European Helicobacter & Microbiota Study Group

Nutrition and gut microbiota

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Abstract: On one side, diet is one of the most prominent factors that shapes gut microbiota, while, on the other side, gut microbiota is an important mediator of diet driven health effects. Addressing interplay between gut microbiota and dietary components and assessing the resulting health impact remains an attractive scientific topic over the last few decades. This review summarizes the most important findings of this research area published in the previous calendar year. Probiotics and prebiotics are traditionally the most frequently studied food components while novel studies indicate that their application could be expanded from gastrointestinal diseases to other conditions linked to gut microbiota dysbiosis, including behavioral and metabolic disorders. Various restrictive dietary interventions performed on healthy subjects and on subjects with impaired energy metabolism stress the importance of a nutrient source and the difference in individual microbiota composition as synthesis of specific bioactive microbial metabolites is dependent on both these factors. Novel research reports candidate microbiota metabolites derived from dietary components that have a crucial (either protective or hazardous) role in a disease development. Evaluation of dietary impact on both host and microbiota is very important as these responses are not always aligned, as shown for low gluten or low FODMAP (fermentable oligo-, di-, monosaccharides and polyols) diets. Therefore, studying microbiota becomes increasingly relevant in nutritional interventions, as promoting eubiosis of gut microbiota is indispensable for achieving long term health.

Keywords: Diet, Microbiota, Probiotics, Prebiotics, FODMAP.

INTRODUCTION

Gut microbiota responds to several environmental factors and nutrition is certainly one of the most relevant factors. Health effects of nutrients, both beneficial and hazardous, can be modified by microbiota, while specific food components or dietary patterns have the ability to shape microbiota and thereby impact health. Gut microbiota creates a milieu of enzymes to digest and metabolize food, causing the expansion of the human metabolic capacity and formation of diverse metabolites, including amino acids, short-chain fatty acids (SCFAs), and vitamins. Traditionally, research in this area is focusing on specific food components, such as probiotics and prebiotics, but it is becoming increasingly relevant to assess microbiota changes in response to specific dietary regimes (e.g., low gluten, high fat, high protein diets). In this review of literature we summarize findings of the most relevant studies that, in the previous calendar year, addressed link between gut microbiota, nutrition, and health.

PROBIOTICS AND PREBIOTICS

Probiotics and prebiotics are potent functional foods, with proven efficacy for treatment of a number of gastrointestinal (GI) conditions[1]. Following the relevant scientific findings in the field of gut-brain axis, different probiotics and prebiotics were recently tested for treatment of behavioral and metabolic disorders. The effect of a galacto-oligosaccharide prebiotic was tested in a randomized placebo-controlled trial (RCT) on autistic children and showed a significant reduction in anti-sociability scores but only in children that were on gluten and casein exclusion diet. The prebiotic induced compositional and metabolic shifts of microbiota in all treated children, but children following exclusion diets responded to the treatment also in a behavioral aspect[2]. A study based on a one arm uncontrolled nutritional trail showed that treatment of autistic children with probiotics might also be beneficial. A mixture of probiotic strains (two *Lactobacilli* and one *Bifidobacterium*) improved both behavioral and GI manifestations, even with low abundance of bacteria in the treatment mixture[3]. One prebiotic intervention showed only a modest effect on frail older people. The composition of the prebiotic mixture was designed to promote gut microbes that are depleted in frail elderly. Although the prebiotic showed the potential to modulate microbiota in the desired direction, it had only a limited effect on the associated immunological and health parameters[4]. An observational study on healthy adults showed that the subjects that regularly consume probiotic containing fermented milk products have higher levels of beneficial bifidobacteria, even when the consumed probiotic contained only *Lactobacillus* species[5]. This observation is in line with an older study that showed higher abundance of bifidobacteria in adolescents that were treated with *Lactobacillus rhamnosus* LGG during infancy, which was linked with reduced incidence of neuropsychiatric disorders[6]. Metabolic disorders are particularly interesting in nutritional interventions and in one RCT two probiotic *Bifidobacterium* strains and prebiotic galacto-oligosaccharides showed the ability to improve intestinal barrier function in adult obese individuals. Despite the improvement of the intestinal permeability the effect on endotoxemia parameters was lacking[7]. Another RCT on obese adults utilizing a different *Bifidobacterium* strain, and a different prebiotic-polydextrose, confirmed beneficial effects of probiotics and prebiotics in obesity mediated *via* improvement of intestinal barrier. The synbiotic in this trial could induce the increase of bacteria belonging to the genera *Bifidobacterium*, *Akkermansia*, and family Christensenellaceae. The abundance of Christensenellaceae appeared to be particularly relevant since this bacterial group showed a negative correlation with android and trunk fat, serum lipid metabolites and several primary and secondary unconjugated bile acids[8].

