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Relationship of Cytokine Status Parameters with the Lipid Peroxidation-Antioxidant Defense System in Obese Adolescents

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Abstract

The aim of this study was to identify the relationships between cytokine status, lipid peroxidation (LPO) products, and total antioxidant activity (TAA) in obese adolescent boys and girls.

Methods and Results: The study included 29 boys and 33 girls with an established diagnosis of exogenous-constitutional obesity of the first degree. Twenty-eight healthy adolescent boys and 24 adolescent girls made up control groups.

The concentration of cytokines (IL-6, IL-8, IL-4, and IL-10) was assessed by enzyme immunoassay. The content of LPO products (conjugated dienes [CDs], ketodienes and conjugated trienes [KD-CT], Schiff bases [SB], thiobarbituric acid reactants [TBARs], total antioxidant activity (TAA) was evaluated. Spectrophotometric methods were used. The data obtained indicated a statistically significant increase in the level of IL-6 (P=0.018) and the IL-6/IL10 ratio (P=0.033) in obese boys, compared with the control. There was also an increase in the content of LPO products in this group relative to the control group: KD-CT (P=0.043) and SB (P=0.021). In the group of obese girls, there was an increase in IL-6 values (P=0.018), a decrease in IL-4 (P=0.040), and an increase in CDs (P=0.035) and KD-CT (P=0.044). The following correlations were found in the control group of boys: CDs–KD-CT (r=0.91; P=0.001), TBARS–IL-8 (r=0.73; P=0.027), and SB–IL-4 (r=0.79; P=0.011); there were no statistically significant correlations between study parameters in obese boys. The following correlations were recorded in the girls of the control group: CDs–KD-CT (r=0.99; P<0.0001), TAA–IL-10 (r=-0.80; P=0.033), TAA–IL-4 (r=-0.78; P=0.040); in obese girls, it was SB–IL-4 (r=-0.67; P=0.048).

Conclusion: Data analysis showed high activity of proinflammatory cytokines and LPO products in obese adolescents, regardless of gender, with a reduced concentration of anti-inflammatory factors and correlations between parameters of inflammation and OS in girls. An important component of the pathogenetic approach in treating obesity should be the control of these parameters.(**International Journal of Biomedicine. 2023;13(3):79-83.**)

Keywords: interleukins • adolescents • lipid peroxidation • obesity

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Abbreviations

BMI, body mass index; **BW**, body weight; **CD,** conjugated dienes; **IL,** interleukins; **KD-CT,** ketodienes and conjugated trienes; **LPO,** lipid peroxidation; **OS,** oxidative stress; **ROS,** reactive oxygen species; **SB**, Schiff bases**; SDS BMI,** standard deviation score of body mass index; **TAA,** total antioxidant activity; **TBARs**, thiobarbituric acid reactants; **TNF-α**, tumor necrosis factor-α.

Introduction

The high prevalence of cardiovascular diseases leads to an increase in disability of the able-bodied population, which prioritizes the creation of new principles for treating and preventing obesity in children and adolescents.[1,2] In developed countries, up to a quarter of the adolescent population is overweight, and 15% are obese.[3] The structure of obesity consists of various forms, among which the exogenous-constitutional form occupies a special place in terms of prevalence (up to 75%-97%).[4]

Obesity is currently considered as a chronic inflammatory process, which is accompanied by the activation of proinflammatory cytokines, such as IL-6, IL-1, and TNFα, known mediators of the early stage of inflammation, as well as IL-8, γ-interferon, IL-18, IL-1.[5,6] Inflammation in obesity is manifested by cellular infiltration, changes in microcirculation, a shift in adipokine secretion and adipose tissue metabolism, and the accumulation of nonspecific markers of inflammation in the blood, which reflect the severity of the process.[7]

Oxidative stress (OS) is also an important component of the pathogenesis of obesity and its possible complications.[2,8,9] Experimental studies have shown a stimulating effect of OS on the proliferation and differentiation of preadipocytes, as well as an increase in the size of adipocytes.[10] It has been found that in obesity, the production of reactive oxygen species (ROS) increases, and the hunger center is activated due to increased oxidative processes.[11-13] OS in obesity is stimulated by factors such as hyperglycemia, elevated lipid levels, chronic increased activity of muscle tissue to maintain excess BW, impaired respiratory function of mitochondria.[14] The consequence of the OS progression in obesity is an increase in the content of cytotoxic compounds, which include endogenous aldehydes acting as damage mediators.[10] Despite the ongoing studies, the relationship between the parameters of the inflammatory process and OS parameters has not been sufficiently studied in obese adolescents.

The aim of this study was to identify the relationships between cytokine status, LPO products, and TAA in obese adolescent boys and girls.

