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Role of the gut microbiota in human health

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ABSTRACT

Introduction: The human gut microbiota has become the subject of extensive research in recent years and the knowledge of the species inhabiting the gut is growing rapidly. Microbiota plays an important role in human health and diseases. It takes part in obtaining and storing energy, as well as in metabolic functions.

The aim of the study: The purpose of the study is to collect and review scientific publications about the impact of gut microbiota on human health.

Material and method: The paper uses standard criteria as the research method. The articles used to create the reviews were published on the PubMed and Google Scholar platforms.

Description of the state of knowledge: Numerous studies suggest that composition of intestinal microbiota has impact on the long-term functioning of the human organism. Depressive disorders appear to be associated with changes in the microbiota. In depressed patients, fewer bacteria of the type Bacteroidetes and higher level of Alistipes are found. A few studies have demonstrated a link between gut microbial signatures and hypertension. Studies have shown that T2DM patients may have an altered composition of gut microbiota, mainly a decreased Bacteroidetes/ Firmicutes ratio and decrease in some functional bacteria when compared to healthy people. Intestinal microorganisms are also a key element in the proper functioning of the immune system by influencing the maturation process of the immune system's cells.

Summary: To sum up, numerous studies indicate that abnormal composition of the intestinal microflora is the cause of not only faster development of metabolic syndrome, but also other diseases. It influences the development of circulatory, nervous or immune system diseases. Its abnormal composition is influenced by many factors such as diet, lifestyle or antibiotic therapy.

Keywords: gut microbiota, health, probiotics, microorganisms

INTRODUCTION

The human gut microbiota has become the subject of extensive research in recent years and the knowledge of the species inhabiting the gut is growing rapidly [1]. Currently, there are approximately 100 billion microorganisms in the human digestive tract [2]. Microbiota plays an important role in human health and diseases. It takes part in obtaining and storing energy, as well as in metabolic functions such as fermentation or absorption of undigested carbohydrates. Intestinal microorganisms are also a key element in the proper functioning of the immune system by influencing the maturation process of the immune system's cells [3]. Numerous studies indicate that the intestinal microflora is an environmental factor affecting predisposition to obesity [4]. By modifying the ecology of intestinal microorganisms caused by dietary factors, antibiotics, probiotics or prebiotics, the relationship between the composition of intestinal microflora and obesity has also been demonstrated. Therefore, the identification of early changes in the intestinal microflora may predict the subsequent development of obesity [5].

THE IMPACT OF GUT MICROBIOTA ON HUMAN HEALTH

Cardiovascular system

Cardiovascular disease (CVD) is a class of diseases that involve the heart or blood vessels. CVD includes atherosclerosis, hypertension, heart failure, atrial fibrillation, myocardial fibrosis, cardiomyopathy [6]. Many risk factors are widely known, such as smoking, poor dietary habits, obesity, diabetes mellitus and high cholesterol, but these cannot explain all CVD incidences [7]. CVD is the main cause of death globally.

