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METABOLIC SYNDROME AND GUT MICROBIOTA - A REVIEW

Ivan Dolanc[1], Ivona Brodić[2], Tamara Sorić[3*], Antonija Jonjić[1], Tea Čaljkušić-Mance[4], Luka Bočkor[1], Miran Čoklo[1]

[1]Centre for Applied Bioanthropology, Institute for Anthropological Research, Ljudevita Gaja 32, 10000 Zagreb, Croatia
[2]Nutrition ID Ltd., Vranovina 30, 10000 Zagreb, Croatia
[3]Nutrition Department, Psychiatric Hospital Ugljan, Otočkih dragovoljaca 42, 23275 Ugljan, Croatia
[4]Department of Ophthalmology, Rijeka University Hospital, Krešimirova 42, 51000 Rijeka, Croatia

[*]e-mail: novoselic.tamara@gmail.com

Abstract

The relationship between gut microbiota and human health is complex, and the role of gut microbiota in pathogenesis of various diseases has been in the focus during the last decade. There is accumulating evidence that dysbiosis can be linked to different diseases, such as metabolic syndrome (MetS). Still, there is no consensus on the most appropriate tools and approaches for microbiota analyses. Numerous factors - diet, lifestyle, chemical microenvironment etc. influence the composition of gut microbiota. We aimed to analyze the current state of the knowledge on complex interplay between gut microbiota and development of MetS, as a basis for future research.

The permanent interplay between immune system, metabolism, and gut microbiota plays a significant role in the homeostasis control and potential obesity development. Increased energy harvest from the diet, changes in gene expression, energy expenditure and storage are mentioned to lead to inflammation, insulin resistance and MetS. Most of the data on its mechanisms were from mouse models, so the question of their informativeness for human microbiota research arose. Current state of the literature (using PubMed database), including GWAS studies of obesity in mice, suggests that they are relevant for human studies of microbiota composition change in response to diet. Besides the role of *Firmicutes/Bacteroidetes* ratio in predisposition to obesity, its difference in obese and lean humans and its decrease with weight loss, confirms the dominating role of nutrition in shaping gut microbiota composition and functions. There is an increasing evidence that microbiota can inflict their reach on physiological functions outside the gastrointestinal tract, and can therefore possibly manipulate our eating behaviour, using metabolic, neural, immune and endocrine pathways.

Our findings implicate a deeper host-microbiota relationship than previously realized, which may contribute to broader and multilayer approaches in future research of gut microbiota and shaping of prevention strategies for tackling MetS.

***Key words**: Diet, Gut Microbiota, Metabolic Syndrome, Modulation, Prebiotic, Probiotic.*

1. Introduction

The relationship between gut microbiota and human health is extremely complex, and the role of gut microbiota in the pathogenesis of various diseases has only been in the focus of researchers in the last decade [1]. There is growing body of evidence suggesting that dysbiosis of the gut microbiota can be associated with different diseases, including metabolic syndrome (MetS) [2].

MetS is defined as a cluster of several metabolic risk factors and its presence is known to be closely associated with numerous negative health implications [3]. According to the results of the study conducted by Scuteri *et al.*, [4], the overall prevalence of MetS across Europe was 24.3% with the use of USA National Cholesterol Education Program (NCEP) ATP III definition. Due to the extremely complex

pathophysiology of MetS, the exact reasons for its growing incidence throughout the world are still not completely elucidated. However, there is accumulating body of evidence proposing the significant influence of gut microbiota on the development of this group of interconnected metabolic disorders.

Sidhu and van der Poorten, [5], define gut microbiota as "a complex and essential part of our bodies that provides vital support for normal metabolic function and protection against illness". In the human body, the gut represents a microbial community that is heavily colonized and includes up to 10^{14} microbes, with the estimated total biomass which exceeds one kilogram in an average adult [6, 7]. The human gut microbiota consists of more than 2,000 different microorganisms, most of which are strict anaerobic bacteria and is prevailed by four bacterial phyla: the Gram-positive Firmicutes and Actinobacteria, and the Gram-negative Bacteroidetes and Proteobacteria [7, 8]. The overall gut microbiota, including the aforementioned bacteria, has a significant influence on host's physiology and disease prevention, and has an essential role in nutrition, and normal metabolic and immune functions [9]. Additionally, the gut microbiota produces numerous chemical mediators that can enter the circulatory system and communicate with distal organs, such as brain and liver, which is of a paramount importance for maintaining vital functions [10]. There is an increasing evidence that microbiota can inflict their reach on physiological functions outside the gastrointestinal tract and can therefore possibly manipulate our eating behaviour, using metabolic, neural, immune and endocrine pathways [9, 10].