Materials and Methods

The study included 29 boys (average age of 13.39±1.85 years) and 33 girls (average age of 14.56±2.01 years) with an established diagnosis of exogenous-constitutional obesity of the first degree. Twenty-eight healthy adolescent boys (average age of 13.96±1.5 years) and 24 adolescent girls (average age of 14.37±1.5 years) made up control groups. Criteria for inclusion in groups with exogenous-constitutional obesity degree 1 were excess BW of more than 95 percentile for a certain gender, height, and age; exclusion of acute or exacerbation of chronic diseases at the beginning of the examination or one month before it; permanent residence of a teenager in the territory of this municipality. Height, body weight (BW), and waist circumference were measured, and BMI (kg/m^2) was calculated. The puberty stage was determined according to Tanner. Overweight was considered to be a BMI >85th percentile for a given gender and age, and obesity was considered to be a BMI >95th percentile.[15] Exclusion criteria were physical development delay, BW deficiency, genetic and symptomatic forms of obesity, and taking medications that potentially affect BW.

All adolescents were subjected to general clinical examination, including anamnestic data collection, physical examination, anthropometric data analysis, blood pressure measurement, nutritional status assessment, determination of blood lipid profile, and glucose tolerance testing.

The study was carried out in accordance with the Helsinki Declaration of the World Medical Association (1964, ed. 2013) and approved by the Committee on Biomedical Ethics under the Scientific Center for Family Health and Human Reproduction (Extract from the meeting No. 5 as of 05.16.2016).

The study material was blood plasma and serum. Blood was collected in accordance with the existing requirements in the morning on an empty stomach from the cubital vein.

The concentration of pro-inflammatory cytokines (IL-6, IL-8) and anti-inflammatory interleukins (IL-4 and IL-10) was assessed by enzyme immunoassay using monoclonal antibody panels (JSC "Vector-Best", Novosibirsk, Russia). Measurements were performed on a microplate photometer (Multiskan Ascent, Finland). The IL-6/IL-10 ratio, reflecting the balance of pro- and anti-inflammatory cytokines, was also calculated.

The content of LPO products (conjugated dienes [CDs], ketodienes and conjugated trienes [KD-CT] and Schiff bases [SB]) was determined by the Volchegorsky method.[16] The level of thiobarbituric acid reactants (TBARs) was determined fluorimetrically by the method of Gavrilov et al.[17] Total antioxidant activity (TAA) was evaluated by the method of Klebanov et al.[18] Measurements were carried out on a spectrophotometer SF-2000 (Novosibirsk, Russia).

Statistical analysis was performed using STATISTICA 10.0 software package (Stat-Soft Inc, USA). The normality of distribution of continuous variables was tested by the Kolmogorov-Smirnov test with the Lilliefors correction and Shapiro-Wilk test. Differences of continuous variables departing from the normal distribution, even after transformation, were tested by the Mann-Whitney U-test. Pearson's Correlation Coefficient (r) was used to determine the strength of the relationship between the two continuous variables. A probability value of $P<0.05$ was considered statistically significant.

The study was conducted in accordance with ethical principles of the WMA Declaration of Helsinki (1964, ed. 2013) and approved by the Ethics Committee at the Scientific Centre for Family Health and Human Reproduction Problems (Irkutsk, Russia). Written informed consent was obtained from all participants (patients or parents/guardians of each patient).

Results and Discussion

The data obtained indicated a statistically significant increase in the level of IL-6 ($P=0.018$) and the IL-6/IL10 ratio ($P=0.033$) in obese boys, compared with the control (Figure 1).

There was also an increase in the content of LPO products in this group relative to the control group: KD-CT (P=0.043) and SB (P=0.021). In the group of obese girls, there was an increase in IL-6 values (P=0.018), a decrease in IL-4 (P=0.040), and an increase in CDs (P=0.035) and KD-CT (P=0.044) (Figure 2).

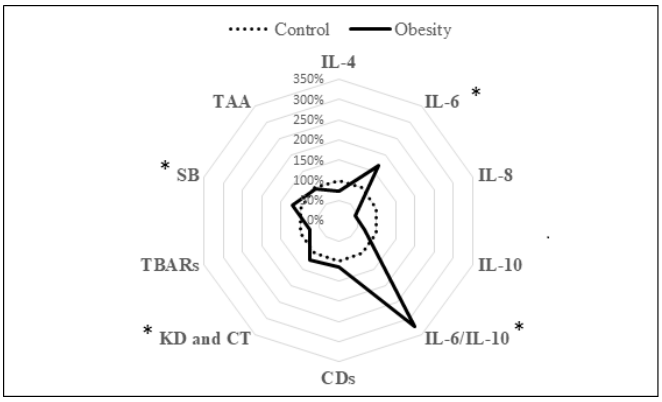

Fig. 1. *Cytokine status parameters, TAA and LPO products in obese boys; 100% - control group; *- statistically significant differences between group with obesity and control group (P<0.05).*

