Modern Pediatrics. Ukraine. 2022; 5(125):10-17. DOI:10.15574/SP.2022.125.10

THE STATE OF THE INTESTINAL MICROBIOTA AS ONE OF THE PATHOGENETIC FACTORS IN THE DEVELOPMENT OF METABOLIC DISORDERS AND A THERAPEUTIC TARGET IN CHILDREN WITH OBESITY (LITERATURE REVIEW, OWN RESEARCH)

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The high prevalence of obesity among children and adolescents at the current stage is an important medical and social problem in paediatric practice. The presence of obesity in children is a significant risk factor for the development of metabolic disorders in the body. Pathogenetic mechanisms of the development of metabolic disorders in obese people remain to be fully understood, but the presence of a chronic inflammatory process in the body is considered to be one of the key factors in their formation. For today, many scientists are studying the state of the intestinal microbiota as one of the likely triggers of chronic inflammation and the development of metabolic changes in obese people.

Purpose – to summarize the literature data and the results of our own research on the effectiveness of the therapeutic effect of probiotic cultures on the main metabolic indicators in children with obesity.

Results and conclusions. At the current stage, scientific researches on the study the role of intestinal microbiota both as a marker of metabolic changes in the body of obese people and as a potential therapeutic target are continuing. According to systematic reviews, the level of pro-inflammatory cytokines in the body of obese people is significantly increased and pronounced dysbiotic disturbances are noted. Addition of probiotic cultures to therapy has been reported by various researchers to improve basic metabolic parameters and reduce inflammatory markers in obese people. As a result of our own research, improvements in carbohydrate and lipid metabolism indicators, the structural and functional state of the liver, and the general condition of obese children who took a synbiotic drug in complex treatment were revealed.

The research was carried out in accordance with the principles of the Helsinki Declaration. The study protocol was approved by the Local Ethics Committee of

all participating institutions. The informed consent of the patient was obtained for conducting the studies. No conflict of interests was declared by the authors.

Keywords: intestinal microbiota, obesity, metabolic syndrome, comorbidity, children.

INTRODUCTION

In recent decades, the world's population has undergone significant changes in health, eating behavior and lifestyle. These changes consist of an increase in the consumption of high-calorie foods and sugary drinks, as well as a significant decrease in the level of physical activity. As a result, there is a constant increase in the prevalence of overweight and obesity, which has reached the scale of a non-infectious pandemic. At the current stage, childhood obesity is a serious problem in the United States, which threatens the health of children and adolescents. According to data from the National Center for Health Statistics (NCHS) regarding the study of the problem of obesity among patients aged 2 to 19 years during 2017–2020, the prevalence of childhood obesity reaches 19.7% — about 14.7 million children and adolescents [33]. The problem of increasing the number of people with excess body weight and obesity is relevant for European countries. The study results, published by a number of authors in 2020, have shown a negative trend towards an increase in the number of obese people among 18 European countries, with the peak growth of this disease predicted for the period 2030–2052 [16].

At the current stage, obesity is no longer considered as just an endocrinological pathology, without timely correction, it is capable of forming pronounced disorders of carbohydrate and lipid metabolism – a metabolic symptom complex, which is defined as metabolic syndrome (MS) and usually develops in children with the "metabolically unhealthy obese" phenotype. The key features of this obesity phenotype are the predominant deposition of excess fat in the abdominal area, the presence of signs of steatosis of the liver and pancreas, disorder of the physiological secretion of insulin and an insufficient level of sensitivity to its action, dyslipidemia, increased levels of C-reactive protein and pro-inflammatory cytokines in the child's body. Despite the fact that at this stage there are several different definitions of MS, in particular in pediatric practice, in almost all modern definitions, the main verifying criteria include abdominal obesity, reduced high-density lipoprotein cholesterol (HDL), hypertension, and elevated plasma triglyceride levels in patients with insulin resistance as a potential unifying pathogenic factor [36]. It should be noted that the urgency of the problem of MS is not only related to its rapid spread throughout the world both in adults and children, but also to the fact that the presence of these symptoms can be a probable prognostic marker for type 2 diabetes mellitus (DM), cardiovascular diseases and other pathologies in patients

with obesity [3,12,35].

