Obesity and the Functional State of the Cardiovascular System in Children

Kholmuradova Zilola Ergashevna	Samarkand State Medical Institute. Department of Pediatrics, Faculty of General Medicine
Khaydarova Khaticha Ramizovna	Samarkand State Medical Institute. Department of Pediatrics, Faculty of General Medicine
Ibragimova Yulduz Botirbekovna	Samarkand State Medical Institute. Department of Pediatrics, Faculty of General Medicine

ABSTRACT

Endothelial dysfunction (ED) is considered one of the pathogenetic mechanisms of a whole range of diseases. An effective way to diagnose ED is to detect specific biochemical markers in the blood that characterize the state of the vascular endothelium. The article highlights the pathogenetic role of a number of factors synthesized by endotheliocytes, the change in the level of which in biological fluids reflects a violation of the basic physiological properties of the endothelium: vasomotor function, angiogenesis regulation function, barrier and adhesive functions. In particular, the involvement of endothelin-1, von Willebrand factor, vasculo-endothelial growth factor (VEGF) and albuminuria is considered.

Keywords: obesity, children, endothelial dysfunction, endothelin-1, albuminuria

Introduction: Currently, obesity is considered as a non-communicable epidemic and is a chronic disease that is widespread, tends to steadily increase and become more severe. It affects not only adults, but also children and adolescents. This is due to severe metabolic disorders, growing cardiovascular morbidity [1]. Usually, the term "endothelial function" or "endothelial function" refers to the ability of endotheliocytes to participate in the production of a wide range of vasoactive substances. At the same time, "endothelial dysfunction" (ED) is understood as a pathological condition, mainly characterized by an imbalance between substances with vasodilating, antimitogenic and antithrombogenic properties (endothelium-dependent relaxing factors) [3]. Adipose tissue produces a huge amount of hormones and cytokines that regulate metabolism, and at the same time can deeply and negatively affect the physiology of the endothelium [4]. This condition can lead to the formation of atherosclerotic plaque [5]. The state of chronic inflammation in obesity induces dysregulation of endocrine and paracrine effects of adipocyte products, which disrupt vascular homeostasis and contribute to dysfunction of endothelial vasodilation and subsequent hypertension [2]. Healthy perivascular adipose tissue (PVAT) provides vasodilation, while PVAT in the state of obesity leads to a change in the profile of released adipocytokines. The result is a decrease in the vasodilating effect [7]. Inflammation of adipose tissue, bioavailability of nitric oxide (hereinafter - NO), insulin resistance and oxidized low density lipoproteins (hereinafter - oLDL) are the main pathogenesis factors in endothelial dysfunction associated with obesity [3].

Purpose of the study: Determination of markers of endothelial dysfunction in overweight and obese children.

Materials and research methods.

The main study group consisted of 62 children and adolescents aged 6 to 17 years with exogenous constitutional obesity. The selection criterion for patients was the determination of BMI and waist circumference in children and adolescents with identified overweight and/or obesity, which was above the 97th percentile for a certain age and gender (WHO, 2007). The study included 28 girls (45.2%) and 34 (54.8%) boys. Groups were divided based on BMI. Group 1 consisted of 23 adolescents with overweight and obesity of the 1st degree (BMI=30.0–34.9), group 2 consisted of 21 adolescents with (BMI=35.0–39.9). Group 3 included 18 adolescents with (BMI > 40.0). The control group consisted of 23 healthy adolescents of the same age without obesity (BMI 18.5–24.99). (Table 1)

Table 1. Distribution of groups by BMI

1 group (23) (30.3±1.2 kg/m2)	Group 2 (21) (33.4±1.1 kg/m2)	Group 3 (18) (36.1±1.4 kg/m2.)	Control group (23) 22.5±0.9 kg/m2.

All patients underwent clinical examination. Body weight was assessed using percentile tables of the ratio of linear height to body weight or body mass index (Quetelet index) for a certain age and sex (WHO, 1998). The volume of the waist (WT) and hips (OB) was determined, the ratio of which is an indicator of abdominal obesity. With WC/VR values >0.85 in girls and >0.9 in boys, their condition was regarded as abdominal obesity (IDF, 1997). Arterial hypertension was diagnosed in accordance with the criteria developed by the Committee of Experts of the All-Russian Scientific Society of Cardiology and the Association of Pediatric Cardiologists of Russia (Moscow, 2009) [5].

Laboratory studies included general clinical blood and urine tests; The lipid spectrum of the blood was determined on a semi-automatic biochemical analyzer Prima and FT (Italy) with kits from Biocon (Germany) according to the standard method after a 12-hour fast. The content of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG) was determined. The level of low-density lipoprotein cholesterol (LDL cholesterol) was calculated using the Friedwald formula:

LDL cholesterol = total cholesterol-HDL cholesterol-TG / 2.2. The atherogenic index was calculated by the formula: Atherogenic index = TC-HDL-C/HDL-C.

A value less than 4 was taken as normal. The concentration of fasting blood serum glucose was studied: values equal to 6.1 mmol/l or more were regarded as fasting hyperglycemia (Recommendations of the VNOK for the diagnosis and treatment of the metabolic syndrome, 2009).

