NITRIC OXIDE IN THE DEVELOPMENT OF ARTERIAL HYPERTENTION IN CHILDREN WITH OBESITY

Gromnatska N.,
MD
Danylo Halytsky Lviv National University, Lviv, Ukraine
Lemishko B.,
MD
Danylo Halytsky Lviv National University, Lviv, Ukraine
Belusova V.,
Hospital of St.Panteleimon of the 1 Territorial Medical Association of Lviv, Ukraine
Pasichnyuk I.,
PhD
Danylo Halytsky Lviv National University, Lviv, Ukraine
Iskiv M.,
PhD
SI "Institute of Hereditary Pathology of National Academy of Medical Sciences of Ukraine, Lviv, Ukraine
Kulya O.
PhD
Danylo Halytsky Lviv National University, Lviv, Ukraine
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The results of research conducted in the last decade testify to the leading role of the vascular endothelium in the regulation of the work of the cardiovascular system, the dynamics of the state of the vascular wall, and the regulation of vascular functions. The intima of vessels provides a dynamic balance between vasodilating and vasoconstrictive factors, regulates the growth and proliferation of subendothelial cells and non-cellular structures, affects vascular permeability [1].

Endothelial cell dysfunction is a characteristic feature of vascular disease and is characterized by a decrease in angiogenic potential and bioavailability of nitric oxide (NO), impaired vasodilation and increased inflammation [2].

The main role in vasodilation belongs to NO [3]. Research in recent years in the field of vascular physiology has shown that the NO molecule, which is synthesized by the vascular endothelium, has a wide range of bioregulatory effects. NO is an unstable short-lived molecule with a half-life of 2-30 seconds, followed by transformation into nitrite and nitrate and excretion in the urine. Both an excess and a deficiency of NO can be significant in the pathogenesis of many diseases, if we take into account its important role in the regulation of the activity of all cells, organs and systems and the vital activity of the organism as a whole in normal and pathological.

Despite the enormous physiological importance of NO, the concentration dependence of its activity, basal concentrations, and how its levels fluctuate during certain pathological conditions [4], such as obesity and hypertension - the main components of metabolic syndrome remain unknown [5].

It is believed that vascular endothelium dysfunction plays a leading role in the formation and progression of hypertension. If in adults the issue of the regulatory influence of NO in hypertension is sufficiently studied, in pediatrics it remains open.

Aim. To identify the value of NO in the formation of hypertension in children with obesity, and to study their interdependence.

Material and methods. From a sample of 1.400 children and adolescents aged 9 to 18, 2 groups were formed. Group 1 - 22 children with obesity and hypertension (average age 12.7±3.7 years) and the control group 2 - 22 healthy children with normal body weight and blood pressure (average age 13.3±2.9 years). The cluster of obesity and hypertension was established in 24.4% of children with obesity and in 1.5% of children in the general population.

Anthropometric indicators were determined in children: weight, height, waist circumference, body mass index (BMI), blood pressure, NO, leptin, total cholesterol (CHD), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C), triglycerides, insulin, glucose, the atherogenicity index (AI) and the HOMA-IR index were calculated. A BMI that exceeded the 95th percentile of the distribution for a given gender and age was considered a criterion for obesity in children. Values greater than the 95th percentile for a given gender, age, and height percentile were an indicator of hypertention.

Pairwise intergroup comparison of quantitative indicators was carried out using the Student's t-test, the study of the relationship between quantitative indicators was carried out using the Spearman (r) paired linear correlation.

Results. The presence of a combination of obesity and hypertension was diagnosed in 22 children, in 22.2% of children with obesity and in 1.5% of children in the general sample. BMI in children of group 1 was 28.6±5.1 kg/m2, group 2 - 18.1±5.4 kg/m2 ($p<0.05$) (table).

Table

Clinical and biochemical indicators in children with obesity and hypertention compared to children with normal body weight and blood pressure

	Group 1	Group 2	p
Body mass, kg	86.4±20.9	50.1±13.2	<0.01
Height, cm	167.6±14.5	161.8±15.5	<0.05
Body mass index, kg/m^2	28.6±5.1	18.1±5.4	<0.05
Waist circumference, cm	94.3±11.5	68.9±7.9	<0.01
Total cholesterol, mmol/l	4.4±1.4	3.6±1.2	<0.01
LDL-C, mmol/l	2.2±0.96	1.82±0.7	<0.01
HDL-C, mmol/l	1.3±0.6	1.3±0.6	>0.05
Triglycerides, mmol/l	1.4±0.3	1,1±0.5	<0.01
IA	3.1±3.6	2.2±1.8	>0.05
Leptin, μmol/l	33.3±5.3	6.3±8.7	<0.001
Insuline, mU/l	12.8±9.5	9.5±6.9	>0.05
Glucose, mmol/l	4.6±0.8	4.5±0.7	>0.5
HOMA-IR	3.1±2.1	2.1±1.6	<0.05
NO, μmol/l	6.4±1.9	3.6 ±2.5	>0,05

