# PATHOGENETIC INTERRELATIONS OF INTESTINAL MICROBIOTA AND DISORDERS OF FAT METABOLISM IN CHILDREN WITH OBESITY

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**ABSTRACT**
The article presents information about the latest scientific studies of the connection of the intestinal microbiota with atherogenic dyslipidemia and its participation in the formation of complications from the cardiovascular system. The biomechanisms of the effect of intestinal microflora on the formation of unstable atheromatous plaques in the circulatory bed were considered. The results of our own studies of 60 overweight and exogenous constitutional obesity of the first degree are also presented, the relationship of intestinal dysbiosis with lipid metabolism disorders is shown.
**KEYWORDS:** adolescents, obesity, dyslipidemia, intestinal microbiota.

## INTRODUCTION

In recent years, the pathophysiology of diseases of various organs and systems, as well as their relationship, has been rethought thanks to the active development of immunology, molecular biology, biochemistry. Back in 1991, scientists from the USA Victor Dzauand and Eugene Braunwald defined the concept of a single cardiovascular continuum (from the English translation continuous – constant, continuous), which assumes a continuous stage of disease development - from risk factors to death [1].

Timely detection and correction of risk factors for the development of cardiovascular diseases occupies a special place in modern manuals on the diagnosis and therapy of diseases of the cardiovascular system. These risk factors are characteristic of many cardiovascular diseases, i.e. they are broadly universal. Risk factors are divided into:

- "unmodified", which do not change and are mainly used to predict the disease; they include a burdened genetic history, race, gender and age;
- "modifiable", i.e. changeable risk factors: overweight and obesity, unbalanced diet, stress, bad habits, physical inactivity, heart rate, state of microbiocenosis of the digestive tract, cholesterol level, impaired glucose tolerance, high blood pressure, etc.;

- "mild": high level of C-reactive protein and inflammatory cytokines (interleukin 6, TNF-alpha) low level of high-density lipoproteins, aggregate state of liquid blood, etc. [2].

The risk of complications from the cardiovascular system increases to 21.8% with the simultaneous influence of several risk factors. The results of numerous studies have proved that the vast majority of risk factors begin to affect already in childhood, therefore preventive measures should be carried out among children and adolescents [3].

Recently, obesity has been considered a new non-infectious epidemic of the XXI century, which has significantly rejuvenated over the past decade. Overweight and obesity in 70-90% of cases are combined with a violation of the composition of the resident microflora of the digestive tract – dysbiosis [4].

Scientific achievements of the last two decades have allowed us to reach a qualitatively new level of understanding of the relationship of intestinal microflora with a wide range of chronic diseases, such as obesity, fatty hepatosis, type 2 diabetes mellitus, oncology, osteoporosis and diseases of the cardiovascular system [5].

The attitude towards microorganisms - "commensals" (from the medieval Latin language commensalis - companion), which inhabit the human body, most of which are located in the intestine, was rethought. "Commensals" are an ecosystem containing one hundred trillion microorganisms performing various functions, including the synthesis of vitamin K and the biochemical transformations of some nutrients. The intestinal microflora also makes it possible to extract energy from indigestible food elements (fiber). There is an opinion that the intestinal microbiota contributes to the development of obesity, due to its active participation in the accumulation of food energy and biocontrol of energy balance. Microbial "commensals", in addition to satisfying their own needs, contribute to obtaining calories from consumed foods and accumulate this energy in fat depots, i.e. form adipose tissue [6]. Experiments conducted in England in 2015 showed that obesity is not the root cause, but a consequence of dysbiosis of the digestive tract. The intestines of microbial-free mice were seeded with the microflora of obese mice and the animals gained weight faster than in the case of bacterial contamination from mice with normal weight [7]. It has been repeatedly revealed that obesity is accompanied by an increase in the number of pathogenic bacteria of the Firmicutes type and the Enterobacteriaceae family (Esherichiacoli), with a simultaneous decrease in representatives of the normal intestinal microflora Bacteroidetes (Bacteroides, Prevotella), Bifidobacterium and Lactobacillus. It was also found that eating foods saturated with fats leads to inflammatory changes in the intestinal mucosa and an indirect reduction in the number of lactobacilli, which leads to the development of obesity, type 2 diabetes mellitus. High-fat food creates conditions for the growth of bacterial strains producing pro-inflammatory cytokines in Peyer's plaques and suppresses the growth of Lactobacillus reuteri strains synthesizing anti-inflammatory substances [8].