Even though there is still no consensus on the most appropriate tools and approaches for microbiota analyses, it is well-known that the intestinal flora differs both qualitatively and quantitatively in each individual and that its composition and function is affected by different psychological (i.e. stress and anxiety), environmental (i.e. industrial pollution and environmental temperature), and physical influences (i.e. diet and physical activity) [11].

In the present study we aimed to analyze the current state of the knowledge (using PubMed database) on complex interplay between gut microbiota and development of MetS, as a basis for future research.

2. Metabolic syndrome and gut microbiota

2.1 The impact of gut microbiota on MetS development

As already mentioned in the introduction section, balanced gut microbiota contributes beneficially to the host in numerous ways. As it has a direct influence on physiological and pathological processes [12], when unbalanced it has been found to play a significant role in the development of various chronic non-communicable diseases [1, 13], as well as in the onset and progression of the MetS [13].

The consistent interplay between immune system, metabolism, and gut microbiota has a considerable impact on the control of metabolic homeostasis, as well as on the potential development of obesity [14]. The association between gut microbiota and MetS is based on several known mechanisms, including increase of energy harvest from the diet, changes in gene expression of the host, energy expenditure and storage, modulation of host's tissue fatty acids composition, and change in gut permeability [15]. All the above-mentioned changes could lead to inflammation, insulin resistance, and metabolic endotoxemia [15], which are all closely related to MetS.

Most of the data on these mechanisms of action were obtained from mouse models, so the question of their informativeness for human microbiota research arose. Current state of the literature suggests that mouse models are relevant for human studies of microbiota composition change in response to diet.

Although in general the mammalian digestive tract is strongly conserved, there are also some substantial differences. For example, humans have smaller cecum and colon and longer small intestine. There is also a difference in morphology and distribution of cells, such as goblet and Paneth cells [16]. To the similarity point, Bacteroidetes and Firmicutes are two major phyla both in human and in mice [17] and the mouse enterotypes correlate with species-richness and inflammation, the finding that has also been replicated in the human obesity studies, in which individuals with low species diversity presented more pronounced inflammation [16]. Furthermore, mice fed a high animal-fat diet showed an increased Firmicutes/Bacteroidetes ratio [18], the trend that was also observed in humans [19]. In total, these data suggest that mouse models are relevant for human studies in terms of microbiota composition change in response to diet. Another important genome-wide association study (GWAS) identified genes associated with obesity in mice. The results of the study demonstrated an overlap with a subset of genes associated with obesity in humans, suggesting a set of conserved mechanisms of obesity across the mammalian genomes [20].

Although the gap between mouse models and humans exists and has to be acknowledged, the advantage of manipulation of mouse models and extensive knowledge of mouse genetics and phenotypic characterization is extremely valuable in

understanding disease mechanisms that may result in getting us closer to developing preventive or therapeutic treatments of metabolic diseases [16].

Until today, the exact reason responsible for the impact of gut microbiota on the development of MetS remains unknown. According to the results of the comprehensive review conducted by Festi *et al.*, [21], the influence of gut microbiota on MetS development is affected by a complex interaction between a number of different factors, including diet, lifestyle characteristics, environmental factors, and genetics. However, the latest advancements in the field of sequencing technology have enabled the characterization of the human microbiota and have provided the opportunity for the identification and better understanding of the potential factors and their impact on its composition and function [22].

2.2 The impact of gut microbiota beyond the gut

Co-evolution of humans as hosts and their microbes may have resulted in competing fitness interests in this complex evolutionary conflict for resources and cost/benefit equilibrium changes for both the host and its microbiota.

The substantial amount of research has shown that these complex mechanisms of communication include metabolic, neural, immune and endocrine pathways. Many bacterial metabolic products are secreted into the intestine and reabsorbed into the host system, where they can exert their effect on the host's metabolic pathways. For example, butyrate can act epigenetically through histone deacetylases while folate is a methyl donor that participates in a chain reaction to create a substrate for DNA methyltransferases [23]. Other short chain fatty acids which are bacterial metabolic products are involved in many important functions of a host organism, including energy balance by modulation of adipose tissue and skeletal muscle function [24].

