

SUBCLINICAL INFLAMMATORY PROCESS IN FORMATION OF CARDIOVASCULAR DISORDERS IN CHILDREN WITH OBESITY

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Abstract. The problem of overweight and obesity in children requires constant study of its new aspects. According to modern requirements, for an adequate assessment of multifactorial changes in the metabolic status in obese patients, it is necessary to use data from immunological studies. The article presents the results of our own research on the level of markers of systemic inflammation and their influence on the formation of cardiovascular disorders in obese children. It was found that children with obesity and cardiovascular disorders have significantly higher values of inflammatory markers (IL-6 and CRP-hs) and low levels of the pro-inflammatory cytokine IL-10 ($p < 0.05$), which indicates subclinical damage to the cardiovascular system and chronic inflammatory process in obese children. The features of the obtained correlation relationships confirm the involvement of a chronic inflammatory process in the formation of cardiovascular disorders in obesity in children.

Keywords: children, obesity, cardiovascular disorders, chronic subacute inflammatory process.

The problem of overweight and obesity in children requires constant study of its new aspects. According to modern requirements, for an adequate assessment of multifactorial changes in the metabolic status in obese patients, it is necessary to use data from immunological studies. Advances in immunology have made it possible to expand the range of diagnostic tests used in clinical practice, on the basis of which the idea of adipose tissue as an active endocrine and immune organ has been formed [1]. Data have been obtained indicating that in obesity there is an imbalance in the synthesis of individual pro-inflammatory and anti-inflammatory cytokines, which initiates the development of a subclinical inflammatory process [2]. The negative impact of metabolic disorders on the functional state of cellular immunity factors, the phagocytic link, the expression of various cytokine receptors, the cytotoxic function of immunocompetent cells, etc. has been proven [3]. It has been established that obesity, primarily visceral, is accompanied by inflammation of adipose tissue, characterized by an increase in the formation and secretion of cytokines and chemokines, and a change in the expression of adipokines. These shifts contribute to atherogenesis, as well as the development of insulin resistance, which in turn has a pathogenetic significance in atherosclerosis and is closely associated with cardiovascular morbidity and mortality [4]. Local inflammatory processes in adipose tissue are accompanied by chronic mild systemic inflammation. The leading manifestation of this systemic inflammation is an increase in the level of inflammatory markers, primarily C-reactive protein (CRP) [5]. CRP is an independent predictor of CVD. Therapeutic measures that reduce the level of CRP, reduce the risk of CVD. Adipose tissue is metabolically very active and is one of the highly vascularized tissues capable of regulating vascular tone [6]. Adipose tissue is also an endocrine organ that secretes more than 30 hormone-like substances that regulate metabolic and immune processes. Moreover, the metabolic and secretory activity of visceral fat is higher than that of subcutaneous fat, which corresponds to the idea of its greater significance in the development of atherosclerosis [7]. It is noteworthy that perivascular fat is similar in its characteristics to visceral fat. The spatial proximity of perivascular fat to the vascular endothelium makes it extremely interesting in the light of the analyzed problem. Changes in the secretion of

adipokines and cytokines in obesity play a pathogenetic role in the development of atherosclerosis, insulin resistance, metabolic syndrome, type 2 diabetes mellitus [8]. On the other hand, it is the visceral adipose tissue that is given the leading role in violation of the formation and secretion of adipokines and cytokines. An increase in the mass of visceral adipose tissue in obesity is accompanied by an increase in the secretion of pro-inflammatory cytokines (TNF- α , IL-6, IL-1), chemokines (MCP-1, RANTES). The degree of shift in the level of these substances correlates with obesity, and to a greater extent with an increase in the mass of visceral fat [9].

