

Changes in the Composition of Intestinal Microbiota in Type 2 Diabetes and Obesity

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Annotation: Recent evidence suggests that some bacteria influence the endocannabinoid system outside the gastrointestinal tract, mediated by gut hormones and metabolites from other systems. The symbiotic relationship between the intestinal microbiota and the body ensures the proper development of the human metabolic system. When the numbers of certain bacterial species begin to decline, the symbiosis is disrupted, leading to deterioration in the host's metabolic health. At the same time, disturbances in the composition and, in turn, functionality of the intestinal microbiota can disrupt the function of the intestinal barrier and subsequently serve as a switch for metabolic endotoxemia. Chronic inflammation, caused by the entry of bacterial particles into the bloodstream through disruption of the intestinal barrier, has a significant impact on the accumulation of body fat and the development of insulin resistance. This article describes the complex axis between the microbiota and host metabolism.

Keywords: Short-chain fatty acids; Microbiota; Insulinresistence; Symbiosis; Obesity.

Introduction

In recent years, there has been an increasing interest in studying the relationship between a person and their intestinal microorganisms. Such microorganisms are "superorganisms", by which much work is controlled. One such important task is the control of metabolism. Energy consumption and accumulation in the control of metabolism is carried out by a certain group of bacteria. Changes in the amount of bacteria in the same group lead to colon accumulation, insulinresistence and obesity. In this article, it is possible to learn about how the change in the state of the human intestinal microbiota is mainly due to the fact that diabetes is specific in 2 species and obesity, and how the amount of which group of bacteria changes.

The contribution of gut microbiota to health and disease in many authoritative research publications and comprehensive review articles over the past few decades cannot be ignored. 1-2 kg of microorganisms in the human intestine contain 150 times as many genes as the human genome itself. This concept is attracting scientists from gastroenterology, physiology and microbiology, and alters their understanding that the gut microbiota is called a "forgotten organ".

Although a recent study was first confirmed to the baby to pass bacteria from the maternal placenta microbiome as early as the uterus, after birth the neonatal intestinal tract is rapidly colonized by breast milk and the external environment [1]. Of course, it can be seen that the natural method of childbirth is not the same in comparison with cesarean section - the first real microbial colonization of the neonatal intestinal tract. Many publications compare caesarean section births to natural births and breastfed infants to artificially fed infants and identify specific differences in gut microbiota composition between them [19]. Typically, the gut microbiota develops after birth, and after about 3 years of age, the children's gut microbiota will be very similar to that of an adult [15].

The gastrointestinal tract (GIT) of healthy adults is in a highly acidic environment of the stomach, with the duodenum and small intestine containing about 10² microbial cells. The Distal lateral intestine contains approximately 10⁷-10⁸ microbial cells, with the largest portion of microbes located in the colon and containing 10¹¹-10¹² microbial cells. Difficulties arise in the cultivation of microbiota in this highly anaerobic environment, of which only 10-50% are successfully grown in the laboratory [3].

The interaction of the master's organism and microbes, that is, as a result of the fact that bacteria are metabolized along with nutrients, develops "smart communication systems" in the body, developing a huge number of signaling molecules that have a beneficial effect on health. "Farmabiotics", i.e. short-chain fatty acids, conjugated fatty acids, exopolysaccharides, and neuroactive metabolites such as γ -aminobutyric acid (γ -ABA) and serotonin, are produced by microbes and these bioactive metabolites are beneficial to the host's health. Thus, the interaction of the host organism and microbes is essential for optimal Health [16].

Changes intestinal microbiota in obesity and diabetes mellitus.

Before talking about the involvement of the intestinal microbiota in the formation of obesity and associated metabolic disorders, it is appropriate, first of all, to briefly discuss the latest literature, which characterizes diet as a factor contributing to the microbial composition of the intestine. In fact, nutritional factors have a profound effect on the transformation of the intestinal microbiota of animals and humans. The diet is associated with specific compounds of bacteria in the intestine, also known as enterotypes. Given that the role of gut microbiota is to ferment dietary substrates, complex diets can provide growth-stimulating and growth-inhibiting factors for specific phylotypes. Thus, the identification of dietary or specific foods that increase bacterial diversity and promote the growth of beneficial bacteria that produce high levels of bioactive metabolites plays an important role in the treatment of various metabolic disorders in the future [5].

Obesity is accompanied by a change in the ratio of 2 dominant types i.e. Firmicutes to Bacteroidetes in the gut microbiota. Some studies describe that Firmicutes change with an increase in ratio to Bacteroidetes, and the decrease in body weight goes with a decrease in this ratio [21]. Currently, much scientific work is being done on the importance of the Firmicutes:Bacteroidetes ratio in the development of obesity.