The pathophysiological mechanisms of the formation of the metabolic symptom complex in the child's body remain completely unknown and insufficiently studied. Over the past decade, the development of high-performance medical technologies has enabled researchers to determine the composition and functional properties of the intestinal microbiota and its relationship with the development of various pathologies in the human body [39]. Today, it is known and scientifically proven that the microbiota plays an important role in functional diseases of the gastrointestinal tract (GI), obesity, diabetes, and disorders of lipid metabolism in the body. Increasingly, in recent years, scientific works have shown a potential connection between changes in the composition of the intestinal microbiota and the development of obesity [37].

Purpose – to summarize the literature data and the results of our own research on the effectiveness of the therapeutic effect of probiotic cultures on the main metabolic indicators in children with obesity.

Materials and methods

In order to summarize literature data on the relationship between the state of chronic inflammation and the presence of metabolic disorders in the body, as well as the influence of the intestinal microbiome on the main metabolic parameters in obese individuals, a qualitative systematic review of randomized clinical trials was carried out using the electronic databases "PubMed", "UpToDate ", "Web of Science" and "MedLine". The actual study was performed on the basis of the endocrinology department of the CI "Children's City Clinical Hospital of the Poltava City Council" in Poltava. The study involved 40 children aged 10 to 17 years (18 girls and 22 boys), who made up the main group and had the diagnosed exogenous constitutional obesity in accordance with international recommendations and the current protocol for the diagnosis and treatment of endocrine diseases in children. The control group, formed for the purpose of initial comparison of the main metabolic indicators, consisted of 10 children with normal body weight of the appropriate age and gender. Exclusion criteria were children under 10 years of age (due to difficulties with verification of MS in this category of patients); secondary obesity associated with endocrinopathies and genetic syndromes; neoplasm and severe somatic condition; refusal of patients or their parents to participate in the study. The study was carried out in accordance with the standards of bioethics under the principles of the Declaration of Helsinki, and the informed consent of the patients was obtained. All children underwent a comprehensive examination, which included the anamnestic data, anthropometry and general clinical analyses. In order to detect carbohydrate metabolism disorder as one of the main

criteria of MS, the concentrations of blood glucose and immunoreactive insulin (IRI) were determined for all patients on an empty stomach with the calculation of HOMA index, which is an indicator of insulin resistance in the body according to the formula:

$$\text{HOMA-IR} = \text{insulin } (\mu U/ml) \times \text{glucose (mmol/l)} / 22.5$$

The state of lipid metabolism was assessed by the main parameters of the lipid transport system of the blood serum. The study included the traditional determination of the concentration of total cholesterol (TC), triglycerides (TG), HDL, low-density lipoprotein (LDL), and calculation of the atherogenic index of plasma (AIP). In order to obtain information about the structural and functional state of the liver, all patients underwent ultrasound examination of the liver and determination of biochemical parameters of the liver. Survey and examination of patients was carried out with assessment of the main clinical syndromes. Each clinical sign was evaluated in points according to the following scale: 1 — presence of a symptom; 0 — absence. Excess body weight / obesity is calculated by the percentage of excess weight from the required weight using percentile tables according to age and gender.

Taking into account the purpose of the study, all children with obesity, after completing the examination against the background of protocol treatment of exogenous constitutional obesity and compliance with dietary recommendations, received the synbiotic complex "Santigen®" (a food supplement manufactured by Ananta Medicare. The product is not a medicine), containing strains of the following bacteria *Lactobacillus sporogenes* (50×10^6 CFU), *Streptococcus faecalis* (30×10^6 CFU), *Clostridium butyricum* (2×10^6 CFU), *Bacillus mesentericus (*1×10^6 CFU). They have a wide range of pre- and probiotic properties. Also, they are capable of activating specific and non-specific immunity and provide antagonistic activity against pathogenic and opportunistic bacteria. An important characteristic of the selected synbiotic complex is the presence in its composition of a strain of *Clostridium butyricum* capable of producing butyric acid (butyrate) — one of the main short-chain fatty acids (SCFA), which, according to literature, have pronounced anti-inflammatory functions and are able to affect the permeability of the intestinal wall. This synbiotic complex also includes strains of *Bacillus mesentericus* and *Lactobacillus sporogenes*, the therapeutic effects of which consist in the ability to restore the ecological balance of intestinal microflora, stimulate immunity and normalize digestive processes. Gram-positive commensal bacteria *Streptococcus faecalis* included in the synbiotic complex "Santigen®" have pronounced immunomodulatory properties, and increase the chemotactic, phagocytic and lytic properties of macrophages. According to the research design, the course of using the synbiotic complex "Santigen®" lasted 4 weeks, and the dosage regime

was 1 to 2 sachets twice a day (depending on the age of the child).