Among the large number of cytokines synthesized by activated T cells, macrophages, and B cells, interleukin-6 plays a key role in the development of autoimmune inflammation and cardiovascular catastrophes [10]. IL-6 is a pro-inflammatory cytokine with a wide range of immunoregulatory properties, as well as a mediator of the formation, growth and progression of tumors of various nature and localization. The study of the mechanisms of intracellular signal transmission from IL-6 has helped to understand many of the general principles of the action of cytokines. It has been established that IL-6 enhances glucose-stimulated insulin secretion, weakens insulin-induced glycogen synthesis in the liver, and administration of recombinant IL-6 causes dose-dependent hyperglycemia [11]. The action of IL-6 is based on the ability to activate the hypothalamic-pituitary-adrenal axis with an increase in the secretion of ACTH and cortisol, which leads to the formation of abdominal obesity, the development and progression of insulin resistance, hypertension, hypertriglyceridemia, and a decrease in HDL. It has been shown that the concentration of IL-6 in adipose tissue is directly proportional to body weight, impaired glucose tolerance and insulin resistance. This indicates an important role of this cytokine in the mechanisms of development of metabolic disorders in obesity. IL-6 is also involved in the pathogenesis of atherosclerosis [12]. Apparently, the leading role in the mechanism of its pathogenetic action belongs to the development of insulin resistance due to the interruption of the intracellular insulin signaling pathway. In addition, it stimulates the production of triglycerides. In a study of 306 patients with type 2 diabetes over 40 years of age, it was found that, despite an increased level of systemic inflammation, the severity of atherosclerosis of the coronary arteries (determined by electronic computed tomography) correlates with the level of IL-6 in the blood plasma, but not with the level SRP. In patients with hypertension, a close correlation was established between the functional state of the endothelium and the content of TNF- α and IL-6 in the blood. It was concluded that these cytokines play an important role in the development of atherosclerosis in systemic inflammation [13].

Purpose of the study. To study the secretion of inflammatory markers in children with obesity and cardiovascular disorders.

Materials and methods. This study was conducted on the basis of the teenage dispensary in Tashkent. 50 children were selected for the survey. In accordance with the purpose of the study, after collecting an anamnesis and complaints, performing a physical examination and electrocardiography, the examined children were divided into 3 groups: the main group - 20 children with primary exogenous-constitutional form of obesity of the 1st degree with signs of cardiovascular disorders; a comparison group - 20 children with a primary exogenous constitutional form of obesity of the 1st degree without signs of cardiovascular disorders and a control group - 10 children with normal weight. In the groups of observed children, there were 23 (46%) boys and 27 (54%) girls, respectively. The distribution by sex and mean age was even.

In accordance with WHO recommendations, the standard deviation of BMI (SDS BMI) was used as a diagnostic criterion for overweight and obesity in children. According to WHO recommendations, obesity is BMI $+2.0$ or more SDS BMI, overweight is $+1.0-2.0$ SDS BMI, the norm is 1.0 SDS BMI [17].

The laboratory study included: determination of the levels of highly sensitive C-reactive protein (CRP-hs), IL-6, IL-10 in blood serum. The levels of CRP-hs, IL-6, IL-10 were determined in blood serum by solid-phase, chemiluminescent enzyme immunoassay using reagent kits (Siemens, Germany) on an IMMULITE 2000 device (manufacturer, Germany). According to the