Intestinal microbiota diversity of obese individuals is characterized by higher fatness, increased insulinresistance, dyslipidemia, and increased systemic inflammation (C-reactive protein elevation) in people with lower rates when compared to higher and lower human populations. Bacteroides, Parabacteroides, Ruminococcus, Campylobacter, Dialister, Porphyromonas, Staphylococcus and Anaerostipes were more dominant in those with the obese phenotype, while Faecalibacterium, Bifidobacterium, Lactobacillus, Butyrivibrio, Alistipes, dominermansia, Coprococcus and Methanobrevibacter were more lean and had increased levels in phenotypic individuals rich in microbiota identified. Data has shown that obese individuals have decreased gut microbiota diversity, reduced butyrate-producing bacteria, decreased hydrogen and methane production, increased mucus degradation, and increased oxidative stress management potential [12].

Akkermansia muciniphila is a gram-negative, anaerobic, oval-shaped bacterium that lives on the intestinal mucosal epithelial floor. It accounts for 3-5% of the total intestinal microbiota mass. Scientific research turned out that A. muciniphila increases tergenesis and glucagon-like peptide-1 (GLP-1) levels, reduces proteins involved in adipocyte cell differentiation and gene expression of glucose and fructose transport in the small intestine, reduces glucose absorption from the intestine [2].

Faecalibacterium prausnitzii is also found in large quantities in the gut microbiota and has an estimated 4% content. Inflammatory bowel disease, obesity and various metabolic disorders F. it goes with a decrease in the amount of prausnitzii. F. the main function of prausnitzii is accompanied by the strengthening of solid compound proteins in epithelial cells, strengthening the intestinal barrier and lowering the inflammatory process. The reduction of the chronic inflammatory process plays an important role in preventing obesity and inflammatory metabolic disorders [13].

In a study by Qin et al, patients with Chinese diabetes type 2 were studied to have interesting links between gut microbiota composition and clinical data. In this, healthy control group patients are exposed to butyrate-producing bacteria (Clostridiales sp. SS3/4, E. rectale, F. prausnitzii, Roseburia intestinalis, etc.), while patients with diabetes mellitus are particularly susceptible to butyrate-producing bacteria. intestinalis and F. there has been a decrease in prausnitzii. Interestingly,

colobization of conditionally pathogenic bacteria *Bacteroides caccae*, various Clostridiales, *Escherichia coli* and the sulfate-reducing species *Desulfovibrios* has also been identified in diabetes 2 species of patients. Diabetes 2 various patients have associated changes such as increased intestinal microbiota glucose membrane transport, response to oxidative stress, transport of a branched amino acid chain, reduced sulfate, and decreased butyrate biosynthesis. Overall healthy and diabetic type 2 patients with gut microbiota Gene >3% differed from each other [18].

Probiotic supplements can create conditions for reduced body weight by reducing intestinal permeability, reducing the inflammatory process, and modulating metabolism. It has been shown that taking probiotics and prebiotics in patients with metabolic syndrome can lead to a decrease in body weight, a normalization of lipid profile, and a normalization of carbohydrate metabolism. Dietary supplements containing microorganisms *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus* and *Enterococcus* have been found to play an important role in the prevention or treatment of obesity [14].

There has been an increase in *Lactobacillus gasseri*, *Streptococcus mutans*, some Clostridiales species, and *Lactobacillus* in European female diabetics. The same patients showed a decrease in butyrate-producing bacteria-namely *Roseburia*, *Eubacterium eligens*, *Bacteroides intestinalis*, and some Clostridium species. R among these bacteria according to MGC model analysis. *intestinalis* and *F. prausnitzii* diabetes mellitus has been found to have high discrimination for 2 species [7]. In addition, lean people have a significant decrease in insulinresistence when transplanting the intestinal microbiota to those with metabolic syndrome, an increase in the rate of glucose reduction from 26.2 to 45.3 mkmol/kg/min, R. changes such as increases in the amount of *intestinalis* and butyrate can be seen. With this, it is possible to determine the effect of butyrate-producing bacteria on high levels of metabolic homeostasis [22]. Both studies found an increase in the amount of *Clostridium hathewayi* and a decrease in the amount of *Roseburia* in patients with Type 2 diabetes in the same way in Chinese individuals and European women, which is thought to be associated with the development of Type 2 diabetes [18,7]. These two countries are fundamentally different from each other in geography, genetics, and diet. Therefore, it is difficult to say that one particular group or type of small bacteria is the cause of the development of diabetes mellitus and its complications.