The statistical analysis of the obtained results was carried out using statistics applications, such as "SPSS 17.0", "Excel for Windows" and "STATISTICA". The primary processing of the obtained results was performed using the methods of variational statistics. To compare the statistical populations of the examined groups of children, the two-sided Student's t-test was used under the condition of a normal distribution, and in the case of a non-normal distribution, the non-parametric Mann-Whitney U test was used. Fisher's exact test was used to establish the presence of a statistically significant difference between the frequency of occurrence of the characteristic.

Results and discussion

According to some authors, the trigger for the progression of comorbid pathology of the digestive system in MS is inflammation, which is closely related to the development of steatohepatitis, steatopancreatitis, choledocholithiasis, intestinal endotoxemia, concomitant diseases and their complications, and mainly obesity, which is an obligatory condition for MS. In recent years, more and more scientific works have shown that the level of pro-inflammatory cytokines, which have a negative effect on the metabolism of peripheral tissues, is significantly increased in the blood circulation of people with MS [21,32]. In recent decades, it has also been established that chronic, so-called "metabolic" inflammation, present in the body during excess body weight and obesity, directly leads to the development of insulin resistance and the progression of type 2 diabetes mellitus. Also, the results of the study, which show a higher susceptibility to respiratory viral infections, as well as the development of severe asthma in people with insulin resistance compared to people sensitive to the action of insulin are interesting. In one of the works, the relationship between the severity of the disease and the state of the intestinal microbiota was directly studied [23]. At the current stage, the attention of scientists is drawn to the development and study of pharmacological treatment methods aimed at reducing inflammation in metabolic diseases and positively affecting glucose tolerance in both animals and humans. Such treatment strategies include interleukin (IL) 1 receptor blockade [18], IL 1 and TNF antagonism [5,7], as well as inhibition of NF-κB proinflammatory pathway [9]. It should be noted that, according to the literature, several years ago the concept of constant activation of nuclear factor κB was proposed as one of the key links in the formation of the pathological circle "insulin resistance — inflammation — atherosclerosis" [30].

Today, more and more scientific works clearly prove the relationship between obesity and increased production of proinflammatory mediators, as well as their impact on metabolic processes in the body. In 1993, a study that revealed a significant increase in the expression of TNF-alpha in adipose tissue and its

direct role in the development of insulin resistance associated with obesity was published [15]. In 2007, another study, published in the journal "Diabetologia", also confirmed the relationship between reduced sensitivity to insulin and increased levels of TNF-alpha in blood plasma [26]. Adipose tissue macrophages are known to be the main source of the well-studied pro-inflammatory cytokine IL-6. Animal studies, conducted in different years, have shown that chronically elevated levels of IL-6 reduce the sensitivity of the liver to the action of insulin *in vitro*, thereby provoking the development of insulin resistance and indirectly reducing the sensitivity to insulin in muscle tissue as well [25,38].

As you know, inflammation is a biological reaction of the body's immune system in response to the impact of various pathogens, damaged tissues or the action of toxic compounds. Currently, lipopolysaccharides (LPS) of the bacterial wall of gram-negative bacteria are considered as one of the potential trigger factors for the development of the inflammatory reaction, the number of which, as established in the course of research, probably increases in the bloodstream of people with type 2 diabetes mellitus [11]. Today, there is a hypothesis that substantiates the excessive entry of LPS into the systemic bloodstream as a result of pathological changes in the permeability of the intestinal wall [10], one of the reasons of which is undoubtedly changes in the microbiotic composition of the intestine. Research, conducted over the past decades, also revealed a relationship between the increased concentration of bacterial lipopolysaccharides and some aspects of the metabolic syndrome in the human population, in particular, with the development of dyslipidemia and insulin resistance against the background of obesity and chronic inflammation in the body [19].