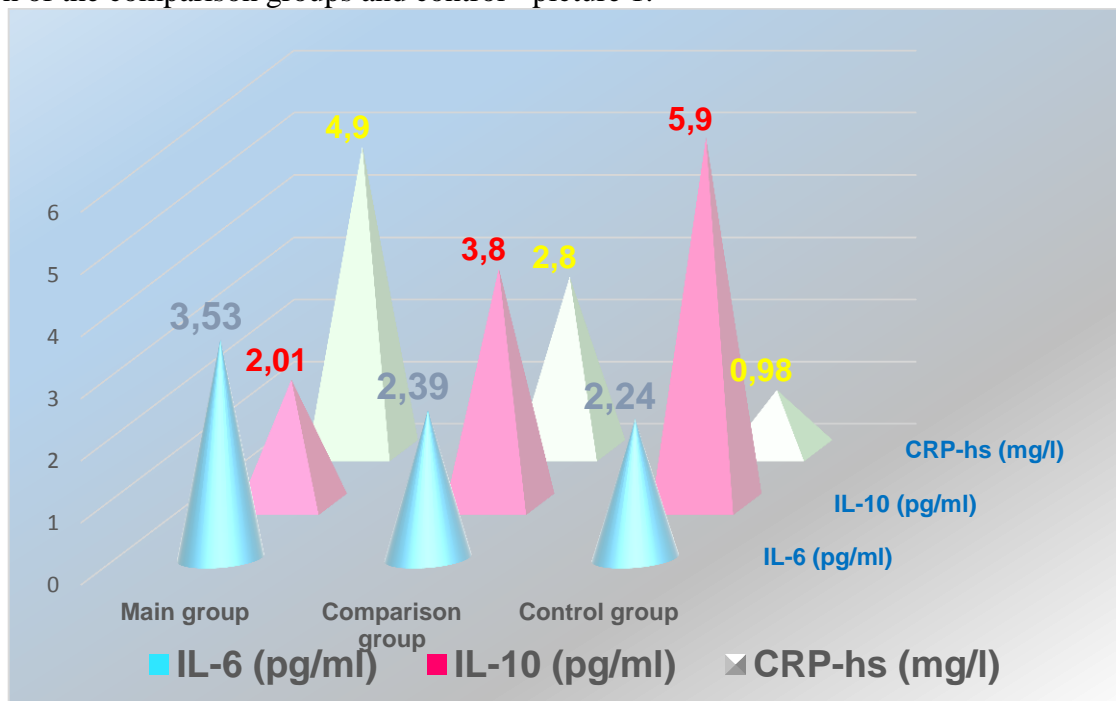
instructions, the normal values of CRP-hs are considered to be from 0 to 5 mg / l. For samples with a concentration of CRP-hs below the threshold of sensitivity of the test (0.2 mg/l), a value of 0.1 mg/l was indicated. The reference level of IL-6 was taken as 0-7.0 pg/ml, IL-10 - 0-31 pg/ml. These indicators are the same for children and adults, regardless of gender.

The functional state of the cardiovascular system was carried out according to the results of ECG in 12 standard leads on an electrocardiograph with a CARDIOVIT AT-2 plus thermal printer (SCHILLER). ECG was recorded at rest with the child in the supine position.

The state of the autonomic nervous system (ANS) was assessed using indicators obtained during cardiointervalography (CIG): initial autonomic tone (IVT) - according to the tension index (TI) in a horizontal position; vegetative reactivity (VR) - according to the ratio of IN in a vertical position to IN in a horizontal position; stability of regulation - according to the coefficient of variation (CV), IN, M (RRav), R1, m0 in a horizontal position; CIG was performed on a digital electrocardiograph VDS=201. We recorded 300 consecutive cardiocycles in the supine position and 100 consecutive cardiocycles in the orthostatic test.

Statistical data processing was carried out using MS Excel for Windows 7 software. Statistical significance was determined using correlation analysis (Pearson's method), at $p < 0.05$ the differences were considered statistically significant.

Results and discussion. Analysis of data from studying the level of markers of systemic inflammation showed that children of the main group with obesity and cardiovascular disorders had significantly higher values of IL-6 and CRP-hs and a lower level of IL-10 ($p < 0.05$) compared with children of the comparison groups and control - picture 1.



