International Journal of Endocrinology

Огляд літератури
/Literature Review/

UDC 613.2:613.25:616.34-008.87 DOI: https://doi.org/10.22141/2224-0721.16.8.2020.222886

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# Gut microbiota composition changes associated with obesity: new lights from metagenomic analysis

For citation: Mìžnarodnij endokrinologìčnij žurnal. 2020;16(8):654-661. doi: 10.22141/2224-0721.16.8.2020.222886

**Abstract.** *The worldwide prevalence of obesity more than doubled between 1980 and 2014. The most frequent cause, which leads to the obesity development, is an imbalance between energy intake and expenditure. In this complex process, genetic susceptibility, environmental and lifestyle factors are involved. The gut microbiota is a part of a complex network. Numerous studies have shown that the gut microbiota interacts with the host metabolism and plays an important role in various processes. The core gut microbial profile mainly embodies bacteria, belonging to the Gram-positive Firmicutes and the Gram-negative Bacteroidetes. An increase in gut Firmicutes/Bacteroidetes ratio is detected in obese patients and during high-fat diet consumption in human and animal studies. Strains belonging to the genera Lactobacillus and Bifidobacterium are commonly used as probiotics and are most studied for the treatment and prevention of obesity-associated disorders. Moreover, several potential bacterial candidates, such as Akkermansia muciniphila, Faecalibacterium prausnitzii, Prevotella copri, Roseburia or Ruminococcus, have been identified and novel mechanisms of action intervening their positive effects for obesity have been elucidated. Consequently, the gut microbiota is gaining significant research interest in relation to obesity and associated metabolic disorders in an attempt to better understand the etiology of obesity and potentially new methods of its prevention and treatment. However, traditional culture methods are very limited for identifying microbes. With the application of molecular biologic technologies, especially metagenomic next-generation sequencing, progress has been made in the study of the human intestinal microbiome.*

**Keywords:** *Akkermansia muciniphila; Faecalibacterium prausnitzii; gut microbiota; insulin resistance; metagenomics; obesity; Roseburia; Ruminococcus; Prevotella copri; probiotics; review*

## Introduction

Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health. The worldwide prevalence of obesity more than doubled between 1980 and 2014 and for today World Health Organization has declared obesity a global epidemic and took it under control [1, 2]. In 2014, more than 1.9 billion adults older than 18 years (39 %) were overweight. Overall, about 13 % or 600 million of this adult population (11 % of men and 15 % of women) were obese [3]. Overweight and obesity cause a number of diseases, namely, cardiovascular diseases [4], type 2 diabetes mellitus (T2DM) [5], dyslipidemia [6], premature death, hepatobiliary disease (non-alcoholic fatty liver disease, gallbladder dyskinesia, cholelithiasis) [7, 8] and a number of cancers [9, 10]. Diabetes mellitus is a chronic disease that alters the metabolism of carbohydrates, proteins, and fats, which is caused by inability of β-cells to secrete insulin or failure of peripheral cells to respond normally to insulin [11]. In recent decades, the incidence of diabetes mellitus has increased worldwide and according to the International Diabetes Federation, 8.8 % of the world's population



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(~ 425 million) had this disease in 2017, which is estimated to reach 628.6 million in 2045 [12]. It will have a profound impact on the quality of life, economic costs and demand for health care.

The most frequent cause, which leads to the obesity development, is a imbalance between energy intake and expenditure [13]. Obesity is associated with T2DM and insulin resistance, which is due to the increased secretion of unsaturated fatty acids from adipose tissue [11]. In general, various factors (genetics, lack of physical activity, and obesity) play an important role in the development of T2DM, but the change in gut microbiota is a new and important factor that is associated with increased metabolic disorders, such as obesity and associated diseases [14, 15].

