

# NUTRITION AND MICROBIOTA

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**Abstract:** Close interaction between gut microbiota, diet and health has long been recognized and is intensively studied. Recent research shows that microbiota signatures may serve as important biomarker in personalized nutrition allowing for a noninvasive yet highly efficient therapy of chronic diseases. Probiotics' research brings the first human trial with next generation probiotic – *Akkermansia muciniphila* and demonstrates its safety and great potential for the treatment of metabolic disorders, but also shows that sequential application following a defined administration protocol, might be of particular relevance for therapy success. Plant-based dietary choices enrich gut microbial diversity, while recent studies show that spices, berries and nuts, known as nutritionally rich foods, appear to have prebiotic effects. Veganism and restricted feeding, which are recognized as promising approaches for combating obesity and related disorders are conferring their beneficial effect, at least partially, through microbiota modification.

**Keywords:** Gut microbiota, Nutrition, Precision nutrition, Prevotella, Firmicutes to Bacteroidetes ratio, Obesity.

## INTRODUCTION

This review focuses on the most prominent findings regarding interaction between gut microbiota and nutrition that were published in the period from the April 2019 until the March 2020. In the preceding year over 2000 scientific articles were published, out of which 510 reported results obtained from human subjects, while 60 published outcomes of clinical studies conducted in adults (>18 years). The research has been greatly focused on the relevance of individual taxonomic categories among human gut commensals, and their involvement in disease progression and prevention. The research results highlight the role of individual gut microbial profiles in the nutrition-based personalized modifications aimed at alleviation of the disease and associated risk factors.

Gut microbiota plays an important part in nutrient bioavailability. Richness in the gut microbial community predisposes good health outcome, as commonly accepted<sup>1</sup>. Individual clusters of microbial communities, which might, to some extent, be explained by enterotypes, are becoming significant hallmarks for personalized nutrition approach in disease management. However, microbial species (or, if uncultured, so-called operational taxonomic units – OTUs) are a matter of increasing research, in the context of the involvement of individual species in health and disease.

## GUT MICROBIOTA AND NUTRITIONAL INTERVENTIONS IN HEALTH AND DISEASE

The gut microbiota is associated with metabolic syndrome, among other conditions, and a recent study indicated presence of gender-specific features affecting the microbiota dysbiosis in the state of metabolic dysbalance<sup>2</sup>. In addition to clustering of microbiota profiles between patients and healthy individuals, there is a considerable variation of microbiota profiles be-

tween individual patients, that might be critical for a disease treatment. In line with this, data published by Rodriguez and coauthors highlighted that gut microbiota characterization could be a facilitating tool for personalized prebiotic intervention in disturbed metabolic conditions<sup>3</sup>. The study showed that in obese subjects, levels of *Anaerostipes*, *Akkermansia* and *Butyricoccus* reinforced inulin-induced decrease in the body mass index<sup>3</sup>. The microbiota profile was used in one case-spouse study to design personalized lifestyle intervention plan. Abundance of particular microbial genera differentially associated with risk of weight gain, inflammation, weight and appetite regulation, and fat accumulation, was used to define category of risk for the treatment plan. Integration of microbiota and genetic profiles in a personalized approach yielded weight loss and blood pressure optimization, upon four months in this case study<sup>4</sup>.