Neural pathways can be manipulated by altering levels of precursors and microbial synthesis and release of neurotransmitters that can cross the intestinal mucosal barrier. For instance, *Lactobacillus* and *Bifidobacterium* can produce γ-aminobutyric acid [25], and *Escherichia* spp. has been shown to produce dopamine [26]. Acetylcholine, histamine and serotonin have also been shown to be produced by different microorganisms [25]. More recently a theory has emerged that even linked the gut microbiota to the neurodegenerative disorders development, such as Parkinson's disease (PD) and Alzheimer's disease. The common future of these two disorders is protein misfolding and formation of aggregates in the brain. In recent years there were several papers documenting a role of microbiota in neurodegenerative diseases. Chen *et al.*, [27], reported the possible role of bacterial amyloids in α-synuclein production and aggregation in rats that were orally exposed to *Escherichia coli* producing curli (extracellular fibers produced by *Escherichia coli* and other enteric bacteria). Increased production of α-synuclein resulted in increased accumulation that was accompanied by enhanced cerebral inflammation (micro- and astrogliosis, up-regulation of Toll-like receptor 2, interleukin 6, and tissue necrosis factor). Sampson *et al.*, showed that intestinal microbiota from Parkinson patients induces motor impairment in α-synuclein overexpressing mice [28]. In a mouse model of Alzheimer disease, it was shown that antibiotic exposure lowers microbiota diversity and ameliorates amyloidosis and neuroinflammation [29] and that germ-free Alzheimer disease transgenic mice had reduced pathology compared to transgenic animals with normal intestinal flora [30]. It is also important to mention that transgenic animals have altered intestinal flora in comparison to non-transgenic animals, and that transfer of microbiota from transgenic to germ-free transgenic animals fully reproduced cerebral amyloid beta phenotype [30]. Although most of the data were obtained in animal models, there is also clinical evidence for the gut microbiota-neurodegenerative diseases axis. Recently it was found that α-synuclein aggregates in gut neurons in PD. As constipation is an early future of PD, this may suggest that microbiota may be responsible for the disease onset. Moreover, bovine spongiform encephalopathy and kuru originate from gut entry of misfolded proteins [31]. PD patients have altered intestinal microbiota [32], while the detailed analysis of gut microbiota in AD patients is still lacking [33].

All these results point to the fact that gut microbiota impact physiological functions far beyond the gut, and can even exert their effect in the central nervous system. Due to these observations an idea has emerged that gut microbiota choose what we eat through potential mechanisms mentioned before [34]. The recent study further confirmed manipulation of eating habits by gut microbiota. The authors manipulated the microbes inside *Drosophila melanogaster* and found that essential amino acids and coordinated action of *Acetobacter pomorum* and lactobacilli modulated the flies' choice of food [35].

2.3 Dietary modulation of gut microbiota

Diet represents one of the key elements in the pathophysiology of many chronic non-communicable diseases and is considered as one of the most important modulators of the gut microbiota composition and functions [36] that could be both positive and negative depending on the diet quality. Due to the fact that infant feeding patterns occupy an important place in the colonization of the gut microbiota, the essential

place of the diet in shaping the intestinal microbial community is visible from the first days of life [37 - 39].

It is well understood that any change in the lifestyle pattern or in the diet quality may affect microbial stability. When speaking more specifically about diet, previously conducted studies have confirmed beneficial effects of numerous nutrients and the overall diet quality on the modulations of gut microbiota [40].

As stated by Turnbaugh *et al.*, [22], switching from the diet low in fat and rich in plant polysaccharides to a so-called "Western" diet with a high fat and high sugar content resulted in a change of gut microbiota within a day. "Western" dietary pattern is also characterized by the high intake of ultra-processed food, which is according to the Zinöcker and Lindseth, [41], one of the factors responsible for the changes of the gut microbiota and inflammation-related processes. Furthermore, a comparative study of fecal microbiota in European (n = 15) and rural African children (n = 14) showed a significant microbial diversity depending on the group's diet. The diet of European children was characterized by high intake of fat, together with the low intake of dietary fiber. On the other hand, the diet of children living in a rural part of Burkina Faso was mainly vegetarian, with low fat and animal protein content. Their diet also had high amounts of plant polysaccharides, starch, and dietary fiber [19]. When looking at the composition of the children gut microbiota, the Burkina Faso children had significantly higher amounts of Bacteroidetes and lower amounts of Firmicutes ($p < 0.001$). Additionally, their intestinal flora was rich in *Prevotella* and *Xylanibacter*, which contain bacterial genes that are completely missing in the European children. Another major difference in the gut microbiota composition of the study participants was a significantly higher level of *Enterobacteriaceae*, mostly *Escherichia* and *Shigella*, in European children ($p < 0.05$) [19]. According to the authors, those differences in the gut microbiota composition are the result of the microbial adaptation to the diet, with consequent enrichment of bacterial species hydrolyzing complex polysaccharides in the high-fiber diet group of rural African children, whose microbial diversity potentially protects from inflammation and non-infectious colonic disease through short-chain fatty acids (SCFA) production [24], Interestingly, higher level of SCFAs has been found in feces of obese individuals when compared to lean individuals, both in mice and humans [42]. This implicates that SCFAs have a dual role in possible modulation of obesity, depending on the SCFA species. On the other hand, the Western dietary pattern promotes the overgrowth of Gram-negative pathogens, with consequent increased intestinal translocation of lipopolysaccharides, culminating in an inflammatory cascade which may lead to the development of insulin resistance, obesity and diabetes [43].