Today, the intestinal microbiome is considered the main metabolic internal organ, consisting of more than a thousand microorganisms and containing a second genome (called the metagenome), which is hundreds of times larger than the human genome itself. That is why the intestinal microbiota is of great importance for human health, and plays a key role in digestion processes, producing metabolites that can affect human life, and has a direct impact on the state of the immune system of the human body. Therefore, the immunomodulatory properties of the intestinal microbiota are of particular interest, taking into account its influence on the regulation of chronic inflammation processes in the body, which, according to the results of scientific research, is observed in people with obesity and type 2 diabetes mellitus [20,34]. It should be noted that, according to literature, the question of the relationship between the occurrence of chronic inflammation and the presence of metabolic disorders in obesity and type 2 diabetes mellitus has been studied by scientists for more than 25 years. At the same time, scientific observations to identify the causal relationship between the state of the intestinal microbiota and existing

metabolic disorders in the human body is a relatively new scientific direction that is currently only developing and requires further research.

Modulation of intestinal microbiota is currently considered a new potential tool for improving metabolic processes associated with obesity and type 2 diabetes mellitus. In recent years, more and more studies have shown the relationship between the state of the microbiota and metabolic disorders in the body, while the main attention is paid to the change in the quantitative and qualitative composition in the structure of the human microbiome. According to the results of research, an increase in the number of bacteria of *Firmicutes* (in particular, *Staphylococcaceae*, *Lactobacillaceae*, *Ruminococcaceae*, *Lachnospiraceae* and *Clostridiaceae*) and, accordingly, a decrease in *Bacteroidetes* (*Bacteroidaceae*, *Porphyromonadaceae* and *Rikenellaceae*), which was observed both in experiments on animals and studies in the human population [37] in obese individuals. A recent study has shown that people with high Prevotella concentration are more susceptible to weight loss compared to people with *Bacteroides predominance* regardless of the nature of the diet [14]. One of the latest hypotheses linking the state of the intestinal microbiome with the development of metabolic disorders and chronic inflammation is the production of intestinal metabolites that enter the systemic bloodstream and exert various effects on the host's body. These metabolites are associated with specific intestinal microbiota. Among the most well-known intestinal metabolites are SCFAs — acetate, butyrate, and propionate, which are formed by intestinal microbiota as a result of fermentation of indigestible food components, such as complex carbohydrates (fiber) [4]. In addition, as shown in some clinical studies, the consumption of a sufficient amount of fiber contributes to the expansion of the class of microorganisms capable of producing SCFAs, and also improves glucose tolerance in patients with type 2 diabetes mellitus [40]. Several studies conducted in overweight and obese adult populations have shown that adding inulin (a high-fermentable fiber) to the diet not only improves endogenous insulin sensitivity, but also reduces IL-8 [6], indicating a beneficial effect of a fiber-enriched diet on inflammatory parameters.

One of the studies on the state of the microbiota in type 2 diabetes has shown that a reduced number of anti-inflammatory bacteria, in particular, such as *F. prausnitzii*, is associated with a disturbance of the production of SCFA by the intestinal microbiota [27]. It is known that SCFAs, which are the result of microbial degradation of dietary fibers, have a beneficial effect on the host's metabolism. The researchers hypothesized that one of the pathogenetic mechanisms of the development of type 2 diabetes mellitus may be both reduced production and reduced absorption of SCFAs, in particular butyrate, which has a high anti-inflammatory activity [31]. However, there is currently no solid

evidence base for this concept. At the same time, another recent study also revealed a causal relationship between increased butyrate production and increased insulin sensitivity in individuals with metabolic disorders in the form of insulin resistance [29].

At the current stage, numerous studies, dedicated to the study of individual strains of probiotic cultures that have pronounced immunomodulatory and metabolic properties, are being conducted. Today, there are data proving that *Lactobacillus, Streptococcus*, and *Bifidobacterium* bacteria can exert a protective effect on the development of metabolic diseases in the human population [13]. Since 1963, many scientific publications have appeared on the widespread use of gram-positive anaerobic bacilli *Clostridium butyricum* in patients with diseases of the immune system in the Asian population (Japan, Korea and China). There are also studies showing that probiotics of the strain *Clostridium butyricum* (bacteria that produce butyrate) reduced the accumulation of lipid droplets in hepatocytes in fatty liver degeneration, and reduced insulin resistance and the level of lipids and endotoxins in liver cells [2]. According to research results, it has been proven that the strain of *Clostridium butyricum*, which actively synthesize butyrate, has a pronounced therapeutic effect on the initial symptoms of obesity caused by a high-fat diet, and has a therapeutic effect on the state of insulin resistance in experimental animal models [22].