RESTRICTIVE AND ENRICHED DIETS IMPACT ON MICROBIOTA AND HEALTH

Wheat removal from the diet is associated with health benefits in predisposed individuals (such as celiac disease patients) but it is becoming increasingly prevalent among general population. A crossover nutritional study with high-gluten and low-gluten diet on 60 healthy Danish individuals showed that low-gluten diet induces lower self-reported bloating that could be linked with lower hydrogen exhalation. While the authors have suggested that the positive effect of low-gluten diet in non-celiac individuals could be linked to gut microbiota-diet interactions, they also indicated that the observed changes were most likely driven by the reduction of dietary fibers intake due to the removal of gluten-rich foods rather than by the reduction of gluten intake itself. It is relevant to note that microbiota response to low-gluten diet was marked by reduction of beneficial bacteria including *Bifidobacterium*, butyrate producers *Eubacterium hallii,* and *Anaerostipes hadrus*, although within the test period no adverse effects on gut permeability and other health parameters were detected[9]. Recently it has been shown that lactobacilli isolated from the small bowel of healthy individuals can hydrolize fragments of gluten that are resistant to human digestive enzymes and thereby the activity of these lactobacilli has a potential to decrease the presence and the activity of gluten immunogenic peptides[10]. The same group of researchers now showed that wheat amylase trypsin inhibitors (ATI) might also be relevant for the pathology of wheat associated disorders as ATI could induce inflammatory effects. These inflammatory effects could be reduced by supplementation of specific lactobacilli capable of ATI degradation[11]. The first study to assess the effects of whole grain wheat on liver fat in a RCT showed that refined wheat increases liver fat and might contribute to non-alcoholic fatty liver disease, whereas incorporating feasible doses of whole grain wheat in a diet promotes liver health[12]. Another study from Roager at al[13] showed that whole grain diet when compared to refined grain diet reduced energy intake, body weight, and the low-grade systemic inflammation markers (CRP and IL-6), without significantly altering the whole body insulin sensitivity, gut microbiota or gut functionality in terms of intestinal integrity and transit time. The results of this study indicated that the health benefits of the whole grains diets are not necessarily mediated through changes in the gut microbiota. One important health beneficial grain component is soluble, non-starch polysaccharide β-glucan. Dietary interventions with β-glucans from barley induced an increase in abundance of beneficial *Bifidobacterium* spp. and *Akkermansia municiphila* and this microbiota shift was associated with amelioration of metabolic dysfunctions in patients with metabolic syndrome[14].

Special high fat diets (such as keto or Paleolithic) are becoming increasingly popular among general population. The effect of high amount of dietary fat on health and microbiota was studied in a six-month RCT with 217 healthy young adults using iso-caloric diet with variable amount of fat. The study clearly showed that high-fat diet had overall unfavorable effects, including the decrease of butyrate producing and anti-inflammatory *Faecalibacterium* and increase of *Bacteroides* and *Alistipes,* of which the former was positively associated with blood lipid markers including total cholesterol. The microbiota shift induced by low fat diet included the reduction of faecal concentrations of hazardous indole (cardiovascular risk) and p-cresol (carcinogenic), and the increase of the beneficial butyrate[15].

Indolepropionic acid (IPA) was recently recognized as an important microbial metabolite in an observational study that showed an inverse correlation of this microbial metabolite with type 2 diabetes (T2D) risk[16]. IPA is a metabolite of amino acid tryptophan, and although the exact role of this metabolite is still not determined, it was shown that the serum levels of IPA are correlated with intake of food that is rich in fibers[16]. An opposite, negative effect on T2D risk was assigned to another microbiota metabolite imidazole propionate, which production is linked to high protein intake. The degradation pattern of protein component (amino acid histidine) in individuals with specific gut microbiota composition leads to synthesis of imidazole propionate. This microbial metabolite acts as antagonist of insulin receptors, and thereby promotes insulin resistance[17]. Based on this novel data, it can be concluded that low fiber and high protein intake, typical for Western diets, predispose for microbial transformations with direct effect on human metabolism that can induce metabolic diseases. These studies also stress the influence of gut microbiota in individualized response, as the production of imidazole propionate occurs only in individuals whose microbiota contains species capable of producing this metabolite. Another recent study stressed the importance of microbiota variation in response to dietary intervention and showed that increased capability for carbohydrate metabolism by gut microbiota is associated with decreased weight loss in overweight and obese patients undergoing a lifestyle intervention program. The nutritional intervention consisted of volumetric approach that is based on intake of larger amounts of low energy density foods (fruits, vegetables) with lesser intake of foods with greater nutrient density. The weight loss on this diet was influenced by microbiota composition at baseline and individuals with relatively higher abundance of *Phascolarctobacterium* responded better to this diet (weight loss of at least 5%), than the individuals with relatively higher abundance of *Dialister*[18].