Biomechanisms of the involvement of intestinal microflora in the development and progression of atherogenic dyslipidemia are realized in two ways. With the rapid transport of intestinal bacteria metabolites into the blood, low-density lipoproteins interact chemically with the main component of the bacterial cell wall - lipopolysaccharide, which leads to a change in lipoprotein metabolism. Lipopolysaccharide damages enodothelial cells, activates the synthesis and release of superoxide anion, oxidation of low-density lipoproteins that promote the release of proinflammatory cytokines (IL-1,6, TNF-alpha) from macrophages. The latter transform into

foam cells, cumulate in the intima of the vessels and then form into an atherosclerotic plaque. The second mechanism is the production of trimethylamine–N-oxide during the exchange of phosphatidylcholine coming from food (meat, eggs, offal). In the intestine, trimethylamine-N-oxide is transformed into a variety of metabolites, such as phosphocholine, choline and glycerophosphocholine, which increase the ability of macrophages to accumulate cholesterol and form foam cells, i.e. provoke changes associated with atherosclerosis. In addition, it was found that lacto- and bifidobacteria are able to secrete deconjugases, which, with bile acid salts, transform taurine- and glycine-containing amides of bile acids into insoluble precipitates. The latter bind to colon cholesterol and remove it from the feces, reduce the excretion of cholesterol from liver cells and affect the number of bioresetors in blood cells for low-density lipoproteins [9]. It follows from the above that the development and progression of dyslipidemia should be considered in direct connection with the intestinal microbiota.

This work is devoted to the diagnosis of disorders of intestinal microbiocenosis and lipid metabolism in exogenous constitutional obesity in adolescents as risk factors for the formation of cardiovascular disorders.

**The purpose of study:**

1. To assess the state of lipid metabolism based on laboratory research methods.
2. To analyze the microbial composition of the colon microflora in overweight and obese adolescents.
3. To study correlations between body mass index, severity of intestinal dysbiotic changes and severity of lipid metabolism disorders.

## MATERIALS AND METHODS

The study was conducted on the basis of a teenage dispensary and a children's diagnostic center in Tashkent. Clinical examination was conducted in 60 children. The average age of the examined children was 15.05±0.42 years, including 30 girls and 30 boys. The subjects were divided into 3 groups: the main group consisted of 30 children with primary constitutionally exogenous form of obesity of the first degree, the comparison group consisted of 20 overweight children and the control group included 10 children with normal weight who did not have a burdened history of lipid metabolism disorders and dysbiosis of the digestive tract. During the study, anthropometric parameters were determined: height and body weight, body mass index (body mass index = weight/height 2), the values of which were compared with tabular values for a given age, waist and hip circumference in cm, as well as their ratio were determined [10].

The state of the lipid spectrum of blood serum was assessed by the traditional results of the concentration of total cholesterol (mmol/L) and its forms: low-density lipoproteins, high-density triglycerides (determined in blood serum on a biochemical analyzer "Minray BS-200" (China) using commercial kits "Human", Germany), and also determined the coefficient of atherogenicity. To assess the normal parameters of the lipidogram, age and sex norms were used [4].

Bacteriological examination of feces and analysis of the qualitative and quantitative composition of the intestinal microbiota were carried out according to the protocol of

management of patients - "Dysbiosis", nutrient media and test systems Himedia (India) were used for authentication and seeding of microorganisms.