Similarly, a study conducted by Yasunenko *et al.*, [44], compared gut microbiota between Amerindians from the Amazons in Venezuela, rural Malawian residents and the population from the urban American area. According to the obtained results, gut microbiota composition significantly differed between the studied population groups, which highlights the impact of lifestyle, including diet, on the gut modifications [44].

When observing the results of previously conducted studies it can be concluded that nutrition plays a key role in shaping gut microbiota composition and function. Besides the role of Firmicutes/Bacteroidetes ratio in predisposition to obesity, its difference in obese and lean humans and its decrease with weight loss, confirms the dominating role of nutrition in shaping gut microbiota composition and functions [19]. Nutritional modulations of the gut microbiota that could have beneficial effects in the prevention and treatment of different metabolic disorders, including MetS, should include high amounts of fiber-rich cereals, fruits, vegetables, fish, olive oil, and nuts, together with the low intake of meat, processed meat products, and trans-fatty acids, and moderate intake of red wine [45].

2.4 Probiotic and prebiotic modulation of gut microbiota

Although antibiotics are widely used for the treatment and prevention of bacterial infections, they do not only affect pathogens, but potentially even some desirable bacteria residing in the digestive system, which could consequently lead to dysbiosis of the gut microbiota [46]. It is well-known that antibiotics mostly have just a temporary impact on the human gut microbiota; however, more recent information applies that the impact of several antibiotics could be prolonged for an extensive period of time [47]. Widespread use of antibiotics has also been associated with the breakthrough of antibiotic-resistant pathogens [47].

On the other hand, probiotics can alter human gut microbiota in a more biological way [46]. The term probiotic means "for life" and according to the definition those are "live microorganisms which when administered in adequate amounts confer a health benefit on the host" [48]. Probiotics can exert beneficial effects on the gut environment and the overall human health through several potential mechanisms, including the amelioration of the gut barrier function, competition with pathogens, production of anti-microbial compounds, and others [46, 49]. However, there is no unique beneficial effect characteristic for all probiotics [50].

Recently, many different organisms, mostly those that are naturally present in the human gastrointestinal tract, have been studied with the purpose of exploring their potential use as probiotics. According to Aoki *et al.*, [51], the most common probiotic microorganisms are *Bifidobacterium* and *Lactobacillus* spp. Until today, numerous published studies have confirmed that both *Bifidobacterium* and *Lactobacillus* spp. have beneficial effects in targeting MetS. According to the results of a recently published systematic review of nine randomized clinical trials, the intake of probiotics in patients diagnosed with MetS may positively affect some of the MetS features; however, the overall impact was not considered clinically relevant [52]. Another review concluded that the use of probiotics can positively modulate human gut microbiota and consequently exert variety of health benefits to the host [53]. Despite the numerous studies that have confirmed positive impacts of different probiotic strains on MetS through the modulation of gut microbiota composition, there are also studies that have led to opposite results. One of those studies is a randomized pilot study conducted on 28 subjects with the diagnosis of MetS [54]. The authors of the mentioned study highlighted that the presence of MetS is connected with a higher Bacteroidetes/Firmicutes ratio and the dysfunction of the gut barrier which did not change significantly after 12-weeks *Lactobacillus casei* Shirota supplementation [54].

Similar to probiotics, prebiotics are also often associated with gut microbiota modulations and are in the focus of researchers since their introduction to the scientific literature. They were first described by Gibson and Roberfroid, [55], as "a non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improve host health". Prebiotics are also known for escaping the digestion in the small intestine and reaching the colon in an intact form, where they are subject to complete or partial fermentation by the gut microbiota [56]. Until today, numerous interventional studies have confirmed beneficial effects of several food components with prebiotic activity, including fructo-oligosaccharides and galactooligosaccharides, on human gut microbiota [57]. They have the ability to boost the proliferation of several beneficial microbes or prebiotics and thus consequently maximize positive changes of the human gut microbiota [58].

3. Conclusions

- Our findings implicate a deeper host-microbiota relationship than previously realized, which may contribute to broader and multilayer approaches in future research of gut microbiota and shaping of prevention strategies for tackling MetS.
- Moreover, it may contribute to prevention of risks from a wide spectrum of human diseases, including tumors and neurodegenerative diseases.

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