Nutrition and Microbiome

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Contents

Abstract

The prevalence of overweight and obesity has reached epidemic proportions globally over the past few decades. The search for new management approaches continues and among them, targeting the gut microbiota can be envisioned. To date, numerous data showed the involvement of the gut microbes in the regulation and control of host metabolism. There are also increasing evidences highlighting the interactions between environmental factors, intrinsic factors, gut microbiota, and metabolic diseases. Diet emerges as the most relevant factor influencing the gut microbiome. Eating habits, as well as short-term consumption of specific

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diets, alter the gut microbiota composition. Moreover, nutritional disorders are associated with changes of the gut microbiota composition and/or function, as shown in obesity or type 2 diabetic patients versus healthy lean subjects. Targeting the gut microbiota for improving metabolic health appears as a new approach to manage obesity and cardio-metabolic risk. In this review, we have detailed the results of human interventions targeting the gut microbiome by prebiotic supplementation, prebiotics being defined as "substrates that are selectively utilized by the host microorganisms conferring a health benefit." If the potential benefit of this approach is obvious in preclinical models, the efficacy of prebiotics in humans is less reproducible. The inter-individual variability of response to dietary intervention can be dependent on the gut microbiota and we summarized the basal gut microbiota characteristics driving the metabolic response to dieting, prebiotic and dietary fiber intervention in the context of obesity and related metabolic diseases.

Keywords

Gut microbiota · Metabolic health · Nutrition · Prebiotics

1 Introducing the Role of the Microbiome for Human Health

1.1 The Definition of Microbiome

In the last decade, the role of microbiome in health has gained interest in science, medicine, and more generally for a broad audience. Key scientific outcomes highlight the link between the microbiome and the regulation of host physiological functions including the regulation of immunity, appetite, metabolism, and behavior (Zheng et al. 2020). In order to standardize the emergent studies focusing on the microbiome, a panel of experts recently revisited the microbiome definition (Berg et al. 2020). In this new definition, the microbiome encompasses both the microorganisms, including viruses, bacteria, archaea, unicellular eukaryotes, and fungi, and their "theater of activity" (structural elements, metabolites/signal molecules, and the surrounding environmental conditions). The microbiome probably comprises thousands of different bacterial species, the highest density of bacteria being present in the large intestine.

The dominant gut microbial phyla are Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, and Verrucomicrobia, with the two phyla Firmicutes and Bacteroidetes being the most represented. Within each phylum, some well-known genera are prominent: *Lactobacillus, Eubacterium, Ruminococcus, Roseburia,* or *Faecalibacterium* within Firmicutes, *Bacteroides* and *Prevotella* within Bacteroidetes, *Bifidobacterium* within Actinobacteria, *Escherichia* and *Desulfovibrio* within Proteobacteria and *Akkermansia* within Verrucomicrobia phylum.

1.2 Observational Studies in Humans Identified the Diet as a Strong Modulator of the Gut Microbiome

Many factors are known to influence the composition and/or activity of the gut microbiome from the first colonization after birth (birthing process, infant feeding method. . .) and throughout the entire life (environment, medication, diet, physical activity, stress. . .) (Cresci and Bawden 2015). Of note, the diet emerges as the most relevant factor in influencing the gut microbiome which composition varies among different populations, cultures, and dietary habits. Evidences about the role of diet and eating habits on the microbiome came with the comparison of fecal microbiota of humans and other mammalian species living in zoos and the wild (Ley et al. 2008). Interestingly, the diet influences bacterial diversity, which gradually increases from carnivory to omnivory and to herbivory. The gut microbiota of humans living a modern lifestyle is typical of omnivorous primates. Another study even suggested that long-term diets can be linked to different gut microbial enterotypes partitioning, dominated by either *Bacteroides* (for diet enriched in animal fat and protein) or *Prevotella* (for diet rich in carbohydrates) (Wu et al. 2011). Besides eating habits, short-term consumption of specific diets entirely composed of animal products also alters the microbiome composition by increasing the abundance of *Alistipes, Bilophila,* and *Bacteroides* and decreasing the levels of some genera/species metabolizing dietary plant polysaccharides (*Roseburia, Eubacterium rectale, Ruminococcus bromii*) (David et al. 2014). Then, the microbiome from US residents with a typical diet rich in protein appears less diverse than microbiome from Malawians and Amerindians consuming diets dominated by corn and cassava (Yatsunenko et al. 2012).

In addition to its impact on the gut microbiota composition, diet also influences the production of gut microbial metabolites and thus the microbiome function (for review see Delzenne et al. (2020)). For instance, the metabolome from vegan individuals contains a higher level of metabolites produced by the gut microbiota and differs from the omnivore's metabolome. This suggests that microbiome can rapidly adapt its structure and function in response to diet. The most well-described bioactive metabolites, produced by the gut microbiota, are the short-chain fatty acids (SCFA, including acetate, propionate and butyrate) generated by microbial fermentation of dietary polysaccharides and having several beneficial properties (energy source for colonocytes, modulation of intestinal inflammation, regulation of metabolism. . .) (Samuel et al. 2008; Donohoe et al. 2011). Unfortunately, some other bioactive compounds resulting from microbiome–diet interactions can have deleterious effects for host physiology, whereas the effects of a large proportion of gut-derived metabolites are still unknown (for review (Rodriguez et al. 2021)).

