as iron excess. This programmed cell death participating both in physiological and pathological conditions, clears the debris during tissue injury [13]. The mechanism of apoptosis is complex. Therefore, a good understanding of this mechanism is important, because it plays a pivotal role in the pathogenesis of many diseases. In some, the problem is too much apoptosis as in the case of degenerative diseases while in others, too little apoptosis as in cancer, during which malignant cells do not die [14].

sTWEAK is a parameter, which exhibits alterations in type 1 diabetes, type 2 diabetes, metabolic syndrome, cancers [15]-[19]. This parameter along with anemia and obesity is known to be associated with cardiovascular findings [16], [17], [20]-[22].

The aim of this study was to investigate the potential relationship between iron-related parameters and sTWEAK in OB children. The possible mechanisms within the context of apoptosis are suggested in relation to obesity, anemia, cardiovascular diseases and cancer.

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

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

S. G., Prof. Dr., is with the Tekirdag Namik Kemal University, Faculty of Medicine, Department of Medical Biochemistry, Tekirdag, Turkey (e-mail: savasguzel@yahoo.com).

II. Patients and Methods

A. The Study Population and Grouping

The study population was composed of two groups, being normal weight (n = 43) and OB (n = 43) children. Mean age values and gender ratios of groups were matched. Informed consent forms were filled by the parents of the participants. The study protocol was approved by the Tekirdag Namik Kemal University Ethical Committee. Groups were constituted according to tables prepared by the World Health Organization [23]. Age and sex-adjusted body mass index (BMI) percentiles varied between 15 and 85 for the group of children with normal-BMI (N-BMI), 95 and 99 for OB children. Anthropometric measurements (weight, height, waist circumference, hip circumference, head circumference, neck circumference) were performed. Systolic (SBP) and diastolic blood pressures (DBP) were measured.

B. Laboratory Tests

Analysis of the routine biochemical tests was performed using auto-analyzer. Serum iron, TIBC, percent transferrin saturation and ferritin concentrations were determined within the scope of iron-related parameters. sTWEAK levels were measured by enzyme linked immunosorbent assay principle-based research kits.

C. Statistical Evaluation of the Study Data

Data were evaluated and interpreted using the statistical package program SPSS. Mean and median values were determined. Normality of the distribution was tested by Shapiro-Wilk test. T test or Mann-Whitney U test was used to determine the statistical significance between the groups. Bivariate correlation analysis was performed. Linear regression plot was drawn.

III. Results

TABLE I
Values for BMI, Waist Circumference, Blood Pressure, sTWEAK and Iron Related Parameters of the Groups (Mean ± SD)

Parameter		N-BMI Group 1	OB Group 2	p
BMI	kg/m^2	17.6 ± 3.0	23.7 ± 3.4	p < 0.001
WC	cm	64.8 ± 11.8	80.9 ± 8.4	p < 0.001
SBP	mm Hg	102 ± 10	115 ± 17	p < 0.001
DBP	mm Hg	69 ± 8	74 ± 11	NS
sTWEAK [m]	ng/L	351	325	NS
iron	µg/dL	91 ± 34	75 ± 31	NS
TIBC	µg/dL	265 ± 51	299 ± 50	NS
Saturation	%	37.2 ± 19.1	26.7 ± 14.6	p < 0.05
Ferritin	ng/mL	41 ± 25	44 ± 26	NS

N = normal, WC = waist circumference, [m] = median.

Two groups (N-BMI vs. OB) did not differ from one another in terms of age and gender ratio (p > 0.05). In Table I, BMI, waist circumference, SBP, DBP, sTWEAK, serum iron, TIBC, percent transferrin saturation, ferritin values were listed. There were statistically significant differences between BMI, waist circumference, SBP (p < 0.01) and percent transferrin saturation values (p < 0.05) of the N-BMI and OB groups. Fig. 1 shows the transferrin saturation percent values of the two groups. Serum iron, TIBC, DBP, ferritin and sTWEAK values did not differ between the groups (Table I).