In several studies, changes in the gut microbiota have been cited as contributing to the development of diseases of the cardiovascular system-namely hypertension, atherosclerosis, myocardial infarction, and heart failure. In China, a large intestinal microbiota metagenome analysis found intestinal dysbiosis in patients with cardiovascular disease. According to him, Enterobacteriaceae (of which *E. coli*, *Klebsiella* spp., and *Enterobacter aerogenes*), *Ruminococcus gnavus*, *E. tape* and *Streptococcus* spp, which is usually present in the oral cavity. an increase in quantity has been observed. Against this, butyrate-producing bacteria *F. prausnitzii* and *R. intestinalis*, *Bacteroides* spp., *Prevotella copri* and *Alistipes shahii* have been found to have decreased significantly [6]. Another study has identified bacterial DNA si in atherosclerotic plaque, and it is possible to know about the high content of Proteobacteria, the low number of Firmicutes, and the presence of large amounts of *Chryseomonas* [8].

Bacteria of the *Lactobacillus* group have a positive effect on nahorgi glucose and glycated hemoglobin (HbA1c), while *Clostridium* has a negative effect on these indicators. As a result of this change, Type 2 diabetes mellitus develops. Newly diagnosed Type 2 diabetes patients were found to have increased *Lactobacillus* levels, reduced *Clostridium* levels [27]. Shih et al examined the condition of the gut microbiota in patients whose diabetes was in 2 types of treatment but did not drop from glycated hemoglobin (HbA1c) >8%. It found that these same patients had higher levels of *Bacteroides vulgatus*, *Veillonella denticariosi* compared to control group patients, and decreased levels of *Akkermansia muciniphila*, *Fusobacterium* [26].

It can be seen that various intestinal microbial metabolites, such as short-chain fatty acids, metabolites of TMAO and tryptophan, are closely related to the pathogenesis of the development of Type 2 diabetes mellitus. In a previous study, short-chain fatty acids (QZYK) in adipocytes thinned the insulin-Fed signal by activating g protein-coupled receptor 43 (GPR43) [9].

Studies have found increased levels of Firmicutes and decreased levels of other bacteria (*Faecalibacterium prausnitzii*, *Roseburia*, *Dialister*, and *Flavonifractor*) in diabetic type 2 patients. Bacteria with a decrease in this amount perform tasks that are beneficial for the health of the body. These include important functions such as short-chain fatty acids, butyrate production, maintaining intestinal barrier integrity, providing energy homeostasis, reducing inflammation, and modulating glycemic response [20]. An increase in *Escherichia coli* in the gut microbiota leads to an increase in bacterial infections in diabetics [28].

The immunomodulatory and probiotic properties of *Lactobacillus* are now well studied. Nevertheless, the positive effects of *Lactobacillus* on prediabetes and diabetic patients have also been found to have glycemic indicators i.e. glucose levels in the nahrung empty stomach, glycated hemoglobin (HbA1c), and insulinresistance indicator (HOMA-IR). The effects of chronic inflammation in diabetic patients have been considered [25]. *Lactobacillus* probiotic strains have been found to have positive effects against diabetes when given to mice in an expressive study [23]. But how it directly affects will still have to be analyzed in depth as a result of scientific research.

In the Mendelian randomized study, it turned out that the development of intestinal microbiota and type 2 diabetes mellitus are interconnected. As a result of the Study, 2 generations of *Flavonifractors* and *Haemophilus lar* have protective factors for Type 2 diabetes mellitus, and on the contrary, representatives of the 3 families *Clostridiaceae*, *Actinomyces*, *Candidatus Soleaferrea* have been found to have a risk factor effect for Type 2 diabetes [10]. *Candidatus Soleaferrea* it is associated with intestinal inflammation and low-grade inflammation. A change in the immune system leads to inflammation, which is a risk factor in the development of Diabetes Mellitus Type 2. The role of *Candidatus Soleaferrea* in the development of type 2 diabetes mellitus has been identified [24].

Blastocystis spp. and *Prevotella copri* microorganisms have been found to affect postprandial glucose metabolism. Mice fed *Prevotella copri* have been found to have improved glucose metabolism [11]. Another study found that *Prevotella copri* produces BCAA and that it leads to insuliresistency and impaired glucose tolerance. An increase in the amount of *Bacteroides vulgatus* and *Prevotella copri* compared to healthy patients with insulinrezistency and, as a result, an increase in BCAA ni and a decrease in *Butyrvibrio crossotus* and *Eubacterium siraeum* leads to a decrease in catabolism of BCAA [17].