The study was conducted in compliance with the ethical principles set forth by the Helsinki Declaration of the World Medical Association (World Medical Association Declaration of Helsinki, 1964, 2013), and was performed with the informed consent of parents and patients. Statistical data processing was carried out using the programs "MS Excel for Windows 7". Statistical significance was determined using correlation analysis (Pearson's method), at $p<0.05$ the differences were considered statistically significant.

## RESULTS AND DISCUSSION

The average values of anthropometric indicators were: body mass index (kg/m2) in obese adolescents - 31.74±0.73, overweight – 27.52±0.96, in children with normal weight 22.51±1.32; waist circumference (cm) in obese adolescents - 98.32±1.92, overweight – 90.52±1.86, in children with normal weight - 67.69 ± 2.77; hip circumference (cm) in obese adolescents - 106.59 ± 2.63, overweight – 100.39 ± 1.83, in children with normal weight - 90.69 ± 3.39; the ratio of waist circumference to hip circumference in obese adolescents is 0.88± 0.02, overweight - 0.82± 0.03, in children with normal weight – 0.78± 0.03.

To study lipid metabolism, we evaluated the indicators of total cholesterol, triglycerides, high-density and low-density lipoproteins of blood serum, and also assessed the atherogenicity coefficient in 60 examined children. The results of the study of the lipid spectrum in the analyzed groups are presented in Table 1.

**Table 1**

**Blood serum lipidogram status in obese, overweight and normal weight adolescents (M±m)**

| **Parameters** | **Main group n=30** | **Comparison group n=20** | **Control group n=10** | **P1-P2-P3** |
|---|---|---|---|---|
| Cholesterol, mmol/l | 4,95±0,86 | 4,5±0,85 | 4,02±1,08 | |
| Triglycerides, mmol/l | 2,05±0,17 | 1,82±0,44 | 0,92±0,48 | <0,05 |
| High-density lipoproteins | 0,98±0,02 | 1,10±0,06 | 1,21±0,08 | <0,010 |
| Low-density lipoproteins | 3,22±0,17 | 2,9±0,53 | 2,39±0,32 | <0,05 |
| Atherogenicity coefficient | 3,30±0,20 | 2,6±0,32 | 2,40±0,36 | <0,05 |

Note: P1-P2-P3 the reliability of differences between the values of indicators in the studied groups of children

It was found that there were no significant differences in the concentration of total cholesterol among the examined children. However, changes in the cholesterol content in the composition of lipoproteins were detected in overweight and obese children. In overweight

children (comparison group), the average values of serum lipoproteins were within optimal values, but the levels of high-density lipoproteins were lower, and low-density lipoproteins were higher, relative to the control parameters. It should be noted that the content of high-density lipoproteins decreased to 0.98±0.02 in obese children (P<0.010). It is known that low levels of high-density lipoproteins are associated with a high risk of atherosclerosis and coronary heart disease, which is associated with impaired production of their chylomicrons and very low-density lipoproteins in the intestine [14]. An unfavorable change in the composition of serum lipids in obese adolescents was a tendency to increase the fraction of low-density lipoproteins, which is rich in cholesterol and triglycerides and represents the most atherogenic class of lipoproteins (Fig.1).