Similar studies were conducted in different years also in the children's population and showed positive results. In a clinical study involving obese children and adolescents, a symbiotic complex consisting of several strains of probiotics was used to significantly reduce body mass index (BMI) compared to a control group. In addition, there were signs of reduced inflammation (decrease in IL-6 and TNF levels), improved tissue sensitivity to insulin, and a cardioprotective effect by correcting blood lipid profile [17,28]. A group of Japanese scientists conducted an open-label prospective study to examine the effects of beverages containing *Lactobacillus casei Shirota* (LcS) strain on the health status of obese children. After 6 months of using dairy products containing this probiotic strain, a significant decrease in body weight and an increase in the anti-atherogenic fraction of lipoproteins were observed in obese children compared to a group of patients who received only dietary interventions and dosed physical activity [24]. According to the results of a triple-blind clinical study, published by a group of authors in 2017, the use of a multi-probiotic strain in the complex therapy of obesity in children made it possible not only to reliably reduce BMI, but also to improve the lipid spectrum of the blood and the structural and functional state of the liver [8]. It is important that in almost all cases, better results were noted against the background of the use of multi-probiotic strains of cultures.

Our own research consisted of several stages. The first stage was a thorough

collection of complaints from obese children and a comparison of these complaints before and after the course of treatment. After all, it is known that obesity is usually perceived by both patients and their parents as more of an aesthetic rather than a medical problem. In addition, this disease has no specific clinical symptoms. The next important stage of our work was the analysis of laboratory indicators that indicate a disorder of carbohydrate and lipid metabolism as the main criteria of the formed MS. The final separate stage of our research was the study of the structural and functional state of the liver in children with obesity, because it is the liver that is one of the internal organs that primarily reacts to metabolic disorders in the body, and is also directly involved in the formation of the metabolic symptom complex.

Evaluating the clinical symptoms of the disease, it should be noted that the complaints of all children were practically the same, had no specificity and were more related to changes caused by concomitant pathology of the gastrointestinal tract and cardiovascular system. Most often, obese children complained of headaches (36% of girls and almost 60% of boys), against the background of which an increase in blood pressure was quite often observed. 12 (30%) adolescent children (mostly boys) were under the supervision of a paediatric cardiologist with a diagnosis of "Arterial hypertension" and received appropriate protocol therapy. Almost every second obese child had complaints of increased fatigue, weakness, sweating and disorders of memory and attention, which created certain difficulties during school studies, and more than half of the examined children had complaints of increased appetite, which was quite difficult to control. Clinical symptoms from the gastrointestinal tract in the examined children were no less rare. Patients of the main group most often had complaints that are the symptoms of dyspeptic syndrome, in particular, nausea, a feeling of heaviness and fullness after eating, heartburn, belching air and bad breath, which are the most frequent symptoms of gastroesophageal reflux disease as one of the comorbid pathologies in obese children. It should be noted that the vast majority of children in the main group had complaints of constant flatulence (80% of patients), which was often accompanied by acute cramp-like abdominal pain, and frequent constipation (60% of children), which could be explained both by poor nutrition and the syndrome of chronic mesenteric ischemia, which is also characteristic of children with severe obesity, especially of the visceral type, and can certainly be a symptom of existing intestinal dysbiosis.

Table 1

Dynamics of the main clinical symptoms in children with obesity during treatment

Symptoms	Before treatment abs. (%)	After treatment abs. (%)	χ^2 , df=1	p
Astheno-vegetative syndrome				
Fatigue	28 (70)	16 (40)	6,11	0,013
Weakness	22 (55)	8 (20)	9,01	0,003
Memory and attention disorders	16 (40)	1 (28)	0,89	0,344
Pain syndrome				
Headache	28 (70)	16 (40)	6,11	0,013
Abdominal pain	23 (58)	8 (20)	10,32	0,001
Dyspeptic syndrome				
Increased appetite	34 (85)	16 (40)	8,23	0,004
Nausea	16 (40)	7 (18)	2,92	0,088
Flatulence	32 (80)	12 (30)	1,32	0,001
Tendency to constipation	24 (60)	9 (23)	10,11	0,001
Feeling of heaviness and fullness after eating	18 (45)	7 (18)	5,82	0,016