The recently discovered contribution of gut microbiota-derived molecules in the development of heart disease and its risk factors has significantly increased attention towards the connection between our gut and heart [8]. In the study, researchers using a targeted metabolomics approach aimed at identifying plasma metabolites, have identified a novel pathway linking dietary lipid intake, intestinal microflora and atherosclerosis [9]. The pathway identified, represents a unique nutritional contribution to the pathogenesis of CVD. Researchers performed a metabolomic analysis of the plasma of patients with known atherosclerotic disease. They identified three metabolites of dietary phosphatidylcholine—choline, betaine, and, trimethylamine N-oxide (TMAO)—and showed that these phospholipid metabolites were independent predictors for the risk of a clinical vascular event. The pro-atherogenic gut flora-generated metabolite, TMAO, is formed in a two-step process initiated by gut flora-dependent cleavage of a trimethylamine species generating the precursor TMA, and subsequent oxidation by FMO3 [9]. Results indicate that both environmental exposure (dietary lipid) and microbial flora participate in TMAO production and the atherogenic macrophage phenotype and are consistent with the view that trimethylamine, the precursor of TMAO is produced by gut microbiota. It confirms earlier observations in germ-free mice on the bacterial origin of this methylamine [10]. The incidence of cardiovascular events increases with the elevated levels of TMAO in patients with acute coronary syndrome whose troponin T is negative [11]. Gut microbiome, especially Synergistetes phylum, Spirochaetes phylum, Lachnospiraceae family, Syntrophomonadaceae family and Tissierella Soehngeniagenus, present a higher trend in acute MI animal models [12]. TMAO is associated with increased risk of adverse cardiovascular events including MI in stroke patients [13]. It can predict adverse outcomes of all-cause mortality or reinfarction 2 years after MI [14]. A few studies have demonstrated a link between gut microbial signatures and hypertension. It has been illustrated that intestinal flora facilitate vascular dysfunction induced by angiotensin-II (Ang-II) by promoting systemic inflammation responses that lead to high blood pressure [15]. One study found that Klebsiella, Clostridium and Streptococcus are more abundant in hypertensive patients [16]. TMAO does not affect blood pressure directly but prolongs the haemodynamic effects of Ang-II [17]. In heart failure (HF) patients, reduced cardiac output and blood redistribution result in a decrease in intestinal perfusion and disruption of the intestinal barrier. Thus, the microbiota and endotoxins translocate into the blood circulation, aggravate systemic inflammation and exacerbate HF [18]. Elevated TMAO level is relevant to the severity of HF and indicates a worse prognosis [19]. A growing body of data reveal a strong association between TMAO and myocardial fibrosis. TMAO can aggravate myocardial interstitial fibrosis and perivascular fibrosis, damaging heart compliance and function [20]. TMAO can reverse the protective effect of voluntary exercise on myocardial fibrosis induced by high sugar and fat diet [21]. The mechanism by which TMAO aggravates myocardial fibrosis is not fully understood. Moreover all these results suggest that an appropriately designed probiotic intervention may serve as a therapeutic strategy for CVD.

The gut brain-axis

Gut bacteria have the ability to communicate with the CNS in two ways by numerous mechanisms: changes in the composition of the microbiota, stimulation of the immune system, through the neural pathways (vagus nerve), by tryptophan metabolism, the endocrine response of the gut, and metabolites produced by bacteria [22-26]. The gut microbiota affects the central nervous system (CNS) through ability to synthesize and secrete several of neuroactive molecules such as acetylcholine, catecholamines, gamma-aminobutyric acid, histamine, melatonin and serotonin (5-hydroxytryptamine) [27]. CNS functions can also be influenced by short-chain one's fatty acids, which are fermentation products of bicarbonate and have the ability to penetrate the systemic circulation [28]. Moreover, microbiota of the intestine secretes neurotrophins and proteins, e.g. neurotrophic origin factor brain (BDNF), synaptophysin, postsynaptic protein density 95 (PSD-95). Information of hormonal and neuronal changes, changes in the composition of the intestinal tract biota passes straight to the brain through the vagus nerve that forms direct connection between the digestive system and the brain [29]. These interactions can also interact to the pathogenesis of numerous disorders, the etiopathogenesis of which has a component inflammatory - mood disorders, ADHD, autism [30]. Chrobak et al. describe that slight inflammation may play an important role in the pathophysiology of depression and disorder [31]. Stress is one of the strongest factors in everyday life that affect the composition of the gut microbiota. Microbiota of the intestines are influenced by both emotional and physiological stress [32]. Dinan and Cryan showed that in healthy students it occurs in samples during periods of increased stress less *Lactobacillus* bacteria in stool compared to collected samples in a less stressful period [33].