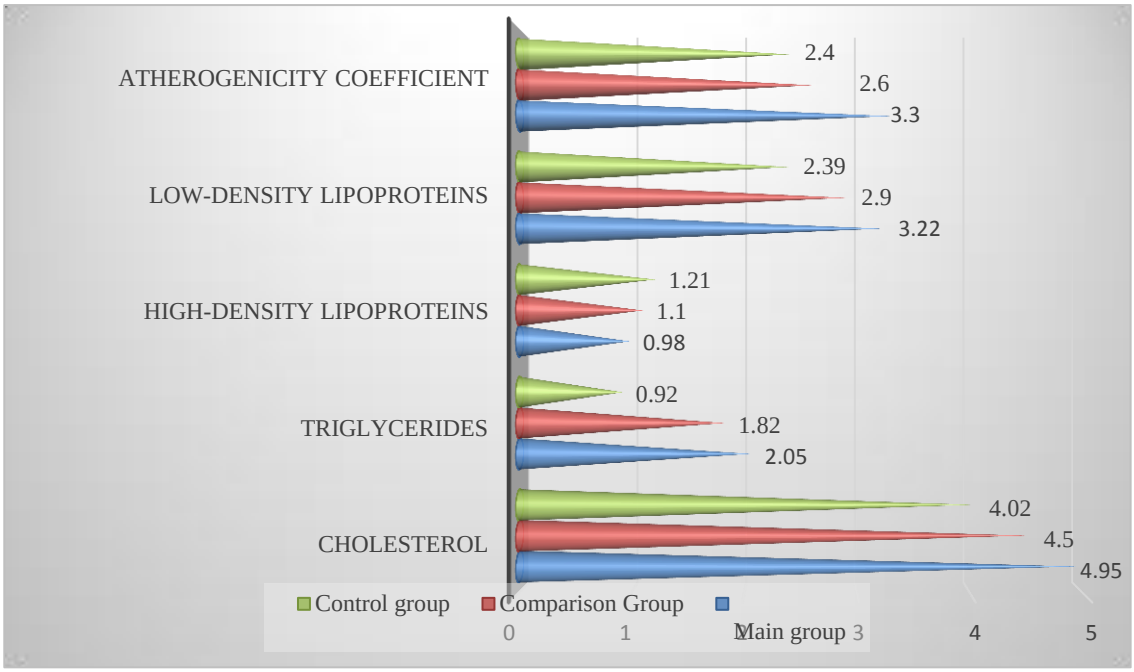


**Figure 1. The state of the serum lipidogram in adolescents with obesity, overweight and normal weight.**

Such a state of the lipid spectrum in obese adolescents against the background of a decrease in the level of high-density lipoproteins and an increase in the values of low-density lipoproteins led to a significant increase in the atherogenicity coefficient to 3.30±0.20 versus 2.40±0.36 in children in the control group (P<0.05).

A bacteriological study of the intestinal microbiocenosis showed that more than 80% of the examined children had abnormalities in its composition. However, the severity of dysbiosis in each group had its own characteristics: thus, in adolescents with normal and overweight, disorders characteristic of the first degree of intestinal dysbiosis prevailed in the form of a deficiency of indigenous flora (bifidobacteria and normal Escherichia coli). Deficiency of bifidobacteria and a decrease in their population density were observed in 13.6% of normal-weight adolescents, in 75.6% of overweight adolescents and in 27.6% of obese adolescents (respectively, up to 9.9 ± 1.05 CFU/g (colony-forming units per gram of faeces); 9.7 ± 1.02 CFU/g; 9.5 ± 1.02 CFU/g; ); deficiency of normal E. coli – in 21.8% of overweight adolescents and in 21.6% of obese adolescents. The second degree of intestinal dysbiosis was registered in 49.5% of obese adolescents, in which, in addition to a decrease in the content of bifidobacteria to

9.0 ± 1.02 CFU/g, an increased content of opportunistic microorganisms to 10.5-10.7 CFU/g and their associations were found. Intestinal eubiosis (microecological norm) was observed in the main and comparative groups with approximately the same frequency (in 22.9% and 24.4% of cases, respectively), and in the control group in 86.4% of cases. The distribution of the degree of dysbiosis in the analyzed groups is shown in Figure 2.

It is known that the main indicator of dysbiosis, which must be corrected first of all, is the growth of conditionally pathogenic microflora [2]. In this regard, we have studied the qualitative and quantitative composition of conditionally pathogenic microorganisms of the Enterobacteriaceae family that persist in the children we examined.