The complex interaction between intestinal microbiota and the host organism has been investigated for over 100 years. Approval of the germ theory of disease led to an original classification of some human disorders, which are caused by microbes, inclusive of conditions that were ultimately going to be revised as non-infectious [16]. The term "microbiome" was first coined by Lederberg in 2001 and refers to all microbes that have been colonized in humans and their genes [17]. It is estimated that about 100 trillion microbes colonize the body of an adult, they are often present in the gastrointestinal tract, so resistant microorganisms in it are collectively referred to as intestinal microbiota [18]. The composition of microbial populations varies throughout the gastrointestinal tract. In the small intestine, aerobic and facultative anaerobes predominate and rapidly metabolize simple carbohydrates, while bacteria in the ileum can break down complex carbohydrates. The colon contains large amounts of anaerobic bacteria that are involved in the fermentation of indigestible fiber in the diet and the conjugation of bile acids [19]. In general, microbiota of mammals is mainly composed of 4 types of phyla, including *Actinobacteria*, *Firmicutes*, *Bacteroidetes*, and *Proteobacteria*, which represent the largest population of the microbiota [18]. And it works in harmony with the host body and provides the conditions for the host to perform important actions that it has not been able to perform alone, so they are vital for the host metabolism and regulation of its physiological conditions [20, 21].

## Microbiota and host metabolism

The gut microbiota is a part of a complex network. Numerous studies have shown that the gut microbiota interacts with the host metabolism and plays an important role in various functions, including the following: key compound in the immune system, protection against pathogens, regulation of intestinal hormone secretion, regulation of gastrointestinal nerve function, synthesis of vitamins K, $B_{12}$, folate, production of short-chain fatty acids (SCFAs) through fermentation of indigestible carbohydrates, and breaking down toxins and drugs [22]. Microbiota affects intestinal peristalsis as well as the expression of various host genes involved in the regulation of metabolism, angiogenesis, mucosal barrier function, the development of the enteric nervous system, and the maturation of mucosal immunity [23].

Intestinal bacteria also produce many types of signaling molecules, such as low-molecular weight compounds. These products can turn on and turn off host genes, pathogenic genes, and microbial metabolism [24]. The intestinal microbiota is also involved in the fat deposition, regulates glucose, lipid, and energy homeostasis via activating the FXR and TGR5 nuclear receptors [25].

Gut bacteria digest fibers in complex plant polysaccharides to SCFAs, such as acetate, propionate and butyrate, which vary in ratio from 3 : 1 : 1 to 10 : 2 : 1, that play a role as a source of energy and regulate food and energy intake [26, 27]. Acetate and propionate enter the bloodstream and are removed by the liver and peripheral organs, where they are used as substrates for gluconeogenesis and lipogenesis. Butyrate is used in colonocytes, goblet and mast cells to energize cellular metabolism, regulates apoptosis, cell differentiation, chemical modifications of nuclear proteins, and nucleic acid [28]. In addition, SCFAs can generate a wide range of cellular responses through G protein-coupled receptors — GPR41 and GPR43 [29]. SCFAs bind to these receptors can stimulate the secretion of GLP-1, GLP-2, and Y-peptide [30].

## Gut microbiota composition in obesity

Analysis of data from the PubMed database shows that research in the field of gut microbiota has developed rapidly over the past 20 years. The first document on the keywords "gut microbiota and obesity" in the PubMed database was posted in 2004. In that study, scientists showed that conventionalization of adult GF C57BL/6 mice with a normal microbiota harvested from the cecum of conventionally raised animals produced a 60% increase in total body fat content, adipocyte hypertrophy, and insulin resistance within 14 days despite a reduced food intake [31]. And already in 2005, an extensive metagenomic study of the gut was conducted by Eckburg et al. This analysis helped in entire genomic germ profiles formation [32].

Based on molecular phylogeny, the analysis of 16S ribosomal RNA sequences of all microorganisms detected in the human intestinal tract showed the presence of three main domains — bacteria, eukarya, and archaea. When analyzing the microbiota of fecal bacteria, two main phylogenetic lines were identified: *Firmicutes* and *Bacteroidetes* [20, 33]. An increment in the ratio of *Firmicutes*/*Bacteroidetes* was confirmed in obese mice compared to those with normal weight [34, 35]. An effect of different types of bacteria on weight loss and other metabolic parameters has been recently analyzed. The significant upshot was revealed for *Lactobacillus* and/or *Bifidobacterium* strains [36].

It has been shown that the use of additional bacteria has a positive correlation with glucose and lipid levels and helps reduce body weight and chronic systemic inflammation [37]. According to another research, lyophilized probiotic strains of bacteria showed a promising result. Specifically, decreased visceral fat levels, levels of adiponectin, leptin in adipose tissue, and total lipid metabolism alterations have been shown in obese rats treated with multistrain lyophilized or alive bacteria [38–41].