After the treatment, a pronounced regression of clinical symptoms was observed (Table 1). One of the most important indicators of positive dynamics was the improvement of children's health, which was expressed in a significant decrease in complaints such as pronounced weakness and fatigue ($p<0.05$). Complaints of headache and increased blood pressure were still observed in 16 (40%) of the examined children, but at the beginning of therapy more than half of the children with obesity were concerned. But the most pronounced positive changes in patients of the main group were observed in the gastrointestinal tract. In particular, there was a tendency to decrease of a subjective sensation as nausea, mainly after eating, and a significant decrease in the frequency of such symptoms as a feeling of heaviness and fullness in the epigastrium, as well as abdominal pain ($p<0.01$). Among other dyspeptic symptoms, which significantly decreased against the background of treatment with the addition of a synbiotic complex, the patients separately noted flatulence and a tendency to constipation, which during the first survey bothered a large proportion of obese patients — 80% and 60% of children, respectively. It should be noted that the tendency to normalize the frequency of bowel movements, and, accordingly, the reduction of abdominal pain and flatulence, which are frequent symptoms of constipation in childhood, were noted by the majority of obese patients, while they did not receive any laxatives in therapy.

During the study of the blood lipid transport system in the examined children, a fairly high frequency of disorders of almost all the main indicators of lipid metabolism in obese children was observed. Although the average indicators of total cholesterol were within the normal range, they were significantly different from similar indicators in children with normal body weight (Table 2). It should be noted that almost 20.5% of the patients in the main group had CKD levels

that exceeded the maximum permissible age norm (≥5.2 mmol/l). Also, patients in the main group had a high average TG level (the optimal level is up to 1.3 mmol/l) and an extremely high average level of LDL (2.9±0.11 mmol/l) with a simultaneous relative decrease in the main antiatherogenic fraction of HDL, which reflected the proatherogenic orientation of the blood lipid spectrum in children with diagnosed obesity. It should be noted separately that almost all indicators of the blood lipid spectrum in patients of the main group had significant negative differences compared to the control group ($p<0.05$). A comparison of the main parameters of the blood lipid profile in obese children before and after treatment revealed positive dynamics in the correction of dyslipidemia. In particular, there was a tendency to decrease or a significant decrease of almost all proatherogenic indicators of the blood lipid spectrum (Table 2). At the same time, it is important to significantly reduce the average TG index to the physiological norm and almost 1.5 times lower than the previous value of the coefficient of atherogenicity — 2.4 U versus 3.32 U at the beginning of the study, respectively ($p<0.05$).

Table 2

The main indicators of carbohydrate and lipid metabolism in examined children

Indicator	Main group		Comparison (control) group
	before treatment	after treatment	
TC, mmol/l	4.76±0.10#	4.53±0.087	4.34±0.13
TG, mmol/l	1.6±0.13*#	1.13±0.067	0.73±0.02
LDL, mmol/l	2.9±0.11#	2,64±0.09	1.9±0.07
HDL, mmol/l	1.18±0.57*#	1.34±0.04	1.47±0.03
AIP, units	3.32±0.22*#	2.4±0.13	1.6±0.09
Fasting glucose, mmol/l	4.66±0.15	4.34±0.09	4.25±0.18
IRI, μU/ml	16.9±1.55*#	12.2±0.89	10.05±0.83
HOMA-IR	3.84±0.41*#	2.35±0.19	1.9±0.10

Notes: * — the reliability of the difference in relation to indicators before and after treatment in children of the main group ($p<0.05$); # — the reliability of the difference relative to the indicators of the comparison group ($p<0.05$).

Monitoring of the state of carbohydrate metabolism has shown that fasting glucose is at the limit of normal in almost all subjects of the main group (82.5%). However, there were no significant differences with the control group, only 5 patients had an increase in fasting blood glucose levels above 5.6 mmol/l, and 2 children were diagnosed with type 2 diabetes. Somewhat different results were noted regarding the level of immunoreactive insulin (IRI), the increased

content of which is called hyperinsulinemia (according to the recommendations of the American Heart Association, the IRI level of 15–20 μU/ml is already considered borderline), as one of the typical symptoms of MS, was recorded in almost a quarter of the examined patients with diagnosed obesity — 9 (22.5%) children. Accordingly, compared to the control group, the average value of the HOMA index was almost twice as high in obese children (3.84 Units vs. 1.9 Units, $p<0.05$), which reflects the already formed state of insulin resistance and is a strong predictor of the development of type 2 diabetes in this category of patients in the future. Against the background of complex therapy and dietary interventions, a significant decrease in the levels of IRI and HOMA index was observed in the vast majority of children of the main group (Table 2).