Neuropsychiatric diseases:

While writing about neuropsychiatric diseases, it should be mentioned that the intestinal microbiota has the ability to convert undigested carbohydrates to short-chain carbohydrates fatty acids (SCFA) such as acetate, propionate and butyrate. These short-chain fatty acids can bind and activate the associated receptors with G proteins (GPR 41 and GPR 43) on intestinal epithelial cells, which leads to secretion of peptide YY (PYY) which inhibits gastrointestinal motility and delays intestinal transit [34]. SCFAs also show the ability to activate the receptors GPR 120, which improve glucose metabolism, GLP-1 release and maintenance of immune homeostasis (reduction of inflammation). Moreover, some researches show that propionate may induce autistic-like behavior in rats [35]. Autism (ASD) is one of the neuropsychological disorders in which microbiota plays a key role. Recent studies have shown that the microbiota in patients diagnosed with autism differs from the control group [36]. The number of *Clostridium* was significantly increased in group of autistic patients. Further evidence for the role of microbiota in autism pathogenesis was obtained by observing improvements in behavior and skills communication after antibiotics and probiotics treatment [37]. Depressive disorders, which are the most commonly diagnosed psychiatric disorders, also appear to be associated with changes in the microbiota. In depressed patients, fewer bacteria of the type *Bacteroidetes* and higher level of *Alistipes* are found [38]. Increasing numbers of *Alistipes* have been observed in others diseases such as, for instance, chronic fatigue syndrome [39]. The quantity and quality of the gut microbiota can also influence the presence of mood changes and anxiety disorders.

Anxiety disorders commonly coexist with irritable bowel syndrome [40]. In a study by Rao et al. supplementation *L. casei* Shirota decreases the incidence of anxiety disorders in patients with chronic fatigue syndrome. The gut microbiota seems to play a significant role in the pathogenesis of many diseases, but the detailed understanding of the mechanisms composing this phenomenon requires further research which may enable future development of new treatments for these symptoms [41].

Parkinson's disease

Parkinson's disease (PD) is a progressive, neurodegenerative disorder of the CNS. This condition is characterized by the formation of Lewy bodies, made of alpha-synuclein in the substantia nigra in the midbrain. Loss of dopaminergic neurons results in motor symptoms such as akinesia, gait disorder, and resting tremor [42, 43]. Studies have shown that dysbiosis of gut microbiota plays an important role in progression of PD [44-47]. It was found that stool of PD patients contained decreased amount of *Prevotellaceae* species and increased amount of *Enterobacteriaceae* species [48]. Lower abundance of *Prevotellaceae* leads to excessive production of α -synuclein in the colon and even support its abnormal folding [49]. *Enterobacteriaceae* overgrowth leads to an increased lipopolysaccharide (LPS) levels. LPS disrupts the intestinal epithelial barrier, penetrates the blood system, where it induces systemic inflammation and cytokine synthesis [50]. Inflammation promotes destruction of the blood-brain barrier, which determines the formation of Lewy bodies and destruction of dopaminergic neurons [51]. Additional reports also point to an increased amount of other pro-inflammatory bacteria such as *Ralstonia*, *Proteobacteria* or *Enteococcaceae* as well as to decreased amount of *Blautia*, *Coprococcus*, *Roseburia* and *Faecalibacterium*, that are considered as an anti-inflammatory bacterium [52]. Probiotics containing bifidobacteria and lactobacilli are reported to reverse the PD-like condition and the probiotic bacterium *Bacillus* spp. may convert L-Tyrosine into L-DOPA which is converted to dopamine [53, 54].

Alzheimer disease

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by formation of β -amyloid plaque and neurofibrillary tangles of hyperphosphorylated tau. This syndrome manifests as memory, language and behavior impairments which leads to loss of performing basic activities of daily living [55]. It has been shown that the diversity and composition of the gut microbiota of healthy people are significantly different than in patients with Alzheimer's disease [56]. A 2017 study reports that the microbiome of AD patients contains significantly less *Firmicutes* and *Actinobacteria*, and significantly more *Bacteroidetes* [57]. Bacterial metabolites induce inflammation that increases intestinal permeability and blood-brain barrier, which promotes the production of beta-amyloid in the brain [58-60]. β -N-methylamino-L-alanine (BMAA) is one of the neurotoxins produced by intestinal cyanobacteria which may cause neurodegeneration and cognitive impairment [61]. LPS induces the formation of A β fibrils which are a potent inducer of NF- κ B known to be involved in neuroinflammation in the AD brain [62, 63]. As in PD, probiotic supplementation may be protective in AD. A randomized, double-blind controlled clinical trial showed a positive effect of the combination of *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus bifidum*, *Lactobacillus fermentum* on cognitive function in AD patients [64].