Some studies have found no correlation between the abundance of major groups of human colonic bacteria,

including *Bacteroidetes*, and body mass index. But the data obtained suggested a specific effect of several phyla or genera on obesity [42]. Additionally, a notable study was conducted by Kalliomäki et al., where the ratio of gut microbiota in infancy was shown to be a probable prerequisite for overweight. *Bifidobacteria* amount was shown to be higher in normal-weight children than in obese ones, while reduced levels of *S.aureus* were observed at normal weight [43].

## Novel strains associated with obesity

### *Akkermansia muciniphila*

*Akkermansia muciniphila* is a species present in fecal specimens of healthy individuals and is one of the dominant bacteria in the gut microbiome closely linked to the progression of obesity [44]. *A.muciniphila* comprises up to 4 % of fecal microbiota, centrally involved in controlling fat storage and glucose homeostasis, this bacterium stimulates the mucosal-microbial networks and thus creates a complete intestinal barrier and influences the formation of immunity [45]. Besides, *A.muciniphila* and its metabolite propionate stimulated expression of fasting-induced adipose factor, G protein-coupled receptor 43, histone deacetylases, and peroxisome proliferator-activated receptor gamma, important regulators of transcription factor regulation, cell cycle control, *lipolysis* and satiety [46]. In preclinical and clinical studies, it was confirmed that in the case of obesity and metabolic syndrome, the amount of *A.muciniphila* was significantly diminished. Therefore, it can be assumed that *A.muciniphila* may become the next-generation therapeutic agent [47]. Wu et al. showed a positive effect of *A.muciniphila*$^{sub}$ on body weight, the level of glucose, and the facilitation of the memory decay caused by a high-fat diet (HFD) in mice [48].

Depommier et al. demonstrated that people who were overweight and had T2DM or hypertension had a low abundance of *A.muciniphila*. The experimental application of *A.muciniphila* during 3 months in obese individuals was shown to promote increased cell sensitivity to insulin, a reduction of insulinemia, cholesterol level, and inflammatory markers. Interestingly, the use of *A.muciniphila* did not affect the correlation between the composition of the bacteria of the gut microbiome [49]. Similar results were observed by Kim et al., who studied the impact of intestinal *A.muciniphila* on non-alcoholic fatty liver disease. They have shown that administration of *A.muciniphila* decreased serum triglyceride, alanine aminotransferase, and IL-6 levels and normalized the bacterial organization of the gut microbiome in HFD mice [50].

### *Prevotella copri*

The *Bacteroidetes phylum* is the second most populous in the human gut after *Firmicutes* (Gram-positive) [51]. *Prevotella copri* is a succinate-producing bacterium, where succinate plays the role of substrate for intestinal gluconeogenesis [52]. Intestinal gluconeogenesis indeed is a gut function initiating various metabolic benefits by generating a gut-brain nervous signal that positively interferes in energy homeostasis and glucose control [53].

Hamilton et al. demonstrated that one week after the beginning of the HFD, paracellular permeability was increased, IL-10 expression and *Clostridia* abundance were decreased. After 6 weeks of HFD, the expression of the pro-inflammatory cytokine IL-1β was ameliorated. In obese rats, the dominant species of intestinal microbiota were *Lactococcus* and *Bacteroides*, and in chow-fed rats — the *Clostridiaceae* and *Prevotella* [54]. In pediatric patient with non-alcoholic fatty liver disease, a high abundance of *Prevotella copri* was associated with severe liver fibrosis (F3) [55].

Péan et al. showed how bariatric surgery affected the glucose homeostasis in a model of spontaneously occurring type 2 diabetes in rats (Goto-Kakizaki rats). After bariatric surgery, glucose tolerance and alteration in the gut microbiome were found to be caused by significant enrichment of caecal *Prevotella copri* [56].

