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RESEARCH ARTICLE
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Measures in the Field of Prevention and Development of Dysbiosis in Adults and Children

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ABSTRACT

The problem of dysbiosis is quite acute in medicine today, since this phenomenon is the primary cause of a number of diseases that quickly turn into a chronic form and reduce the quality of life of patients. To form a mechanism for the prevention of dysbiosis, it is necessary to understand the features of its occurrence and the factors affecting this process. The authors note that a timely approach to the implementation of preventive measures, as well as a properly chosen diet, will reduce the risks of further development of dysbiosis and increase the level of resistance of the body to various diseases.

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INTRODUCTION

In the human body, more than forty trillion bacteria of approximately 1,000 species live in the intestines, oral cavity, respiratory tract, skin and genitourinary tract. There is a bacterial microbiota in every place, but most bacteria live in the intestine. Thanks to advances in next-generation sequencing methods, the exact characteristics of microorganisms composing the gut microbiota have been revealed.

The gut microbiota encodes more than three million genes that can produce different metabolites. Studies on the gut microbiota have shown that it plays an important role in human health, modulating the host's immune defense and regulating the metabolism and function of the host's brain.[1]

An imbalance of the gut microbiota, called dysbiosis, at an early age is associated with the development of various diseases at a later age, including allergic diseases, inflammatory bowel diseases (IBD), irritable bowel syndrome, necrotizing enterocolitis, diabetes, obesity, autism spectrum disorders, cardiovascular diseases, etc.[2]

In this regard, the study of possible measures to prevent the development of dysbiosis is an urgent area of research, since determining the directions of preventive work will reduce the risk of various diseases and improve the quality of life of patients.

MATERIALS AND METHODS

In the process of writing the study, an analysis was carried out on the topic of research, the data obtained were analyzed and summarized using the comparative method, as well as the induction method.

RESULTS

The gut microbiome consists of a diverse and dynamic ecosystem of bacteria, fungi, archaea, viruses and helminths. Recently, a large number of studies have appeared studying the role of the intestinal microbiome in various pathologies, ranging from cancer, inflammatory bowel diseases, affective disorders and neurodegenerative diseases. Most of the studies focused on bacterial populations, mainly due to the information obtained using 16S rRNA.

KEYWORDS:
Bacterial populations, Dysbiosis, Dietary nutrition, Intestines, Microbiome, Prevention.

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The bacteria found in the intestine were generally divided into 11 types. Most bacteria (> 90%) consist of Firmicutes, Bacteroidetes, Proteobacteria and Actinobacteria, while Fusobacteria and Verrucomicrobia are present in small amounts.[3] Although most bacteria have been sequenced and identified, researchers are still in the process of identifying and describing new bacterial strains colonizing the intestine. The gut microbiota contains many organisms, some of which produce metabolites that humans cannot produce. It is important to note that the characteristic shifts in the ratio of populations at the level of types, genera and species between healthy subjects and sick patients inspired causal rather than correlation studies to understand the role of microbes in the occurrence or prevention of various diseases.

The intestinal microbiome is particularly unique in that it is relatively accessible for modulation, which makes it an exciting potential therapeutic option for many different diseases.[4]

The role of microbes is multifaceted, and much of what we know has been obtained as a result of studying microorganism-free animals. Microorganism-free animals are model organisms that are born and kept in sterile conditions. In the absence of microbial colonization, they can be compared with pathogen-free (SPF) animals to determine how the microbiota and its secreted metabolites contribute to homeostatic function and development.

Microorganism-free animals have abnormal immune development with changes in populations and behavior of immune cells. The intestine is the largest immune organ in the body, and its epithelial cells, dense junctions and mucous membrane serve as the main point of interaction between the host and the intestinal microbiota. The gut microbiota can stimulate T-cells that help in protecting the host from intestinal pathogens that cause local and systemic inflammation.

Long-chain fatty acids obtained from the diet interact with intestinal immune cells and reduce the number of populations of Prevotellaceae and Bacteroidetes, increasing the responses of Th1 and Th17 cells and exacerbating inflammatory reactions in mouse experimental autoimmune encephalitis (EAE).

Microbes produce unique metabolites that the host cannot produce. These metabolites have a positive and negative effect on the regulation of the immune system and can affect development. A metabolite of microbial origin that has aroused considerable interest is trimethylamine N-oxide (TMAO). TMAO increases in patients with atherosclerotic disease and increases in men and women with Alzheimer's disease.[5]

Alternatively, it is known that selective microbial communities produce beneficial products by fermentation. At the same time, insoluble fiber, such as inulin, can be digested by intestinal bacteria to form short-chain fatty acids (SCFAs), such as acetate, butyrate, and valerate. SCFAs promote regulatory responses of T-cells and reduce inflammation. Serum levels of SCFAs butyrate are higher in men than in women, which may contribute to variations in Treg content.