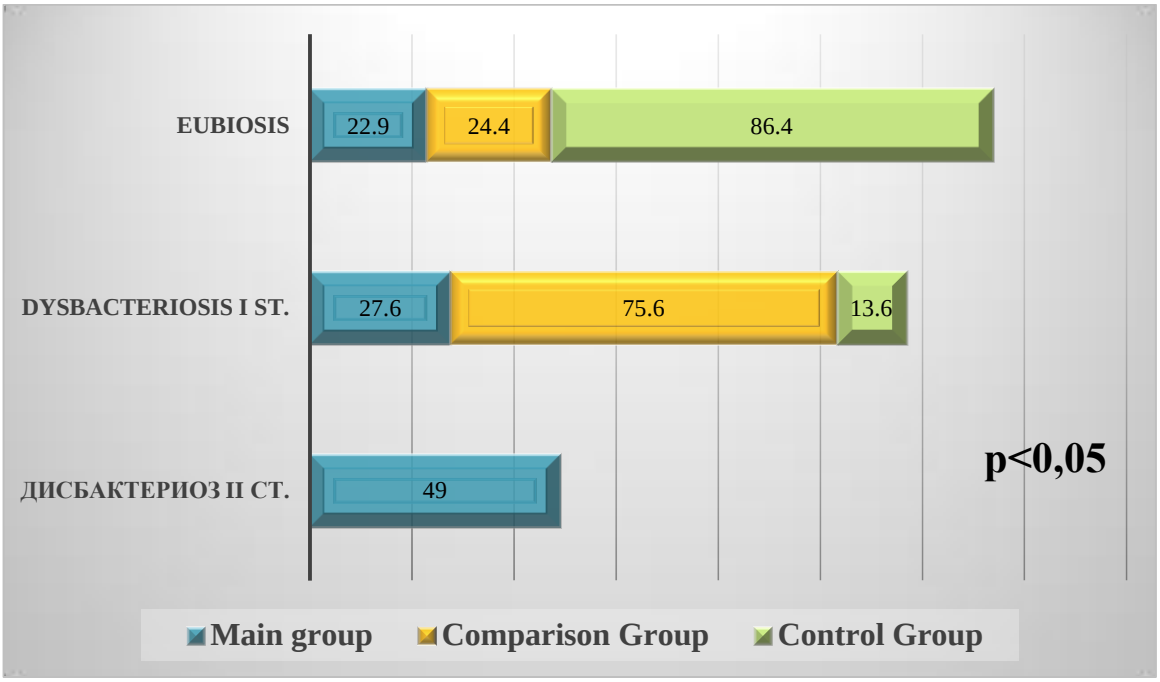


**Figure 2. Distribution of the degree of dysbiosis in the analyzed groups.**

It was found out that conditionally pathogenic bacteria of the Enterobacteriaceae family were not seeded in a group of children with normal weight, in a lower concentration they were seeded in overweight adolescents. In the group of obese adolescents, there was an increase in the concentration of opportunistic bacteria of this family. Such species as Klebsiella spp., Citrobacter spp., were distinguished in obese adolescents more than twice as often as in overweight and normal-weight adolescents, Enterobacterspp. – 10% more often ($p< 0.05$). The average content of these microorganisms was also higher than the general physiological standards (from 4.2 to 6.0 lg CFU/g). The species structure of opportunistic bacteria of the Enterobacteriaceae family in adolescents in the study groups is shown in Figure 3.

It was also found that in adolescents with obesity, two- and three-component associations of opportunistic bacteria were registered in 58.8% of cases, which is an indicator of pronounced disorders in the formation of intestinal microbiocenosis. With such dysbiotic disorders, the functional activity of the intestinal microflora changes, which ultimately leads to violations of lipid and carbohydrate metabolism, as well as the development of atherogenic dyslipidemia and associated cardiovascular complications.