Recently, 2 very interesting studies, which reported opposite data, were published. De Vadder et al. have shown that fiber-enriched diet is associated with increased succinate synthesis and thereby improve glucose tolerance and insulin sensitivity [52]. Moreover, similar changes in metabolic parameters were observed in HFD mice after colonization with *Prevotella copri* and disappeared in glucose-6-phosphatase (–/–) knockout; glucose-6-phosphatase is a specific intestinal epithelial rate-limiting enzyme that regulates gluconeogenesis [52]. On the other hand, Pedersen et al. the same year received the opposite results. The researchers found a positive relationship between *Prevotella copri* and serum metabolomics in patients with insulin resistance, which is characterized by elevated levels of branched-chain amino acids. To confirm this association between *Prevotella copri* and impaired glucose metabolism, probiotic or placebo were administered to HFD animals. *Prevotella copri* has been shown to increase glucose intolerance, total level of branched-chain amino acids in serum and reduce insulin sensitivity [57].

### *Christensenella minuta*

As it is known, *Christensenella minuta* is a Gram-negative bacterium, which is associated with the weight loss. To investigate the impact of host genes on the formation of intestinal microbiota, more than 1,000 fecal samples of microbiota obtained from twins were studied. Many microbial taxa have been identified, the number of which was influenced by host genetics, but the most hereditary taxon was the family *Christensenellaceae*. Furthermore, *Christensenellaceae* was present in greater numbers in people with a low body mass index. Moreover, the injection of cultured bacteria *C.minuta* to germ-free mice is associated with a decrease in weight gain [58]. Gut bacteria from fat mice, when transplanted to genetically lean mice, transform the lean phenotype to obesity-associated one [59, 60]. Subsequent studies demonstrated that skinny germ-free mice plump up on receiving a fecal transplant from a human donor implying that the bacteria help the recipient digest and metabolize more efficiently [59–61]. But if the fecal transplant of the human donor was supplemented with *C.minuta*, the recipient mice were thinner indicating anti-obesity effect [62].

### *Faecalibacterium prausnitzii*

*Faecalibacterium prausnitzii* is a Gram-positive, anaerobic bacterium that is one of the most numerous and important in the human gut microbiota. *F.prausnitzii* is one of the main butyrate producers in the healthy human gut. Studies have been performed to change the amount of *F.prausnitzii* in obese individuals. For example, Balamurugan et al. have compared the fecal samples of obese and lean children from south India. They showed that in the case of obesity, there were no significant differences between the two groups in fecal levels of *Prevotella*, *Bifidobacterium* species, *L.acidophilus* group, or *Eubacterium rectale*. However, the level of *F.prausnitzii* was significantly higher in obese children than in non-obese participants [63].

Feng et al. tried to find out whether the number of *F.prausnitzii* depends on gender and obesity. When comparing fecal samples of the obese group and lean individuals, there were no significant differences in the number of *F.prausnitzii*. However, gender affected the number of bacteria, with a lower level of fecal *F.prausnitzii* in men as compared to women. It can be concluded that in future studies of *F.prausnitzii*, the gender-specific effect must be taken into account [64]. Remely et al. determined how weight loss affects the abundance of *F.prausnitzii* before, during, and after the HFD. It has been shown that after the diet and weight loss, the number of bacteria, such as *Archaea*, *A.muciniphila*, *Clostridium* and *F.prausnitzii*, increased significantly [65].

Hippe et al. found that *F.prausnitzii* was present in different phylotypes in conditions of obesity, T2DM and in normal-weight patients. The lowest content of *F.prausnitzii* was in a group with T2DM and the highest — in a group with normal weight [66].

To test the hypothesis whether the gut microbiota is related to age and obesity, Del Chierico et al. have studied the microbiota profiles in obese adults and adolescents and compared it with samples obtained from normal-weight individuals. It was determined that the composition of intestinal microbiota is different in obese adolescents and adults: the former had high levels of *Actinobacteria*, and the latter — high *Bacteroidetes* amount. A negative correlation was found between the age, body mass index and *F.prausnitzii* abundance [67].

### *Ruminococcus*

*Ruminococcus* is a genus of bacteria in the class Clostridia. They are anaerobic, Gram-positive gut microbes. *Ruminococcus* breaks down cellulose (with the formation of methane), accumulates a reserve iodophilic polymer of glucose in the cytoplasm. In 2016, Togo et al. described a new bacterium species, *Ruminococcus phoceensis* strain AT10 (CSUR = P2086, DSM = 100837), which was isolated from the feces of a 37-year-old woman from Marseille, France, with morbid obesity before bariatric surgery. Bacterial cells were Gram-positive, rod-shaped, and polymorphic, ranging 0.2–0.5 × 1.2–1.5 μm by electron microscopy. Strain AT10 was catalase-positive and oxidase-negative. Strain AT10 exhibited 98.2 % of 16S rRNA gene sequence similarity with *Ruminococcus torque*s ATCC 27756 [68].