Wan et al<sup>5</sup> demonstrated that isocaloric diets with different proportions of fat applied during a 6-month intervention in a randomized controlled clinical trial (RCT), induced changes in microbiota profiles, fecal metabolites, and inflammation biomarkers. The study was performed in 217 healthy, young, non-obese adults residing in China. The higher proportions of dietary fat induced a decline in Firmicutes to Bacteroidetes ratio, while promoting abundance of *Alistipes* and *Bacteroides*, which directly affected serum lipids. In the same study, low-fat diet, mimicking the traditional dietary habits in China until 30 years ago, increased richness of microbiota and elevated *Faecalibacterium* and *Blautia* abundance, the latter directly associated with more favorable serum lipid profiles. The metabolomics' analyses revealed that in comparison with low-fat, high-fat diet increased the fecal levels of palmitic acid, stearic acid, arachidonic acid, indoleacetic acid, indole and *p*-cresol, that was followed by the decrease in short chain fatty acids and the beneficial 3-indolepropionic acid. This study underscores importance of the dietary influence on both, gut microbial taxonomic composition and its functional activity seen through the perplexity of fecal metabolites. Another cross-sectional study<sup>6</sup> in 297 healthy adults confirmed that the richness of short chain fatty acid-producing bacteria (including *Blautia*, *Eubacterium hallii*, and *Megamonas*) is inversely correlated with the level of dietary fat in the habitual diet. Furthermore, a cross-sectional study in 182 pre-diabetic elderly subjects ( $\geq 65$  years old) showed that although *Prevotella* was higher in non-obese subjects, obesity as such was not a risk for type 2 diabetes development. A healthier dietary pattern observed through dimension reduction techniques, corresponded to a specific microbiota profile represented by a decrease in *Prevotella*, and increase in *Faecalibacterium prausnitzii* and lactic acid bacteria, which was associated with lower risk of type 2 diabetes<sup>7</sup>. Furthermore, serum levels of vitamin D biomarkers were shown to be directly associated with levels of beneficial bacteria, while dose-dependent 8-week treatment with oral vitamin D<sub>3</sub> increased the abundance of *Bacteroides* and *Parabacteroides*, associated with more favorable outcome in inflammatory bowel disease. The study was performed in twenty, otherwise healthy, but vitamin D insufficient adults, underpinning the role of vitamin D in health and disease over the microbiota modulation<sup>8</sup>.

Another, four-week cross-over intervention demonstrated that typical Korean diet, in contrast to traditional and recommended American diets, has a potential to increase Firmicutes to Bacteroidetes ratio and stimulate the metabolism of branched-chain amino acid. The findings at the genus level differed considerably between individuals, while measured fecal metabolites were similar between individuals that shared similar microbiota profiles (and could therefore be classified within the same enterotype), confirming a role for microbiota-based precision nutrition in populations undergoing nutritional transition<sup>9</sup>. The link between microbiota composition and a response to a dietary intervention could be explained by the fact that due to the, so called, functional redundancy, one function can be performed by a number of different microbes. Also, different microbes have the capacity to utilize the same nutrient but produce different metabolites. Therefore, identical dietary intervention might promote stimulation of different microbial groups and different microbial metabolites in two individuals, depending on their microbiota composition. The interaction between the microbiota, food and health response is further complicated by the fact that the same classes of nutrients when originating from different dietary sources can have varying chemical structure. These structural differences underpin pathways of microbiota utilization and distinct health effects that one nutrient might have. In line with the latter, recently it has been shown that different types of resistant starch could stimulate either propionate or butyrate production,

providing evidence that precise nutrition is required for achieving targeted manipulations of the gut microbiota metabolic functions relevant to health<sup>10</sup>.

The integrity and inter-relationships among nutrition, gut microbiota, and health implications has been challenged in a twin-cohort study encompassing elderly females and assessing their visceral fat mass<sup>11</sup>. The advanced modeling approach study pinpointed independent associations between the gut microbiota and visceral fat mass, regardless of an array of nutrients, while the nutrients' associations were affected by obesity. Furthermore, the significance of the relationship between order Clostridiales and obesity parameters was the most affected by the dietary confounders, while vitamin E solely induced the greatest effect size decrease, particularly for the visceral fat mass associations with the following genera: *Bacteroides*, *Oxalobacter* and *Acidaminococcus* and the family of Rikenellaceae<sup>11</sup>. Furthermore, in outpatient subjects with non-alcoholic steatohepatitis, nutritional orientation solely without a diet plan, induced reduction in Bacteroidetes and Verrucomicrobiales, while in combination with a diet plan containing 30 g of fibers, provoked and increase in the abundance of all microorganisms<sup>12</sup>, indicating importance of the microbiota in clinical decision-making.