The most consistent findings from studies related to changes in intestinal bacterial composition have been found in the proliferation of *Escherichia/Shigella*, *Escherichia coli* and *Akkermansia muciniphila* bacteria in the family *Enterobacteriaceae*. *Ruminococcus torques* has also been found to have increased levels in patients taking metformin. *Romboutsia*, *Clostridium*, *Roseburia*, and *Roseburia intestinalis* have been found to have reduced levels [29].

One of the contributing factors in the development of obesity, insulin resistance and hepatois of liver fat is intestinal dysbiosis. In a mouse model with a modified gene, a change in gut microbiota has been found following semaglutide injection. An increase in *Alloprevotella* and *Alistipes* has been found, with a decrease in *Ligilactobacillus* and *Lactobacillus*. Semaglutide has effectively alleviated liver damage and fat accumulation in the liver in db/db mice by improving glucose metabolism and lipid profile. In addition, semaglutide has shown the ability to improve gut microbiota and restore gut barrier in db/db mice [30].

Conclusion

Nowadays, many such studies are discovering many new facets in the development, etiology and pathogenesis of diabetes mellitus, obesity and prediabetic condition. We witnessed that most research results recorded similar results. In the case of diabetes mellitus, obesity and diabetes mellitus, *Lactobacillus*, *Streptococcus*, *Escherichia*, *Veillonella* and *Collinsella* were known to go with an increase in the amount and *Faecalibacterium prausnitzii*, *Roseburia*, *Dialister*, *Flavonifractor*, *Alistipes*, *Haemophilus* and *Akkermansia muciniphila* with a decrease in the amount. Information like this can be said that we have a new way in the future in the treatment of obesity, Type 2 diabetes mellitus, in the

diagnosis and, most importantly, in the Prevention of diseases that are accompanied by such metabolic disorders.

References:

1. Aagaard K, Ma J, Antony KM, et al. The placenta harbors a unique microbiome. *Sci Transl Med* 2014;6:237ra65.
2. Depommier C, Van Hul M, Everard A, Delzenne NM, De Vos WM, Cani PD. Pasteurized *Akkermansia Muciniphila* Increases Whole-Body Energy Expenditure and Fecal Energy Excretion in Diet-Induced Obese Mice. *Gut Microbes* (2020) 11:1231–45. doi: 10.1080/19490976.2020.1737307
3. Eckburg PB, Bik EM, Bernstein CN, et al. Diversity of the human intestinal microbial flora. *Science* 2005;308:1635–8.
4. Elaine Patterson, Paul M Ryan, John F Cryan, Timothy G Dinan, R Paul Ross, Gerald F Fitzgerald, Catherine Stanton. Gut microbiota, obesity and diabetes. *PGMJ Online First*. February 24, 2016 as 10.1136/postgradmedj-2015-133285.
5. Flint HJ, Scott KP, Louis P, et al. The role of the gut microbiota in nutrition and health. *Nat Rev Gastroenterol Hepatol* 2012;9:577–89.
6. Jie Z, et al. The gut microbiome in atherosclerotic cardiovascular disease. *Nat Commun*. 2017;8(1):845.
7. Karlsson FH, et al. Gut metagenome in European women with normal, impaired and diabetic glucose control. *Nature*. 2013;498(7452).
8. Koren O, et al. Human oral, gut, and plaque microbiota in patients with atherosclerosis. *Proc Natl Acad Sci U S A*. 2011;108(Suppl. 1):4592–8.
9. Kimura, I., Ozawa, K., Inoue, D., Imamura, T., Kimura, K., Maeda, T., et al. (2013). The Gut Microbiota Suppresses Insulin-Mediated Fat Accumulation via the Short-Chain Fatty Acid Receptor GPR43. *Nat. Commun.* 4, 1829. doi: 10.1038/ncomms2852
10. Kewang Sun, Yan Gao, Huaqing Wu, Xiangyan Huang. The causal relationship between gut microbiota and type 2 diabetes: a two-sample Mendelian randomized study DOI: 10.3389/fpubh.2023.1255059
11. Kovatcheva-Datchary P, Nilsson A, Akrami R, Lee YS, De Vadder F, Arora T, et al. Dietary fiber-induced improvement in glucose metabolism is associated with increased abundance of *Prevotella*. *Cell Metab* (2015) 22:971–82. doi: 10.1016/j.cmet.2015.10.001
12. Le Chatelier E, Nielsen T, Qin J, et al. Richness of human gut microbiome correlates with metabolic markers. *Nature* 2013;500:541–6.
13. Martín R, Miquel S, Chain F, et al. *Faecalibacterium prausnitzii* prevents physiological damages in a chronic low-grade inflammation murine model. *BMC Microbiol* 2015;15:67
14. Morelli L, Capurso L. FAO/WHO guidelines on probiotics: 10 years later. *J. Clin. Gastroenterol*. 2012;46:S1–S2. Doi: 10.1097/MCG.0b013e318269fdd5
15. Palmer C, Bik EM, DiGiulio DB, et al. Development of the human infant intestinal microbiota. *PLoS Biol* 2007;5:e177.
16. Patterson E, Cryan JF, Fitzgerald GF, et al. Gut microbiota, the pharmabiotics they produce and host health. *Proc Nutr Soc* 2014;73:477–89.
17. Pedersen HK, Gudmundsdottir V, Nielsen HB, Hyotylainen T, Nielsen T, Jensen BA, et al. Human gut microbes impact host serum metabolome and insulin sensitivity. *Nature* (2016) 535:376–81. doi: 10.1038/nature18646