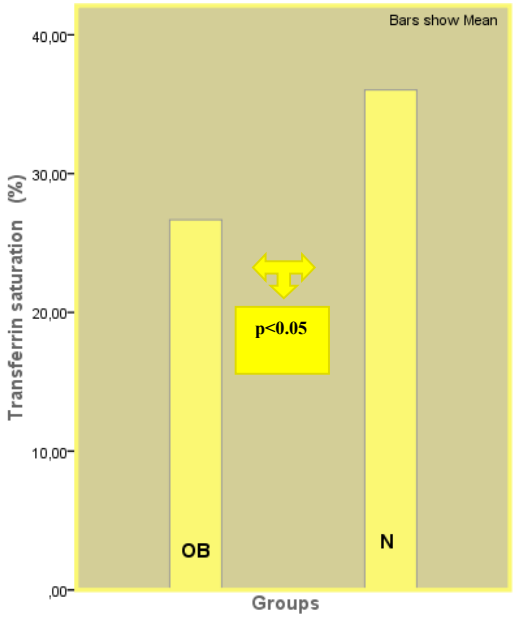

Fig. 1 Mean values for percent transferrin saturation in N-BMI and OB children

In the OB group, statistically significant bivariate correlations were detected between serum iron (r = 0.363; p < 0.05) as well as transferrin saturation percent (r = 0.352; p < 0.05) values and sTWEAK concentrations. In Fig. 2, linear regression plot was shown between iron and sTWEAK levels.

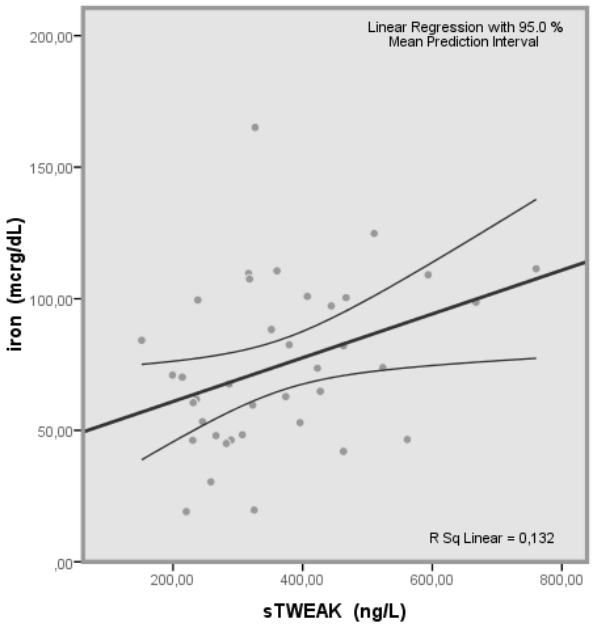

Fig. 2 Bivariate correlation between serum iron values and sTWEAK concentrations in OB children

IV. Discussion

Obesity during childhood is life-threatening, because it is

associated with further severe complications such as diabetes mellitus, metabolic syndrome, cancers and cardiovascular diseases. Two main findings in this study were iron-reduced status of OB children and low levels of sTWEAK, a new-generation cardiac marker.

Iron contributes to changing levels of apoptosis [24]-[26]. Iron loading sensitizes endothelial cells to tumor necrosis factor-α-mediated apoptosis and may facilitate apoptosis-promoting properties [27], [28]. Apoptotic function will be diminished with iron deficiency anemia. Iron deficiency was associated with certain morphological anomalies in neutrophils [29]. It also decreases apoptosis. Children with iron deficiency anemia had lower apoptotic rates than healthy controls [30].

Inhibition of neutrophil and monocyte apoptosis might lead to disruption of the immune balance in iron deficiency conditions. Inhibition of apoptosis may induce a pro-inflammatory state, leading to autoimmune disorders or malignancies in the future [30].

Iron increases apoptosis. Soluble TWEAK is also inducer of apoptosis. Excess adiposity was reported to be associated with poor iron status. The association of obesity and iron deficiency is well known [24].

In the present study, in OB children, low levels of sTWEAK were measured. Both serum iron and sTWEAK concentrations decreased in obesity. Reduced sTWEAK means decreased apoptosis. The association of obesity, iron deficiency as well as decreased levels of sTWEAK can be evaluated together within the context of decreased apoptosis and several types of cancer.

In this study, iron-reduced conditions and low levels of sTWEAK were found in OB children in comparison to those observed in children with N-BMI. Also, a statistically significant correlation was calculated between serum iron and sTWEAK concentrations in OB children. This association was particularly important because it was confined to iron-reduced status, but not to a real iron deficiency state. In such an iron status near to the lower bound of the normal range, the existence of such a relationship possesses a much greater value than the findings detected in iron deficiency anemia. Our findings agree with the mechanism explained in this study.

V. Conclusion

The findings of this study are valuable from the point of obesity, anemia and a new generation cardiac marker, sTWEAK. They constitute the corners of the cardiovascular diseases triangle.

In this study, the association between iron and sTWEAK was reported in OB children. It establishes a link created among obesity, apoptosis, and cancer and accounts for the related mechanism on the matter.

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