Serum insulin levels were determined by enzyme immunoassay. Insulin resistance was assessed using the HOMAR index, which reflects the ratio of glucose (in mg/dl) and insulin (in μIU/ml). The criterion for the presence of IR was considered to be an index value above 2.7 conventional units. To assess the functional state of the endothelium, the method of wavelet analysis of skin temperature fluctuations during cooling of the limb was used.

Albuminuria (AU), vasculo-endothelial growth factor (VEGF), endothelin-1 (ET-1) were determined to identify markers of endothelial dysfunction.

Results of the study and their discussion. All main groups were characterized by the presence of insulin resistance, which was confirmed by an increase in insulin levels and the HOMA-IR index compared with the healthy group (A) ($p < 0.05$).

We obtained positive correlations between the degree of BP increase and the increase in anthropometric parameters: BMI ($r=0.50$; $p=0.01$), WC, WC/OB and proatherogenic components of the blood lipid spectrum: cholesterol level ($r=0.41$; $p=0.004$), TG ($r=0.51$; $p=0.01$). In all the studied groups, the concentration of adiponectin tended to decrease in comparison with the group of practically healthy individuals (Table 2).

Table 2 - The level of adiponectin and IL-6 in the examined groups

Markers	1 group (23) (30.3± 1.2 kg/m2)	Group 2 (21) (33.4± 1.1 kg/m2)	Group 3 (18) (36.1± 1.4 kg/m2 .)	Control group (23) 22.5± 0.9 kg/m 2.
Adiponectin ng/ml	16,9 (15,5-18,4) * *	17,1 (16,0-18,0) * *	16,7 (15,8-18,4) * *	18,5 (17,0-27,0)
IL-6 pg/ml	2,4 (1,1-2,5)*	2,4 (2,1-4,2)*	3,5 (2,2-4,5)*	0,04 (0,80-0,1)

*differences from the comparison group A <0.05
* * differences from the comparison group A <0.1

The level of IL-6 did not differ in patients of the main study groups and was significantly higher than the comparison group, its level increased in proportion to the increase in BMI. An increased content of IL-6 in obesity confirms the presence of chronic inflammation and may be the initiator of cardiovascular complications [8].

Adiponectin is a protein with m.v. 30 kDalton produced by adipocytes [10]. It has an anti-inflammatory, anti-atherogenic effect and stimulates the production of insulin. This adipokine plays a central role in lipid and energy metabolism. In contrast to other adipokines, the concentration of adiponectin in obesity is reduced (Table 2).

In all obese groups studied, the leptin/adiponectin ratio was significantly higher than in comparison group A. It has been shown that the leptin/adiponectin index is not only a useful marker for metabolic diseases, but may also be more closely associated with the risk of developing type 2 diabetes and CVD risk than leptin and adiponectin alone [6,7]. The results of the cold test revealed the absence of restoration of the amplitudes of fluctuations in skin temperature equally in all groups with obesity compared with the control group, indicating the absence of restoration of the amplitudes of fluctuations in patients with obesity, which indicated a violation of vasodilation.

In the study of endothelial dysfunction, an excess of recognized markers was revealed: VEGF, ET-1 and AC in the obese group compared to the comparison group A
(Table 3).

Table 3 - The level of markers of endothelial dysfunction in the examined groups

Indicator	Obese groups (62)	Comparison group (23)	P
Albuminuria (AU) mcg/ml	24,6±15,3	9,41±2,7	0,001
VEGF pg/ml	180 (96,2-288,0)	75 (0–96)	0,001
ET-1 fmol/ml	0,6 (0,3-3.2)	0,3 (0,1-0,4)	0,007
von Willebrand factor, %	85,80 ± 1,68	127,54 ± 6,89 *	0,001

An increase in the IVC vasoconstriction index as the values of leptin (r=0.9; p=0.03), insulin (r=0.52; p=0.02), HOMA-IR (r=0.58; p= 0.008), IL-6 (r=0.59; p=0.05), glycemia (r=0.94; p=0.05), blood pressure (r=0.51; p=0.09) indicates about the multifactorial effect on vascular reactivity, which is most pronounced in obesity.

Thus, the improvement of endothelial function is possible only when the target values of blood pressure, glycemia and weight loss are achieved.

The levels of biochemical markers of ED in the main study groups did not differ, and the relationship between ED markers and indicators of the lipid spectrum, insulin resistance also remained. Overweight and obesity at an early age are associated with progressive endothelial dysfunction and the formation of a complete metabolic syndrome.

Thus, the data obtained indicate a deterioration in the function of the endothelium and an increase in the rigidity of the vascular wall in obese patients. Endothelial dysfunction and metabolic syndrome are closely associated conditions and form a vicious circle leading to metabolic and cardiovascular conditions[9].

Emerging evidence suggests that targeting stressed endothelium or stimulating angiogenesis may help preserve target organ function and slow disease progression [11]. While obesity-induced endothelial dysfunction is at least partially reversible with effective weight control, these interventions are not sufficient to prevent the metabolic and cardiovascular complications of obesity. Clearly, further research into the pathophysiological mechanisms underlying vascular disease in obese children is needed to identify additional targets for pharmacological intervention to prevent the complications of obesity. In addition, some indicators characterizing the dynamics of endothelial dysfunction in obesity in children can be used to assess the clinical status of patients and monitor the effectiveness of their treatment.

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