18. Qin J, Li Y, Cai Z, et al. A metagenome-wide association study of gut microbiota in type 2 diabetes. *Nature* 2012;490:55–60
19. Roger LC, Costabile A, Holland DT, et al. Examination of faecal *Bifidobacterium* populations in breast- and formula-fed infants during the first 18 months of life. *Microbiology (Reading, Engl)* 2010;156(Pt 11):3329–41.
20. Tamanai-Shacoori, Z., Smida, I., Bousarghin, L., Loreal, O., Meuric, V., Fong, S. B., et al. (2017). *Roseburia* Spp.: A Marker of Health? *Future Microbiol.* 12, 157–170. doi: 10.2217/fmb-2016-0130
21. Turnbaugh PJ, Hamady M, Yatsunenko T, et al. A core gut microbiome in obese and lean twins. *Nature* 2009;457:480–4.
22. Vrieze A, et al. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. *Gastroenterology.* 2012;143 (4).
23. Yun, S. I., Park, H. O., and Kang, J. H. (2009). Effect of *Lactobacillus Gasseri* BNR17 on Blood Glucose Levels and Body Weight in a Mouse Model of Type 2 Diabetes. *J. Appl. Microbiol.* 107 (5), 1681–1686. doi: 10.1111/j.1365- 2672.2009.04350.x
24. Zou XY, Zhang M, Tu WJ, Zhang Q, Jin ML, Fang RD, et al. *Bacillus subtilis* inhibits intestinal inflammation and oxidative stress by regulating gut flora and related metabolites in laying hens. *Animal.* (2022) 16:100474. doi: 10.1016/j.animal.2022.100474
25. Zeuthen, L. H., Christensen, H. R., and Frøkiaer, H. (2006). Lactic Acid Bacteria Inducing a Weak Interleukin-12 and Tumor Necrosis Factor Alpha Response in Human Dendritic Cells Inhibit Strongly Stimulating Lactic Acid Bacteria But Act Synergistically With Gram-Negative Bacteria. *Clin. Vaccine Immunol.* 13 (3), 365–375. doi: 10.1128/CVI.13.3.365-375.2006
26. Shih, C. T., Yeh, Y. T., Lin, C. C., Yang, L. Y., and Chiang, C. P. (2020). *Akkermansia muciniphila* is Negatively Correlated With Hemoglobin A1c in Refractory Diabetes. *Microorganisms* 8 (9), 1360. doi: 10.3390/microorganisms8091360
27. Chen, P. C., Chien, Y. W., and Yang, S. C. (2019). The Alteration of Gut Microbiota in Newly Diagnosed Type 2 Diabetic Patients. *Nutrition* 63-64, 51–56. doi: 10.1016/j.nut.2018.11.019
28. Wiwanitkit, V. (2011). Outbreak of *Escherichia Coli* and Diabetes Mellitus. *Indian J. Endocrinol. Metab.* 15 (Suppl 1), S70–S71. doi: 10.4103/2230-8210.83050
29. Metformin, Cognitive Function, and Changes in the Gut Microbiome. Marisel Rosell-Díaz and José Manuel Fernández-Real. <https://doi.org/10.1210/endrev/bnad029>
30. Semaglutide alters gut microbiota and improves NAFLD in db/db mice. Tuohua Mao, Chenxuan Zhang, Shuang Yang, Yingying Bi, Man Li, Jia Yu. <https://doi.org/10.1016/j.bbrc.2024.149882>