Body weight, height, BMI and waist circumference in children of group 1 was probably greater than in children of group 2. The results of lipid phenotyping in children with obesity and hypertension showed pronounced dyslipidemia, the sign of which was a significant difference in the level of cholesterol (4.4±1.4 mmol/l vs 3.6±1.2 mmol/l; p<0.01), LDL cholesterol (2.2±0.96 mmol/l vs 1.82±0.69 mmol/l; p<0.01), TG (1.4±0.3 mmol/l vs 1.1±0.5 mmol/l; p<0.01) in comparison with the control group.

It was found that in obesity with hypertension, the level of leptin in the blood (33.3±35.3 nmol/l and 6.3±8.7 nmol/l; p<0.05) was 2.6 times higher than the similar indicator of healthy children with normal body weight. IA in children with hypertension and obesity was 3.1±3.6, and in 23% of children it exceeded the threshold values (>3.0). In children of the control group, IA was 1.2 times smaller than the similar indicator of group 1(22±1,8).

No significant difference was found in the level of glucose and insulin in the blood serum of children of groups 1 and 2, however, a probable difference was observed in the HOMA-IR.

A positive correlation was established between the age of children with obesity and hypertension with BMI (r=0.9; p<0.05), the level of total cholesterol (r=0.88; p<0.05) and the level of LDL-C (r=0.9; <0.05).

The level of NO in blood serum in children of groups 1 and 2 did not differ and was at the level of 6.4 ± 1.9 μmol/l and 3.6 ± 2.5 μmol/l (p>0.05). NO was significantly negatively correlated with AI (r= - 0.71; p<0.01), triglycerides (r= - 0.73; p<0.01). In children of the control group, the NO was positively correlated with HDL-C (r= 0.72; p<0.05).

Discussion. There is a positive correlation of age with BMI, the total cholesterol and LDL-C, that is, with the growth of children, an increase in body weight and the duration of obesity and hypertention, the proatherosclerotic indicators of lipid metabolism - total cholesterol and LDL-C increased. The obtained data indicate significant atherogenic changes in lipid metabolism and their increase over time in children with obesity and hypertension.

It was established that with an increase in body weight in children with obesity and hypertension, an increase in the level of leptin in the blood was observed. The revealed association of leptin, one of the main regulators of fat metabolism, which clearly reacts to changes in body weight, the formation of obesity, and dyslipidemia, gives grounds for asserting that hyperleptinemia is not only an independent additional component of obesity and hypertension, but also the basis of the etiopathogenesis of their development.

The level of blood NO in children with obesity and hypertension did not differ from that in children with normal body weight and blood pressure. That is, in children with components of the metabolic syndrome, such as obesity and hypertension, the synthesis of NO did not change and there were no signs of NO-associated endothelial dysfunction. It can be assumed that children with obesity and hypertension have a compensatory increase in NO synthesis in response to the action of damaging factors.

However, it was established that dyslipidemia with increased IA and hypertriglyceridemia had a significant effect on the decrease in the level of NO in children with obesity and hypertension.

The inhibitory effect of cholesterol and LDL-C on NO synthesis can be explained by the enhancement of the transcription of the cavelion gene by free cholesterol, which binds to eNOS molecules and inactivates them, by the damaging effect of dyslipidemia and directly by LDL-C on the vascular endothelium due to the increase in the expression of adhesive molecules on the surface of endothelial cells [6].

It is likely that the development of hypertension in obese children is related to the mechanosensors of endothelial cells of the vascular wall, which are displaced by the blood flow, the extent of which depends on the volumetric velocity of blood flow, blood viscosity, and vessel diameter. With the help of mechanosensors, the endothelium changes the thickness of the inner layer of the blood vessel, the mass of its muscular layer and affects blood pressure [7].

Conclusions. Blood NO in children with obesity and hypertension did not differ from its level in children with normal body weight and blood pressure. The main

factors causing NO reduction and endothelial dysfunction in children with obesity and hypertension were metabolic: dyslipidemia and hypertriglyceridemia. HDL-C cholesterol, especially in children with normal body weight, has a protective effect on the endothelium of vessels with an increase in NO synthesis.

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