Other studies suggest that nutritional science in the context of metabolic diseases should not be focusing only on macronutrients since minor food components might also strongly interact with microbiota. One RCT evaluated the effect of diets with matched protein amounts from mushrooms or meat on microbiota and GI symptoms in healthy adults. The study showed an increase in GI symptoms on mushroom diet. This is most likely due to the presence of indigestible carbohydrates, which are typically recognized as prebiotics, but can induce symptoms similar to any other fermentable carbohydrates (i.e., FODMAP). Mushroom rich diets significantly reduced abundance of Firmicutes and increased Bacteroidetes[19], and thereby could contribute to the inversion of Firmicutes/Bacteroidetes ratio that was shown to be increased in a number of conditions including obesity[20] and IBS[21]. Focusing on minor dietary components (polyphenolic polymers – tannins), a study showed that after six weeks of mango intake, the serum levels of gallotannin metabolites were significantly increased in both lean and obese individuals. This intervention induced a decrease in endotoxin levels, probably due to promoted intestinal barrier function, as a consequence of higher production of butyrate and valerate. Interestingly, there was a negative trend between endotoxin levels and the sum of gallotannin metabolites[22]. One more study showed the importance of dietary plant polyphenols for human energy metabolism. Hypercholesterolemic subjects were consuming either 90 g of olive pomace-enriched biscuits or an isoenergetic control biscuits for eight weeks. The results revealed that an addition of olive pomace induced a significant increase in excretion of small phenolic acids in urine, which are an indicator of upregulation of microbial polyphenol biotransformation in the gut. This modest dietary intervention did not induce direct effects on lipid or glucose metabolism parameters, but the serum levels of metabolites that have the ability to protect LDL cholesterol particles from oxidative damage (homovanillic acid and dihydroxyphenylacetic acid) were significantly, up to ten fold elevated, in the test diet[23]. The impact of such modest dietary intervention might be far beyond improvement of metabolic health, since homovanillic and dihydroxyphenylacetic acid are also linked to dopamine pathway and their presence is associated with improvements in age-related decline in muscle and brain function.

NUTRITION AND GASTROINTESTINAL DISEASES

Food constituents have recently been shown to modulate epigenetic mechanisms, which can result in an increased risk for the development and progression of inflammatory bowel disease. Diet is an important factor in the etiology of Crohn's disease (CD), particularly in countries where the rising disease incidence has paralleled changes in eating habits and food industrialization. Some nutrients and food additives have been related to CD risk. As a result of that, recent studies have advocated the inclusion or exclusion of these food components in CD management[24]. Svolos et al[25] evaluated the effects of an individualized ordinary food-based diet (CD-TREAT) as a prescriptive and personalized diet, on the gut microbiota, inflammation, and clinical response in healthy adults and children with relapsing CD. CD-TREAT achieved similar nutrient composition to exclusive enteral nutrition (EEN), by the exclusion of certain dietary components (e.g., gluten, lactose, and alcohol) and matching of others (macronutrients, vitamins, minerals, and fiber) using ordinary food. This diet had good compliance and similar effects to those of EEN on the gut microbiota composition and metabolites in healthy individuals. Furthermore, it could decrease the disease activity and colonic inflammation in children with active CD.

Probiotics and prebiotics are well established complementary therapy in GI diseases. Recent study analyzed the ability of an engineered and wild-type probiotic *Lactococcus lactis* to downregulate inflammatory signals in an *ex vivo* model of inflammatory IBD mucosa. The probiotic *L. lactis* strain was able to bind to TNF-α and decrease production of IL-23 cytokine while secretion of the anti-inflammatory cytokine IL-10 was significantly increased compared to sterile culture. The anti-inflammatory effect was enhanced by recombinant strain bearing TNF-αbinding affibodies, suggesting that probiotics could offer alternative modes of therapy, particularly if such therapies can be based on microorganism which safety has been proven though long history of use in food industry[26]. A recent RCT tested a prebiotic treatment, primarily composed of galacto-oligosaccharides, and showed that prebiotics were as effective as low FODMAP diet in reduction of IBS symptoms. In addition, the prebiotic changed microbiota by increasing bifidobacteria, while the low FODMAP diet increased *Bilophila* sp., which has previously been linked to compromised health. The effects of prebiotic could be detected for two weeks after termination of the trial in contrast to the benefits of the low FODMAP diet that lasted only during the intervention[27]. Therefore, prebiotics might offer more powerful option for treatment of IBS since they are easier to apply, have extended effect, and achieve similar symptom relief as low FODMAP diet, without compromising microbiota composition and, consequently, long term health.

CONCLUSIONS

Interactions between gut microbiota and diet play a crucial role in maintaining health. Functional food components, including probiotics and prebiotics, have a proven positive effect on a number of conditions, but, as recent literature data shows, they also have an unexplored potential for treatment of metabolic, behavioral, and other conditions linked to microbiota dysbiosis. Recent research also stresses the importance of a nutrient source and individual microbiota composition for health effect of food since synthesis of specific bioactive microbial metabolites is dependent on both these factors. Overall, it is evident that technological developments have enabled studying microbiota response in nutritional trials, allowing for evaluation of the effect of a dietary strategy on both host and microbiota. This is very important since certain trends in nutrition, including high fat, gluten-free or low FODMAP diets appear to have an opposite effect on human host and microbiota. They are perceived as beneficial by the host, while the effects on microbiota are seemingly hazardous. This kind of knowledge should be utilized by experts to define nutritional strategies with beneficial effect on both *Homo sapiens* and microbial component of humans, as only such nutrition can confer long term health.

Conflict of interest

The authors declare that they have no conflict of interests.

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