K. Nirmalkar et al. have studied the association between gut microbiota diversity and endothelial dysfunction markers in obese Mexican children and adolescents. Markers of endothelial inflammation (triglycerides, insulin, C-reactive protein, leptin) were increased in children and adolescents with obesity. Moreover, obesity was established to be positively associated with total cholesterol and *Ruminococcus* [69].

The effect of vitamin D on the gut microbiome in overweight or obese people has been studied by Naderpoor et al. It was found that the use of vitamin D did not affect the microbiome α-diversity. However, there was a significant association between community composition and vitamin D supplementation at the genus level. The vitamin D group had a higher abundance of genus *Lachnospira, Coprococcus* and lower abundance of genus *Blautia*, *Ruminococcus* [70].

### *Roseburia*

*Roseburia* is a member of the *Firmicutes* phylum of butyrate-producing, Gram-positive anaerobic bacteria that inhabit the human colon. Usually, an increased abundance of *Roseburia* is associated with weight loss and reduced glucose intolerance. Under the conditions of a HFD, an increase in the amount of deoxycholic acid and taurodeoxycholic acid in plasma and liver tissues was detected. Also, the number of genera *Blautia*, *Coprococcus*, *Intestinimonas*, *Lactococcus*, *Roseburia* and *Ruminococcus* was increased [68].

In obese groups with metabolic disorders (high uric acid concentration, serum lipids, high blood pressure), an increased amount of *Clostridium* XIVa*, Bacteroides* and *Roseburia* was observed. *Blautia, Romboutsia, Ruminococcus, Clostridium sensu stricto* and *Dorea* had a positive correlation with body mass index and blood lipids. In contrast, *Bacteroides, Roseburia, Butyricicoccus, Alistipes, Parasutterella, Parabacteroides* and *Clostridium* IV had a negative correlation with these parameters. Thus, these types of bacteria can be used as biomarkers of metabolic disorders associated with obesity [71]. Zohreh et al. clarified the role of *Roseburia* in the metabolism of the host, the impact on obesity, and its role in certain pathologies. It was shown that *Roseburia* spp. is actively involved in maintaining intestinal immunity, and influences peristalsis and anti-inflammatory properties. In pathologies, such as irritable bowel syndrome, obesity, T2D and allergies, *Roseburia* spp. could alter various metabolic pathways through butyrate-inhibiting NF-κB activation or influence on T-cell proliferation. Also, *Roseburia* spp. may be a biomarker of gallstone formation [72].

## Future perspectives

Gut microbiota is important for metabolism and a large number of studies have shown that the microbiota changes under obesity. So, the question arises whether certain manipulations of intestinal bacteria can improve the composition of the gut microbiome in obese people in terms of weight loss and metabolism improvement. This may be a potential therapeutic strategy for the treatment of obesity in the future.

Moreover, due to challenges in sampling from the intestine of humans, most studies use stool samples for micro-

biota analysis. However, the stool microbiota profile does not fully reflect the gut microbiome. Furthermore, most studies focused on genomics rarely study the transcriptome, proteome or metabolome. Even at the genomic level, deep shotgun sequencing is expensive, making marker-based amplicon sequencing, such as 16S rRNA gene sequencing, prevail. Further, the existing sequencing and analysis technologies seldom identify microbes at species or strain levels. Considering that the functional capacity varies between strains from the same species, identification of microbes and microbial genes associated with the disease is challenging.

**Conflicts of interests.** Authors declare the absence of any conflicts of interests and their own financial interest that might be construed to influence the results or interpretation of their manuscript.