The supply of *Bifidobacterium* may lead to a decrease in the level of pro-inflammatory cytokines TNF- α , IL-5, IL-6, IL-1 β and IL-8 in the serum [65].

Type 1 diabetes

Type 1 diabetes (T1D) is one of the most common chronic diseases of childhood and the second most common autoimmune disease among children. However, it can be recognized at any age. T1D is accompanied by many complications and has life-long morbidity [66, 67]. It is thought to be precipitated by T-cell-mediated destruction of insulin-producing pancreatic β cells. As a result, insufficient insulin production and its deficiency disrupts glucose uptake into tissues leading to the development of life-threatening health complications [68]. The development of T1D is associated with various factors, such as diet, genome, and intestinal microbiota. Gut microbiota is thought to play an important role in stimulating the development of the immune system [69]. There are different mechanisms that may explain the role of the gut microbiota in the pathogenesis of T1D [67]. T1D patients are exposed to increased mucin degradation by bacteria, which results in decreased integrity and increased permeability of the intestinal mucosa. As a result, bacteria penetrate the intestinal mucosa and the immune system is stimulated, which leads to the production of antibodies against them [70]. Additionally, certain groups of bacteria can alter the integrity of the mucosa by affecting zonulin, which is a protein responsible for modulating the intercellular junction and the passage of macromolecules through them [71]. Moreover, study conducted by Cardwell's team showed that the risk of T1D onset in childhood is higher in children delivered by Caesarean section [72]. One of the plausible explanations for this phenomenon is difference in gut microbiotic composition between vaginally born children and children born by Caesarean section. In second case, infants were first exposed to bacteria originating from the hospital environment rather than to maternal bacteria [73].

Type 2 diabetes

Type 2 diabetes (T2DM) is the most popular form of diabetes mellitus involving disorders of insulin action and insulin secretion. T2DM patients, which accounts for approximately 90-95% of cases, are at risk of developing macrovascular and microvascular complications [74, 75]. In addition to the main risk factors such as sedentary lifestyle, poor diet and obesity, some research indicates an increasing role of the intestinal microbiota in the development of T2DM [76]. Studies have shown that T2DM patients may have an altered composition of gut microbiota, mainly a decreased Bacteroidetes/ Firmicutes ratio and decrease in some functional bacteria such as Bifidobacteria when compared to healthy people. The Bacteroidetes/ Firmicutes ratio is an environmental factor that provides genetic material for the increased ability to obtain energy from diet. Moreover, an increase in various opportunistic pathogens and also in endotoxins-producing gram-negative bacteria was discovered [74,77]. Additionally, gut-derived bacterial inflammatory molecules such as lipopolysaccharide and peptidoglycans are believed to accelerate inflammation in T2DM when they accumulate in the intestine [74]. According to Sabatino et al., the reduction in butyrate-producing bacteria such as *Roseburia intestinalis* and *Faecalibacterium prausnitzii* is characteristic for T2DM patients [78].

Moreover, Furet et al. found that the proportion of *Faecalibacterium prausnitzii* species is directly related to a reduction in low-grade inflammation following intervention in type 2 diabetes, regardless of caloric intake. It makes *F. prausnitzii* a potential microbial target used in glucose homeostasis control in T2DM patients [79].

SUMMARY

To sum up, numerous studies indicate that abnormal composition of the intestinal microflora is the cause of not only faster development of metabolic syndrome, but also other diseases. It influences the development of circulatory, nervous or immune system diseases. Its abnormal composition is influenced by many factors such as diet, lifestyle or antibiotic therapy. The range of inter-personal variability in the composition of microbiota in the population has also become apparent and probably affects individual reactions to the administration of drugs and diet manipulation. Probiotics and prebiotics are increasingly being used to change the composition of the microflora. However, there is still no evidence of their effectiveness when used for a long time.

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