Finally, nutrition-driven microbiota modulation might also assist in combating communicable diseases. A recent study<sup>13</sup> examined whether habitual consumption of extra virgin olive modulated lipid profile, inflammatory biomarkers and intestinal microbiota in HIV positive subjects, and demonstrated that the oil decreased proinflammatory genera in intestinal microbial communities.

## DIETARY INTERVENTIONS FOR THE MODULATION OF MICROBIOTA PROFILES

Similar to previous years, food components with pre- or probiotic properties have been the focus of several research studies, with their reach now widening to metabolic disorders. Hence, a study in 26 healthy individuals demonstrated that two-week consumption of diet enriched with dietary fibers, including inulin-like fructans, improved food-related behavior in terms of increased satiety but decreased wish to eat sweet and salty foods, and induced beneficial modifications in the gut microbial community – as it elevated the proportion of *Bifidobacterium*, followed by a decline in Clostridiales, and a tendency to decrease Oxalobacteraceae<sup>14</sup>.

Furthermore, in an RCT, adults who were overweight or obese, received a 20 g/day for 42 days of either inulin-propionate ester, high-fermentable control fiber – inulin or low-fermentable control fiber – cellulose<sup>15</sup>. In comparison with the cellulose group, both inulin-containing treatments improved insulin sensitivity, although the inulin-propionate ester delivery method provided no superior effects over the inulin group. Both inulin-containing treatments decreased the relative abundance of Firmicutes, while inducing an increase of Bacteroidetes. In addition, high-fermentable fiber inulin induced bifidogenic effects, relative to the other two treatments. The microbiota changes were followed by respective modulations in immunological and inflammatory parameters, advocating the beneficial role of inulin-containing dietary interventions in subjects who are metabolically unhealthy. Probiotic interventions also appear as a powerful treatment option for metabolic disorders. Supplementation with *Lactobacillus reuteri* V3401 in metabolic syndrome subjects was associated with an increase in Verrucomicrobia, and also induced alleviation of interleukin-6 and soluble vascular cell adhesion molecule 1 levels<sup>16</sup>. It is relevant to note that the only currently cultured member of Verrucomicrobial phylum is *Akkermansia muciniphila*, a bacterium that has been inversely associated with obesity, diabetes, inflammation, and metabolic disorders, and therefore is, a so called, next generation probiotic. Given the strict regulations for application of live microorganisms in treatment, the first important step has been taken for *A. muciniphila* as its safety has been demonstrated in a pilot study<sup>17</sup>. In this study, although no changes in the overall gut microbiota structure were demonstrated, three months administration of the pasteurized bacteria improved insulin and obesity parameters and liver inflammation parameters.

Although they cannot be officially classified as probiotics, some food groups, such as fermented dairy products, are also of interest due to their microbiota modulation potential. In subjects with metabolic syndrome, 12-week kefir consumption although improving certain metabolic components, inclusive of insulin parameters, TNF- $\alpha$ , interferon- $\gamma$  and blood pressure; did not modulate relative abundance of *Bacteroidetes*, *Proteobacteria* or *Verrucomicro-*

*bia*, however significantly increased Actinobacteria<sup>18</sup>. On the other hand, in comparison with milk, daily consumption of yoghurt favorably balanced insulin resistance and liver parameters in Chinese obese women, possibly through the modulation of gut microbiota composition<sup>19</sup>.

Some probiotics and prebiotics have proven to be successful for alleviating gastrointestinal symptoms and in the previous year a number of novel strains and types of prebiotics was tested for this application. A study<sup>20</sup> showed that a four-week treatment with prebiotics consisting of inulin, lactitol, and aloe vera gel, all with laxative properties, induced a decrease in Firmicutes whilst elevating butyrate-producing bacteria abundance, potentially suppressing constipation adverse effects. Another prebiotic – partially hydrolyzed guar gum – was tested on patients that had loose stools and over seven bowel movements per day. The twelve-week trial resulted in an increase in *Bifidobacterium*, *Ruminococcus* and *Megasphaera* abundance, while exerting the opposite effect on *Bacteroides*, *Phascolarctobacterium* and an unclassified genus within the Lachnospiraceae family<sup>21</sup>. This shift in microbiota composition was followed by an improvement in stool consistency, although no change in bowel movement frequency was observed.