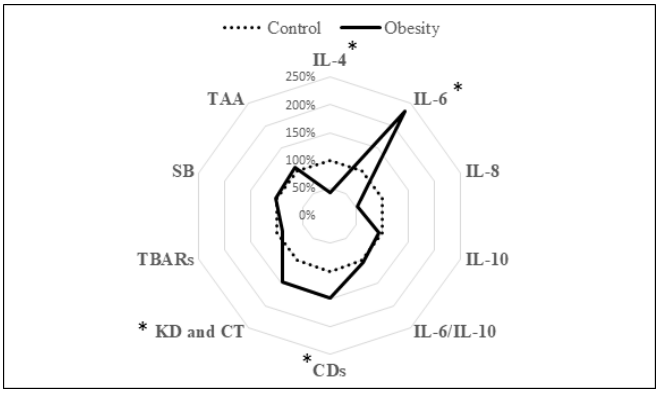

Fig. 2. *Cytokine status parameters, TAA and LPO products in obese girls; 100% - control group; *- statistically significant differences between group with obesity and control group (P<0.05).*

The following correlations were found in the control group of boys: CDs–KD-CT (r=0.91; P=0.001), TBARS–IL-8 (r=0.73; P=0.027), and SB–IL-4 (r=0.79; P=0.011); there were no statistically significant correlations between study parameters in obese boys. The following correlations were recorded in the girls of the control group: CDs–KD-CT (r=0.99; P<0.0001), TAA–IL-10 (r=-0.80; P=0.033), TAA–IL-4 (r=-0.78; P=0.040); in obese girls, it was SB–IL-4 (r=-0.67; P=0.048) (Table 1).

Our study found a significant increase in the values of the proinflammatory IL-6 and the IL-6/IL10 ratio in obese boys, as well as a marked increase in IL-6 level and a decrease in IL-4 level in obese girls.

Increased OS and inflammation often characterize obesity due to the infiltration of adipocytes by immune cells.[14] The inflammatory process is a physiological reaction of the organism to various kinds of stimuli.[7] The resulting response usually leads to the restoration of systemic metabolic homeostasis. In obesity, there is an increase in inflammatory reactions in metabolically active areas, such as adipose tissue, liver, and immune cells.[6] In addition, there is a sharp increase in the level of circulating proinflammatory cytokines, adipokines, and other inflammatory markers.[19] In this context, a certain contribution to the inflammatory nature of obesity is made by TNFα, IL-6, fibrinogen, C-reactive protein, and plasminogen activator inhibitor-1 or resistin, confirming the relationship between inflammation and obesity.[14] It was found that a wide range of mediators of the proinflammatory response are produced by macrophages of adipose tissue together with adipocytes.[20] A potential cause of inflammation in obesity may be hypoxia of adipose tissue, which occurs due to hypertrophy of adipocytes. A disproportionate increase in cell size lengthens the distance over which oxygen must diffuse, which can lead to a hypoxic state in enlarged adipocytes.[19,20]

Table 1.

Correlations* between the parameters in study groups of adolescents.

Control (boys)	Obesity (boys)	Control (girls)	Obesity (girls)
CDs–KD-CT (r=0.91)	-	CDs–KD-CT (r=0.99)	SB–IL-4 (r=-0.67)
TBARS–IL-8 (r=0.73)	-	TAA–IL-10 (r=-0.80)	-
SB–IL-4 (r=0.79)	-	TAA–IL-4 (r=-0.78)	-

* - *Table shows only statistically significant correlations.*

The production of highly reactive ROS is considered one of the most important adverse cellular reactions in response to excessive amounts of nutrients in obesity.[21] The growth of ROS production disrupts the balance between pro-oxidant and antioxidant factors, leading to the dominance of the pro-oxidant state and OS.[22-25] OS, in turn, damages cellular structures and causes an inflammatory response.[20] In addition, OS in obesity is closely associated with insulin resistance and metabolic syndrome.[10,11] Significant markers of OS in obesity are various products of LPO.[26] The latter has a pronounced damaging effect on the structural components of the cells, DNA synthesis, proliferative processes. and other factors.[10] We found higher values of KD-CT and SB in obese adolescent boys, and CDs and KD-CT in obese girls, which may have adverse consequences in the long term.

Correlation analysis showed the presence of close interrelations of inflammatory factors and OS in the control groups; however, a different picture was recorded with obesity. Thus, no correlations were found in boys, which indicated an imbalance of the existing mechanisms in the conditions of pathology. The only negative dependence was registered in obese girls – the end products of LPO (SB) and IL-4. This relationship may indicate the dominance of proinflammatory factors in this group, mediated by the action of OS products. There are studies

which show that the state of inflammation and OS phenomena interact closely in conditions of obesity.[14] Common genetic mechanisms that potentiate inflammation and OS mechanisms have been identified.[20]

Conclusion

In our study, data analysis showed high activity of proinflammatory cytokines and LPO products in obese adolescents, regardless of gender, with a reduced concentration of anti-inflammatory factors and correlations between parameters of inflammation and OS in girls. An important component of the pathogenetic approach in treating obesity should be the control of these parameters.

This work was carried out using the equipment of the Center for the Development of Advanced Personalized Health Technologies, Scientific Centre for Family Health and Human Reproduction Problems, Irkutsk.

Competing Interests

The authors declare that they have no competing interests.

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