SCFA also affects the healthy development of infants and even eliminates the harmful neurological effects found in the offspring of obese mothers. The absence of SCFA butyrate due to the destruction of bacterial populations or the lack of insoluble fiber in the diet may be the cause of diseases such as hypertension.

The composition of species within a single population represents alpha diversity and describes richness (number) and distribution (uniformity). Beta diversity compares the variables of the environment and the differences in microbial composition between populations. Beta diversity indicators include Bray-Curtis dissimilarity (compares differences in microbial abundance between two samples at the species level), Jacquard distance (compares the presence or absence of a species between two populations) and UniFrac (unweighted, compares only differences in sequences and weighted value refers to the relative abundance of species with differences in sequences). Changes and loss of the biological diversity of the gut microbiome that are associated with adverse outcomes are considered "dysbiotic changes". The composition and diversity of the biome varies depending on pathology, medications, the environment and, most importantly, on diet.

The gut microbiome is colonized for the first-time during birth and reflects the composition of the maternal biome. During the first five years of life, the number and diversity of the gut microbiome increases, and then stabilizes with age. Diet is the main modifiable factor that can lead to the selection of various microbes that then thrive in the gut. In particular, it has been shown that a Western diet consisting of foods high in fat, sugar and fiber increases the amount of lipopolysaccharide (LPS) producing gram-negative bacteria.[6]

Obese women are more likely to suffer from atherosclerotic disease, which is associated with pro-inflammatory conditions and intestinal dysbiosis. An increase in adipose tissue due to obesity can lead to an increase in systemic estrogen, which reduces LPS-induced inflammation, and bacteria containing ß-glucuronidase, an enzyme that deconjugates estrogens into their active forms, can contribute to an increase in systemic estrogen.

Estrogen has a broad effect on human physiology, affecting vascular function, inflammatory reactions, the development of multiple cancers, and has also demonstrated neuroprotective effects in stroke, Alzheimer's disease and Parkinson's disease. The richness and diversity of the intestinal microbiome in postmenopausal men and women directly correlate with the amount of excreted estrogen in the urine, and the level of fecal beta-glucuronidase is inversely proportional to the level of excreted fecal estrogen.[7]

In fact, some researchers call the intestinal microbiome an "endocrine organ" because of the productive and closely integrated role it plays with the endocrine system, which can affect the development, manifestation and progression of diseases in men and women in different ways.

DISCUSSION

The diversity of intestinal functions is regulated by the interaction between bioactive compounds of food and the intestinal microbiota (IM). IM plays an important role in controlling the fermentation and assimilation of food nutrients, such as SCFAs (short-chain fatty acids).

IM is distributed throughout the gastrointestinal tract, and their type and activity are associated with various pathophysiological effects, including the development of type 2 diabetes mellitus (DM2). Several metagenomic studies have shown

that dysbiosis in IM directly affects the development of DM2, affecting intestinal permeability, inflammation, the immune system and energy metabolism. Thus, the modulation of IM by bioactive compounds in recent years has gained a significant impetus for the search for suitable bioactive compounds or their compositions with preventive and/or therapeutic potential in DM2.

Several studies conducted in the recent past have described the relationship between the diet, IM and the host in the context of metabolic disorders such as diabetes, obesity and cardiovascular diseases. The researchers emphasize the importance of prebiotics and probiotics in the regulation of IM and, thus, indicates their preventive effect on the occurrence of diabetes and obesity.

Other studies have also shown that prebiotics and probiotics have a beneficial effect on eubiosis compared to dysbiosis and, thus, can be used for the prevention and treatment of DM2. In addition, previous studies also describe strategies for IM modularization using antimicrobial agents, bariatric surgery and its consequences for the treatment of metabolic disorders.[8]

The Human Diet is very complex and contains Nutrients Substances, as well as Biologically active

The human diet is very complex and contains nutrients, as well as biologically active compounds obtained from food. Consequently, the diet is considered a key element of human health. Changes in the diet affect the composition of IM. Alternative nutrition models or improper management of the dietary component can harm healthy microorganisms in GM. Several studies have shown that dysbiosis of IM caused by diet is associated with the onset of DM2 and obesity.