It is known that the liver is directly involved in the formation of the metabolic symptom complex in children with obesity [1], which is why the next important stage of our research was the determination of the main indicators of the structural and functional state of the liver. Analysis of hepatogram indicators in children with obesity at the beginning of the study showed a significant increase in the average level of liver transaminases compared to patients with normal body weight (the average level of alanine aminotransferase (AlAt) was 42.4±3.8 U/l against 19.7±2.6 U/l, and the average level of aspartate aminotransferase was 47.9±4.8 U/l against 23.1±3.2 units/l, respectively, $p<0.05$). It should be noted that an increase in the level of ALT above the limit (recommended today's upper limit of normative values is 22 U/l for girls and 26 U/l for boys) was noted in almost a third of the examined patients — 14 (35%) children and required, according to modern international recommendations, immediate therapeutic interventions in order to prevent the development of metabolic liver pathology associated with obesity. At the same time, in all patients of the control group with normal body weight, the indicators of the level of liver transaminases were included in the recommended age norm. All other indicators of biochemical blood analysis in the examined patients of both groups were on the border of physiological values and had no significant differences ($p\geq0.05$). According to transabdominal sonography of the liver, almost 85% of patients in the main group showed heterogeneity of the liver structure, while almost a third (35%) of the examined showed signs of steatohepatosis, which were described in the form of diffuse small focal inhomogeneity of the liver tissue, hyperechogenicity of the parenchyma, and indistinct vascular pattern. Mild hepatomegaly was observed only in three patients of the main group. It should be noted that the symptoms of steatohepatosis were clearly correlated with an increase in the level of liver transaminases, especially ALT, and were noted mainly in patients with severe obesity with a BMI≥97 percentile. Analysis of the dynamics of parameters of biochemical blood analysis after the completion of the course of therapy and observation showed a tendency to decrease in liver transaminases, especially the level of AlAt (from 42.4±3.8 U/l to 34.2±2.57 U/l) even without the prescription of hepatoprotectors, which may indicate a fairly high effectiveness of dietary

interventions in combination with the correction of intestinal microbiota, provided compliance is observed between the doctor and the patient.

Conclusions

Summarizing the data of the literature review, it can be asserted that chronic inflammation in obese individuals can be as a significant trigger of disturbances in the main metabolic processes and lead to the development of such metabolically associated pathologies as type 2 diabetes mellitus, dyslipidemia, atherosclerosis, metabolically associated fatty liver disease, etc. In view of the results of the studies published today, there is more and more evidence that the intestinal microbiota plays an important and direct role in the formation of metabolic disorders, by modulating the inflammatory process, both by its own composition and by its metabolites. Many modern studies devoted to the analysis of the relationship between the intestinal microbiota and various infectious and non-infectious diseases, including obesity, determine the state of the microbiome not only as a probable marker of the development of a certain pathology, but also consider it as a therapeutic target. A predictor of the development of comorbid pathology of the gastrointestinal tract, cardiovascular system, musculoskeletal system and other organs and systems, which significantly worsens the quality of life of the child. The results of our research also indicate a fairly high incidence of disorders of the structural and functional state of the liver in children with obesity, which necessitates timely preventive therapy and constant monitoring of its condition. Therefore, the approach to the therapy of obesity and associated metabolic disorders in pediatric practice should be comprehensive, taking into account the correction of symptoms of concomitant pathology. According to the results of our own research, the prescription of a synbiotic drug in the complex therapy of obesity to improve the condition of the intestinal microflora not only eliminates dyspeptic symptoms from the gastrointestinal tract, which are quite frequent in this category of patients, but also to be able to additionally positively influence on the main indicators of the metabolic profile in the child's body, thereby preventing the development and further progression of pathologies associated with obesity.

Prospects for further studies

The study of the relationship between the state of the intestinal microbiome and the development of metabolically associated diseases in children at the current stage is a relatively new and rather controversial, but very promising scientific direction. However, it requires a number of further studies.

The authors declare that there is no conflict of interests.