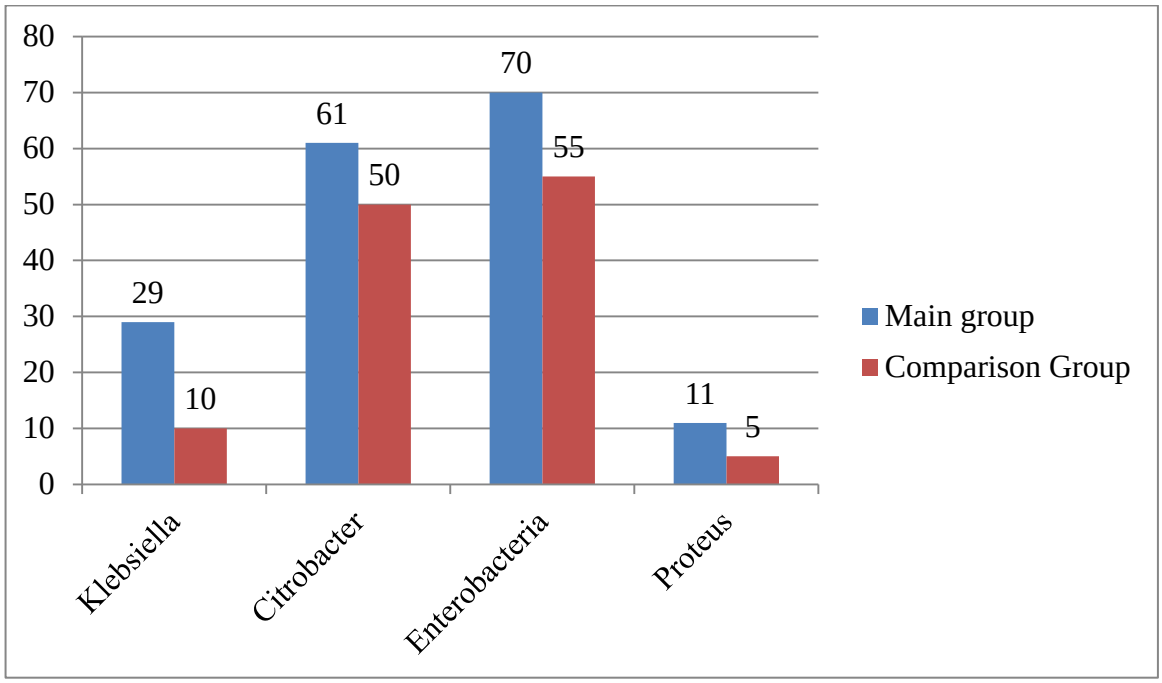


**Figure 3. Species structure of opportunistic bacteria of the Enterobacteriaceae family in adolescents in the study groups.**

We have established direct correlations between body mass index, degree of dyslipidemia and severity of dysbiosis ($r=0.74$, $p<0.01$, and $r=0.54$, $p<0.05$, respectively). It should be noted that there is an inverse correlation between high-density lipoproteins with body mass index and the degree of intestinal microbiocenosis disorders ($r=-0.81$, $p<0.001$, and $r=-0.72$, $p<0.05$, respectively).

## CONCLUSION

1. Adolescents with overweight and exogenous constitutional obesity of the first degree have a proatherogenic character of changes in the serum lipidogram, which is aggravated with an increase in the degree of overweight.
2. Adolescents with exogenous constitutional obesity of the first degree are significantly more likely to have disorders of intestinal microbiocenosis compared to adolescents with overweight and normal weight.
3. The established direct correlations between body mass index, degree of dyslipidemia and severity of dysbiosis in overweight and obese adolescents form the basis for further study of the role of intestinal microflora in the mechanisms of obesity, atherogenic dyslipidemia and associated cardiovascular complications, and also indicate the possibility of preventive measures and therapy of these pathologies by correcting microbiocenosis digestive tract.

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