The Components Present in the Diet Affect the IM by Various Mechanisms

Bifidobacteria, Clostridium and *Bacteroidetes* decrease if the carbohydrate content in the diet decreases. Similarly, an increase in dietary fiber content increases the number of short-chain fatty acids (SCFA) producing bacteria in IM. On the other hand, the Western diet has shown a more significant decrease in the diversity of GMOs due to a lower content of food fibers.[9]

Several studies have shown that the Mediterranean diet, initially rich in polyphenols, reduces the risk of developing DM2 and obesity. A diet high in carbohydrates, fiber, and protein has a positive effect on human health, as it acts as an energy source, helps in the production of SCFAs, the production of microbial metabolites, and contributes to an increase in the number of bacteria producing butyrate. While the keto diet, the Western diet and the high-fat diet cause a decrease in the gut microbiota, including *Bifidobacteria, Bacteroidetes*, which leads to the disease.

The gut microbiota is responsible for initiating, controlling, and managing common host metabolic processes, such as energy metabolism, metabolic endotoxemia, intestinal permeability maintenance, and the host immune system.

The metabolites produced by GM during the fermentation of complex carbohydrates, i.e. SCFAs and bile acids, initiate several metabolic pathways that regulate glucose absorption, insulin sensitivity and inflammation in the body. There are three types of SCFAs, i.e. acetate, propionate and butyrate, produced by bacteria present in the colon.

The Bacteroidetes type is known to produce acetate and propionate, whereas the Firmicutes type produces butyrate by fermentation of dietary fiber. SCFAs help regulate energy expenditure, glucose homeostasis and hepatic lipogenesis, which have a significant impact on DM2 and obesity.

Experts have found that butyrate reduces insulin sensitivity in diabetic mice with a high fat content, stimulating energy consumption and inducing mitochondrial function. Oral administration of acetate in rats with DM2 reduces lipogenesis in adipose tissues and liver. It improves glucose tolerance by inhibiting the transcription factor ChREBP (a protein binding elements that react to carbohydrates), which is necessary for the conversion of glucose into fatty acids in the liver.[10]

Dietary propionate improves the function of ß-cells and promotes the secretion of insulin through the protein kinase of C-dependent pathway. Experts have found that acetate and propionate act on L-cells, releasing GLP-1 (glucagon-like peptide-1) and PYY (peptide YY-hormone), which stimulate insulin secretion, glucose uptake by muscles and reduce the production of glucagon in the pancreas. Understanding GM and host metabolism may be a potential strategy for controlling DM2 by modulating host GM. Bioactive compounds are phytochemicals such as polyphenols, anthocyanins, flavonoids, carotenoids, alkaloids and tannins contained in various parts of plants, including leaves, bark, root, and have functional benefits for maintaining normal health. Fruits and vegetables are also an important source of several biologically active compounds.

Bioactive compounds, such as phenols, flavonoids, alkaloids, anthocyanins, have significant antidiabetic properties by increasing the inhibitory activity of α-glycosidase, improving glucose tolerance, activating P13K/Akt and inhibiting JNK in signaling, improving serum lipid levels and reversing insulin resistance, increasing the expression levels of insulin receptors and glycolytic enzymes and reducing the expression of the substrate of insulin-1 receptors and gluconeogenesis enzymes.[11]

Products saturated with biologically active compounds must go through various metabolic processes in the body, where they find a place for maceration and release of potential biologically active compounds. Microorganisms have always been considered as a stable approach to soaking phytochemicals from food products during fermentation.

The gastrointestinal tract is suitable as a place where biologically active compounds can be extracted after ingestion and used in several metabolic processes. Several studies have shown a two-way relationship between bioactive compounds and IM.

IM plays a crucial role in modulating the production, bioavailability and biological activity of biologically active compounds, especially after eating a meal containing high-molecular polyphenols. In addition, bioactive compounds can be converted from the colon into metabolites, such as SCFAs and bile acids, which can affect the ecology of the intestine and affect the health of the host by participating in several metabolic pathways. On the other hand, bioactive compounds entering

the IM with various dietary schemes modulate the composition of the IM due to the action of aromatic metabolites. In recent years, the focus of research has shifted towards the modulation of IM by bioactive compounds to combat metabolic diseases such as diabetes and obesity.[12].

Studies have shown that bioactive compounds modulate the composition of microflora either through selective prebiotic action or antimicrobial action against pathogenic bacteria in the intestine. Modulation of the colon microbiota may contribute to the control of DM2, although the mechanisms of antidiabetic action are not clearly explained. Studies have shown that allicin modulates the activity of *Firmicutes* to *Bacteroidetes*, therefore, it supports glucose homeostasis and insulin sensitivity. Saponin reduces the ratio of *Firmicutes* and *Bacteroidetes*, which is again useful for controlling DM2. Protocatechic acid increases GLP-1 secretion, and serum insulin also improves insulin resistance by reducing the ratio of *Firmicutes* to *Bacteroidetes*.

Contradictory results were obtained by other studies in which flavonoids from green algae increased the number of *Firmicutes to Bacteroidetes*, but reduced blood glucose levels and improved insulin sensitivity, which may be associated with other niches of microflora in the ecology of IM.