In subjects with irritable bowel syndrome, a fermented milk product containing *Bifidobacterium lactis* CNCM I-2494 induced changes in *Prevotella/Bacteroides* metabolic capacity evident through a decrease in hydrogen production in some patients<sup>22</sup>. In colorectal cancer patients, administration of non-starch polysaccharides showed distinct effects on microbiota prior and post-surgery. In perioperative period, the prebiotic treatment increased the richness of *Bifidobacterium* and *Enterococcus*, without any effect on these groups in the preoperative period when *Bacteroides* increase was noted, while in post-operative period, the abundance of *Escherichia-Shigella* was enriched in the prebiotic group<sup>23</sup>. Overall, the study pinpointed that although surgical stress increased the abundance of particularly opportunistic pathogens, prebiotic consumption supported a more beneficial microbiota balance<sup>23</sup>.

Finally, efficacy of commercial multispecies probiotics with evidence-based health effects was tested for a novel indication – subjects with early chronic kidney disease<sup>24</sup>. The study showed that a sequential application of several types of probiotics mixtures following a defined administration protocol, led to correction of gut dysbiosis evident through notably decreased fecal Lactobacillales and *Bifidobacteria*<sup>24</sup>. In addition to the microbiological shift, an improvement of inflammatory indices, iron status and serum calcium levels was observed, the latter relevant not only for renal diseases, but also for cardiovascular and musculo-skeletal health.

## MICROBIOTA AND FOOD CHOICES

Plant-based dietary choices enrich gut microbial diversity whereas low dietary fiber Western diet induces gut microbial dysbiosis, degradation of intestinal mucin layer and gut impermeability coupled with inflammation, which further increases chronic disease risk<sup>25,26</sup>. Specific foods and food groups, such as berries, nuts or spices are particularly interesting due to their beneficial health effects, which can be, as recent research data shows, at least partially attributed to microbiota modification. A pilot study<sup>27</sup> showed that consumption of mixed spices (cinnamon, oregano, ginger, black pepper, and cayenne pepper) at culinary doses resulted in a reduced Firmicutes to Bacteroidetes ratio in healthy adults, outlining prebiotic potential of habitual spice consumption. Another study<sup>28</sup> demonstrated that the effects of flaxseed lignan supplementation were mediated by enterolactones, and the excretion of the enterolactones was significantly associated with fecal microbiome. Another study in healthy men<sup>29</sup>, showed that consumption of aronia extract and the whole berry powder, elevated the abundance of *Anaerostipes* and *Bacteroides*, respectively, although failed to influence microbial richness assessed from the stool samples. Since the changes correlated with endothelial function, the study results highlight the potential of aronia polyphenols for cardiovascular primary prevention<sup>29</sup>. Furthermore, subjects with diabetes were instructed to follow a dietary plan inclusive of high-fibre, polyphenol-rich and vegetable-protein functional foods for three months<sup>30</sup>. The dietary intervention led to a decrease in *Prevotella copri*, and enrichment of anti-inflammatory *F. prausnitzii* and *A. muciniphila*<sup>30</sup>. Proper plant food choices and their incorporation into dietary patterns are of importance for achieving a favorable gut microbiota balance.