Picture 1. Results of a laboratory study of IL-6, CRP-hs and IL-10 in the analyzed groups of children

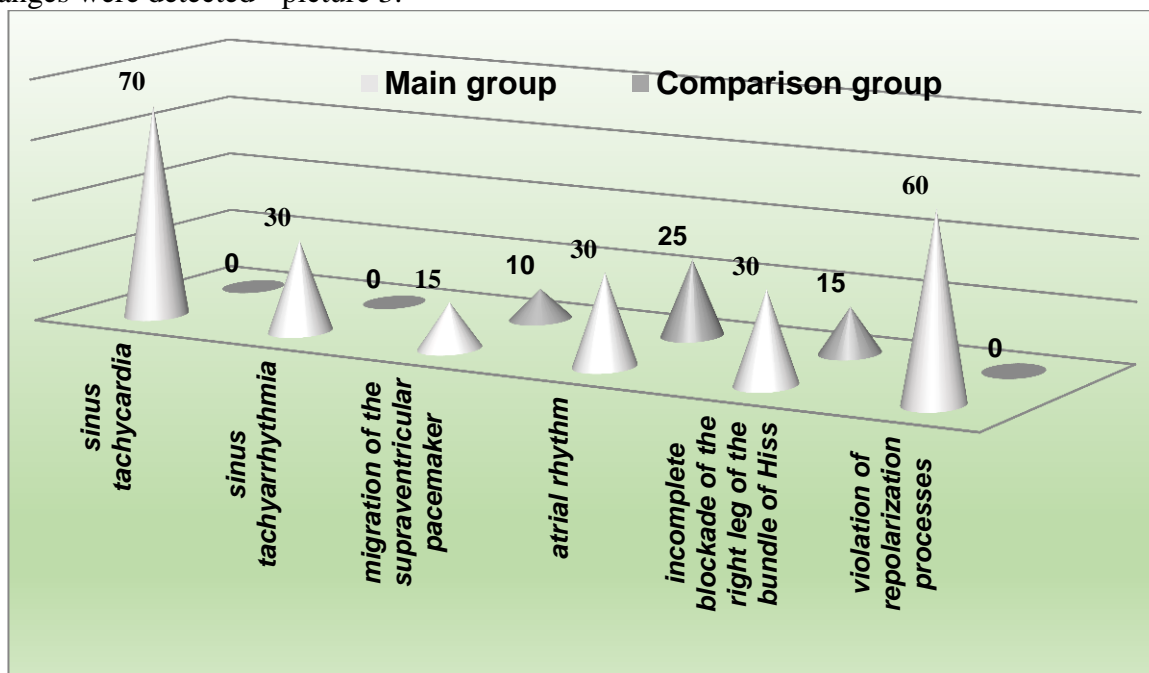
To obtain more complete information about the features of the relationship between the studied parameters, we conducted a correlation analysis, which revealed a positive correlation between the concentration of IL-6 and CRPhs with body mass index and waist circumference ($r = +0.72$; $r = +0.67$; $p < 0.05$ and $r = +0.69$; $r = +0.52$; $p < 0.05$, respectively), and inverse correlation of IL-6 and CRPhs with IL-10 ($r = -0.546$; $p < 0.05$ and $r = -0.61$; $p < 0.05$, respectively) - picture 2.



Picture 2. Correlations between anthropometric parameters and markers of systemic inflammation.

The data obtained indicate a subclinical lesion of the cardiovascular system and a chronic inflammatory process in obese children. The nature of the relationships obtained proves the participation of IL-6, CRP-hs in the formation of cardiovascular disorders in children with obesity, which coincides with the literature data.

Analysis of the ECG data showed that in the main group of children with obesity were identified: cardiac arrhythmias in the form of sinus tachycardia and tachyarrhythmia, sinus bradycardia; violations of the automatism of the sinus node in the form of migration of the supraventricular pacemaker and atrial rhythm, conduction disturbances in the form of an incomplete blockade of the right leg of the Hiss bundle. It should be noted that in the vast majority of children of the main group, violations of the processes of repolarization were detected, which indicates a violation of the electrolyte balance in this contingent of children. In the control group, no ECG changes were detected - picture 3.