Bifidobacteria spp. enhance the expression of proteins involved in the insulin signaling pathway and the expression of the hormone adiponectin, which regulates blood glucose levels and reduces inflammatory adipokines. The researchers reported that Bifidobacterium spp. significantly increased energy extraction and fat accumulation, as well as reduced the expression levels of TNF-α and LPS (lipopolysaccharides) in diabetes models. In addition, Bifidobacteriumspp reduces endotoxemia and inflammation, and improves glucose tolerance and insulin secretion by promoting the synthesis and secretion of hormone and GLP-1. Consequently, an increase in the number of *Bifidobacteriumspp*. helps to control DM2 with some biologically active compounds.[13]

Studies have shown that berberine, polyphenols, phenolic acids such as gallic acid and ellagic acid increase the level of *Bifidobacteriumspp*. that helps to maintain SD2. Similarly, *Lactobacillus spp*. Improve the glucose tolerance and normalize the inflammatory tone due to a decrease in LPS, as well as an increase in SCFAs production and inhibition of pathogenic intestinal microflora, which may be useful for maintaining DM2.

Various biologically active compounds increase the level of Lactobacillus spp. in IM for T2DM control. *Allicin, flavanols, alkaloids, betacyanins, protocatechic acid, florizine, polyphenols* increase the activity of *Akkermansia spp*. in IM. Antidiabetic action of *Akkermansia spp*. is described by different researchers. These mucin-decomposing bacteria can preserve the thickness of the mucus layer, thereby reducing intestinal permeability and leakage of LPS. It also improves insulin resistance by inhibiting JNKI and activating P13K signaling pathways. *Akkermansia spp*. promotes the secretion of GLP-1 from L-cells to suppress glucagon secretion.[14]

In addition, a number of microflora in IM is modulated by certain bioactive compounds. The potential antidiabetic effect of IM modulation by bioactive compounds is associated with an increase in the levels of B*ifidobacterium spp., lactobacilli spp , Ackermancy spp*. , as well as to the reduction of the relation of *Firmicutes* to *Bacteroidetes*. Consequently, certain biologically active compounds with the ability to modulate the intestinal ecosystem may be useful for use as prevention and therapy of DM2.

The main predictor of the composition of the human gut microbiota is diet. Scientific data confirm the importance of diet and its composition for changing the gut microbiota. Long-term consumption of the Western diet, excessive use of antimicrobials (antibiotics) and host factors, including age, sedentary lifestyle, etc., cause intestinal dysbiosis, which subsequently causes an increase in bacterial lipopolysaccharides, oxidative stress, release of pro-inflammatory substances, intestinal inflammation and permeability. All these changes over time cause the development of insulin resistance and DM2.

On the other hand, biologically active compounds from a healthy diet have a positive effect on maintaining intestinal eubiosis, which causes a weakening of the above-described pathological changes in the intestine, while improving insulin sensitivity and intestinal motility, which contributes to the prevention and treatment of DM2. In addition to these factors, the effect of specific micronutrients in the diet, the frequency of consumption of the Western diet, etc. on GM requires further investigation. Therefore, additional studies are needed to clarify the complex interactions between biologically active compounds in the diet, GM, as well as in the occurrence and progression, as well as in the prevention and treatment of DM2.

CONCLUSION

Thus, it can be concluded that the prevention of dysbiosis will avoid the development of various diseases. DM2 becomes the most dangerous metabolic disorder after obesity, which is associated with various health risks. Global health organizations and disease control committees have announced the severity of DM2 and recommended taking preventive and curative therapeutic measures to control this metabolic disorder. Several studies conducted in recent decades have proved that DM2 is mainly caused by a combination of an unhealthy diet and relative inactivity of insulin.[15]

Systemic studies of diet-induced DM2 have concluded the importance of GM and its role in the prevention of DM2. Various types of GM, such as *Firmicutes, Bacteroidetes, Lactobacillus and Bifidobacterium*. play a vital role in the control of DM2. Several scientific data have shown that lifestyle and dietary changes can affect healthy IM, which causes dysbiosis of IM responsible for DM2.

Recently, researchers have proven that diet-induced dysbiosis of IM can be solved by including dietary supplements such as polyphenols, prebiotics and biologically active compounds. Several systematic studies have recently confirmed the antioxidant and antimicrobial effects of bioactive compounds on IM. Various in vitro and in vivo studies have proven that the modulation of IM by bioactive compounds helps to prevent DM2 by improving glucose homeostasis, increasing insulin sensitivity and increasing the production of short-chain fatty acids.

Author Contributions

All authors contributed in reviewing the final version of this paper.

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