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*Received 27.10.2020*
*Revised 25.11.2020*
*Accepted 02.12.2020*

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## Зміни складу мікробіоти кишечника, пов'язані з ожирінням: нові результати метагеномного аналізу

**Резюме.** Поширеність ожиріння зросла більше ніж удвічі з 1980 по 2014 р. Найчастішою причиною його розвитку є дисбаланс між споживанням та витратами енергії. Цей складний процес обумовлений генетичною схильністю, факторами навколишнього середовища та способом життя. Мікробіота кишечника є частиною складної мережі. У численних дослідженнях показано, що мікробіота кишечника впливає на метаболізм організму і відіграє важливу роль у різних процесах в організмі. Основу мікробіоти кишечника становлять бактерії, що належать до грампозитивного філотипу *Firmicutes* і грамнегативного *Bacteroidetes*. У дослідженнях за участю людей і тварин виявлено збільшення співвідношення *Firmicutes*/*Bacteroidetes* у кишечнику пацієнтів з ожирінням і при дотриманні дієти з високим умістом жиру. Штами, що належать до родів *Lactobacillus* та *Bifidobacterium*, зазвичай використовуються як пробіотики та є найбільш вивченими для лікування та профілактики ожиріння. Більше того, серед бактерій було виявлено декілька потенційних кандидатів, таких як *Akkermansia muciniphila*, *Faecalibacterium prausnitzii*, *Prevotella copri, Roseburia* та *Ruminococcus*, і з'ясовано нові механізми дії, що обумовлюють їх позитивні ефекти при ожирінні. Отже, мікробіота кишечника набуває значного дослідницького інтересу щодо ожиріння та пов'язаних із ним метаболічних розладів, дозволяє краще зрозуміти етіологію ожиріння та розробити потенційні нові методи його профілактики та лікування. Однак традиційні методи культивування на поживних середовищах дуже обмежені щодо ідентифікації мікробів. При застосуванні молекулярно-біологічних технологій, особливо метагеномного секвенування нового покоління, було досягнуто значного прогресу у вивченні мікробіому кишечника людини.

**Ключові слова:** *Akkermansia muciniphila*; *Faecalibacterium prausnitzii*; мікробіота кишечника; інсулінорезистентність; метагеноміка; ожиріння; *Roseburia*; *Ruminococcus*; *Prevotella copri*; пробіотики; огляд

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## Изменения состава микробиоты кишечника, связанные с ожирением: новые результаты метагеномного анализа

**Резюме.** Распространенность ожирения возросла более чем вдвое с 1980 по 2014 г. Наиболее частой причиной его развития является дисбаланс между потреблением и расходом энергии. Этот сложный процесс обусловлен генетической предрасположенностью, факторами окружающей среды и образом жизни. Микробиота кишечника является частью сложной сети. В многочисленных исследованиях было показано, что микробиота кишечника влияет на метаболизм и играет важную роль в различных процессах в организме. Основу микробиоты кишечника составляют бактерии, относящиеся к грамположительному филотипу *Firmicutes* и грамотрицательному *Bacteroidetes*. В исследованиях с участием людей и животных обнаружено увеличение соотношения *Firmicutes*/*Bacteroidetes* в кишечнике пациентов с ожирением и при соблюдении диеты с высоким содержанием жира. Штаммы, принадлежащие к родам *Lactobacillus* и *Bifidobacterium*, обычно используются как пробиотики и являются наиболее изученными для лечения и профилактики ожирения. Более того, среди бактерий было обнаружено несколько потенциальных кандидатов, таких как *Akkermansia muciniphila*, *Faecalibacterium prausnitzii*, *Prevotella copri, Roseburia* и *Ruminococcus*, и выяснены новые механизмы действия, обусловливающие их положительные эффекты при ожирении. Итак, микробиота кишечника представляет весомый исследовательский интерес в отношении ожирения и связанных с ним метаболических расстройств, позволяет лучше понять этиологию ожирения и разработать потенциальные новые методы его профилактики и лечения. Однако традиционные методы культивирования на питательных средах очень ограничены в отношении идентификации микробов. При использовании молекулярно-биологических технологий, особенно метагеномного секвенирования нового поколения, был достигнут значительный прогресс в изучении кишечного микробиома человека.

**Ключевые слова:** *Akkermansia muciniphila*; *Faecalibacterium prausnitzii*; микробиота кишечника; инсулинорезистентность; метагеномика; ожирение; *Roseburia*; *Ruminococcus*; *Prevotella copri*; пробиотики; обзор