Picture 3. Changes in the electrical activity of the heart in children of the main and comparative groups (%).

To study the effect of obesity on the functional state of the central and autonomic nervous systems, we evaluated the results of cardiointervalography, echo- and electroencephalography. The results of the study of the state of the autonomic nervous system are presented in table 1.

Table 1.

Indicators of cardiointervalography of the analyzed groups of children

Parameter	Main group n=20	Comparison group n=20	Control group n=10
Initial vegetative status			
Sympathicotonia	50%	10%	0%
Vagotonia	40%	20%	10%
Eitonia	10%	70%	90%
Autonomic reactivity			
Hypersympathicotonic	80%	30%	10%
Asympathicotonic	20%	0%	-
Normatonic	-	70%	90%
Stability of regulation of vegetative processes			
Sustainable	10%	80%	90%
Transition process	20%	10%	10%
Dysregulation	70%	0%	0%

When assessing the initial vegetative tone, it was found that the number of children with eutonia was inversely proportional to the degree of weight gain. Thus, in children in the control group with normal weight, eutonia was documented in 90% of children, while in the group of comparison children in 70%, in obese children with cardiovascular disorders only in 10% of children. The data obtained indicate the dependence of the state of the initial vegetative tone on the degree of weight gain.

Assessment of autonomic reactivity in an orthostatic test found that hypersympathicotonic autonomic reactivity was observed in 80% of children with obesity and cardiovascular disorders, regardless of the initial autonomic tone, which indicates an overstrain of regulatory systems. In the control group, normotonic autonomic reactivity was observed in 90% of children. Steady regulation of vegetative processes was noted only in 10% of the children of the main group, a transient process was found in 20% of children, and dysregulation of vegetative processes was detected in the vast majority of children - 70%.

After receiving the survey data, it seemed relevant to conduct a correlation analysis to identify the relationship between the main obtained indicators of ECG, CIG and markers of the systemic inflammatory response in obese children. The data of the correlation analysis performed using the Pearson method between various studied indicators are shown in Table 2.

Table 2.

Correlation of indices of systemic inflammation markers with parameters of cardiointervalography and electrocardiography in children with obesity and cardiovascular disorders.

Investigated violations	IL-6	CRP-hs	IL-10
Indicators of cardiointervalography			
Centralization index	0,45**	0,48**	-0,43*
Tension index	0,74**	0,61*	-0,45*
Parameters of electrocardiography			

Heart rhythm disorders	+0,32*	+0,26*	-0,38*
Violation of repolarization processes	+0,52**	+0,49*	-0,48*

Note: Statistical significance of the correlation coefficient: * - $p < 0.05$; ** - $p < 0.01$.

Correlation analysis showed that in children with obesity and cardiovascular disorders there was a direct relationship between the levels of IL-6 and CRP-hs in blood serum with the tension index and with the index of centralization in terms of CIG and disturbances in heart rhythm and repolarization processes in the myocardium ($p < 0,05$) according to ECG data, and the inverse correlation of IL-10 with all the parameters studied ($p < 0.01$). Thus, in children with obesity of the main group, autonomic regulation disorders are accompanied by an increase in the level of inflammatory and a decrease in anti-inflammatory cytokines.

Findings

1. Children with obesity and cardiovascular disorders have significantly higher levels of IL-6 and CRP-hs and lower levels of IL-10 ($p < 0.05$) compared with their peers with obesity, but without cardiovascular disorders, which indicates a subclinical damage to the cardiovascular system and chronic inflammation in obese children.
2. The nature of the obtained relationships between anthropometric parameters and inflammation markers proves the participation of IL-6, CRP-hs in the formation of cardiovascular disorders in obesity in children, which coincides with the literature data.
3. In children with obesity and cardiovascular disorders, metabolic disorders are detected that are related to the degree of overweight, changes in the profile of inflammatory markers and indicators of activity and the autonomic nervous system.

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