## DIETARY HABITS AND CALORIC RESTRICTIONS: VEGANISM AND INTERMITTENT FASTING

Adhering to a vegan diet remains a matter of open debate for social behavioralists, however, clinical benefits of dietary habits based on absolute avoidance of animal-based food, are yet to be understood. A systematic review summarizing studies which reported a relationship between dietary habits and gut microbial composition, included a cross-sectional study<sup>31</sup> in 36 vegans matched for the same number of omnivores, to explore the gut bacterial differences. The observational analyses showed discrepancies across the hierarchical taxonomic levels; at the genus level, *Bacteroides* was more abundant in omnivores than vegans, while *Prevotella* and *Faecalibacterium* were higher in vegans. At the species level, *Dialister invisus* was more abundant in omnivores, while vegans presented with higher levels of *Prevotella copri* and *F. prausnitzii*<sup>31</sup>. The review presented perplexing and heterogenous associations between nutrition and microbiota, pointing out the necessity for future research in the field.

Recognizing the importance of nutrition by general population has popularized a number of dietary regimes which promote good health. Both low FODMAP and low gluten diets have been commonly associated with distinctive effects on gut microbiota<sup>32</sup>. In the previous year low FODMAP diet was confirmed safe in patients with quiescent inflammatory bowel disease<sup>33</sup>, while Paleolithic dietary regime came into focus<sup>34</sup>. Individuals following this dietary regime avoid grains and dairy products and have a higher intake of protein and fat. As a direct consequence of grain intake reduction, beneficial activity of carbohydrates' utilizing microbes are suppressed, which was evident through microbiota shifts – reduction of *Bifidobacterium* and *Roseburia*. In addition to the suppression of beneficial bacteria, Paleolithic diet promoted abundance and activity of *Hungatella* that was also followed by an increase of trimethylamine-N-oxide, a metabolite associated with cardiovascular risk<sup>34</sup>.

Types of physical activity may also crucially determine the bacterial abundance in the gut, as seen in athletes consuming low-carbohydrate, low fiber diet<sup>35</sup>. This confirms the role of the gut microbiota in the development of personalized lifestyle strategies based on complex interactions between dietary and physical activity habits.

Restricted feeding is one of the promising approaches for combating obesity and related cardiometabolic co-morbidities. The principle of intermittent fasting relies on the regular daily or timely cycles of feeding windows, separated by periods of complete caloric restriction. The beneficial implications of intermittent fasting require further multidisciplinary research. A three-week caloric restriction in non-obese subjects triggered a weight loss followed by a significant increase in plasma amino acids, but interestingly only slight modifications in the gut microbial community, although *Prevotella* abundance was linked with body weight loss<sup>36</sup>. On the other hand, baseline levels of seven gut microbial species, rather than amino-acid levels, exerted predictive power with regards to the weight loss<sup>36</sup>. Furthermore, a time-restricted feeding (TRF) with 16 food-free hours daily and no restrictions or recommendations during the feeding period, was examined in healthy volunteers and demonstrated that the TRF was associated with *Prevotella*, *Faecalibacterium* and *Dialister* species, resulting in the highest abundance of Bacteroidetes phylum, followed by Firmicutes, which contrasts typical distribution of the phyla abundance in which Firmicutes are the dominant fraction<sup>37</sup>. This study demonstrated that TRF as a nutritional regimen might modulate gut bacterial abundance, and host interaction with nutritional status. Different aspects of intermittent fasting warrant further exploitation in terms of precise dietary therapies based on individual biomarkers and predispositions.

## CONCLUSIONS

To conclude, modulation of gut microbial abundance and functional capacity, via tailored nutritional interventions and even personalized nutrition regimes, has emerged as a powerful tool for future disease combating, but also chronic disease prevention and the risk factor alleviation. The findings from the current year are in line with the several review papers<sup>32,38-42</sup> from the preceding year, outlining the power of nutrition in microbiota profiling for health and wellbeing. The following gut microbe factors are proven to be powerful targets: *Prevotella*, *F. prausnitzii* and Firmicutes: Bacteroidetes ratio, and further research should focus on establishing gut microbiota profiling as a diagnostic and screening tool to support the emerging precision medicine strategies.

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## Conflict of Interest

The authors disclose no conflict of interest.

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