1.3 Nutritional and Metabolic Disorders Are Associated with Microbiome Changes

Several data support that changes in the composition of the human gut microbiota affect host metabolism and are linked to a variety of diseases (Nicholson et al. 2012). Two important studies highlighted a link between gut bacterial richness and metabolic alterations resulting from nutritional disorders observed during obesity (Cotillard et al. 2013; Le Chatelier et al. 2013). *Cotillard* et al. demonstrated that a diet-induced weight loss (high-protein and high-fibers during 6 weeks and 20% increase in total energy for additional 6 weeks) improved low gene richness and clinical phenotype in obese or overweight people (Cotillard et al. 2013). The fecal gut microbiota from obese individuals was also characterized by a decreased proportion of *Bacteroidetes* versus *Firmicutes* phylum compared to lean people, and this proportion increases upon weight loss (Ley et al. 2006). However, differences in the major phyla proportion is not observed in other cohorts of obese individuals (Duncan et al. 2008). Actually, it seems complicated to draw conclusion based on gut microbiota composition between lean versus overweight/ obese since the dietary habits can obviously be very different between participants. In addition, many other potential cofounding factors (medication, physical activity. . .) can interfere with the interpretation of the data related to the microbiome.

Besides an impact on the bacterial richness or on the major phyla, a regulation in the abundance of certain gut microbial genera or species can be observed in pathologies associated with metabolic disorders. For instance, the comparison of fecal microbiota between obese and lean children/adolescents showed a decreased abundance for some butyrate-producing bacteria belonging to the genera *Ruminococcus*, *Eubacterium,* or *Roseburia* (Zhu et al. 2013). *Bacteroides* abundance was significantly increased and *Prevotella* abundance was decreased in non-alcoholic steatohepatitis patients (NASH) versus patients without NASH, whereas the higher abundance of *Ruminococcus* is found in patients with significant fibrosis (Boursier et al. 2016). Increased level of *Escherichia coli* was also observed in obese patients with NASH versus to whom without NASH (Zhu et al. 2013). Lanthier et al. recently highlighted a reduced abundance of *Clostridium sensu stricto* in obese individuals with a severe fibrosis, compared to patients with a light/ moderate fibrosis, and the abundance of this genus negatively correlated with elasticity measurement (Lanthier et al. 2021). Another example is the decreased abundance of several butyrate-producing bacteria and an enrichment of opportunistic pathogens in T2D subjects (for review (Delzenne et al. 2015)).

Interestingly, a lower intake of carbohydrates decreased concentrations of butyrate and butyrate-producing bacteria (*Roseburia spp.* and *Eubacterium rectale* subgroup of cluster XIV) in feces of obese subjects (Duncan et al. 2007). A higher *A. muciniphila* abundance is associated with a healthier metabolic status in overweight or obese humans (Dao et al. 2016).

Taken together, these data demonstrate that it is difficult to elaborate a precise and recurrent bacterial signature for pathologies resulting from nutritional disorders, since in addition to the difference in dietary habits, many other environmental

confounders may compromise the interpretation of the data. However, it is clear that a gut dysbiosis (corresponding to an alteration of both microbiome composition and function) includes an important reduction of bacteria having the abilities to ferment carbohydrates and to produce short-chain fatty acids.

In order to explain the progression of metabolic disorders following the gut dysbiosis associated with nutritional disorders, preclinical studies have demonstrated that mice fed a high-fat diet had higher plasma lipopolysaccharides (LPS) level associated with gut microbiota changes, higher inflammation, fatty liver, and insulin resistance (Cani et al. 2007). Actually, LPS are important outer membrane components of gram-negative bacteria and their increase in systemic circulation creates a low tone inflammation called "metabolic endotoxemia," this process being linked to an alteration of gut microbiota and thereby, a loss of intestinal barrier function. Thus, the gut microbiome changes and the loss of intestinal barrier integrity could be the starting point to development of metabolic alterations in peripheral organs in response to diet (for review Rodriguez and Delzenne (2021)).

2 Targeting the Microbiome for Improving Metabolic Health in Humans

In line with the previous paragraph, one strategy to envision the improvement of weight control and metabolic alterations resulting from inadequate diet is the manipulation of the gut microbiome with specific dietary advices. In this context, the use of prebiotics, defined as substrates that are selectively utilized by host microorganisms conferring a health benefit (Gibson et al. 2017) represents a major interest. The number of preclinical studies using this approach is very important and the topic has been recently reviewed (Rodriguez and Delzenne 2021). We propose in this section to focus especially on human intervention studies targeting the microbiome to improve metabolic health. The majority of studies evaluating the impact of prebiotics on metabolic health concern supplementation with high-fermentable dietary fibers (inulin-type fructans, resistant starch, arabinoxylans, pectins, or β-glucans) but also with complex food components as polyphenols.

2.1 Inulin-Type Fructans

Inulin-type fructans (ITF) are certainly the most studied prebiotics. They are composed by repetitive fructosyl units linked by β(2,1) bonds and fermented by intestinal bacteria. Their intake has been suggested to alleviate several features of metabolic alterations in preclinical models (including gut permeability, systemic inflammation, or peripheral lipids accumulation) but to date, few studies evaluated their benefit in human health on both the gut microbiota composition and the metabolism (or metabolic disruptions).

In healthy humans, 10 g/day of very-long-chain inulin extracted from globe artichoke (Cynara scolymus), 20 g/day of inulin extracted from chicory root or

16 g/day of ITF (50:50 inulin to fructooligosaccharide FOS mix) increased the bifidobacteria after 2–3 weeks of supplementation (Costabile et al. 2010; Healey et al. 2018; Baxter et al. 2019). In healthy adults, ITF did not systematically increase the SCFA production. No change in the SCFA level was observed upon treatment with inulin from globe artichoke or ITF. Inulin from chicory increased the level of total SCFA but did not significantly modify the individual SCFA (butyrate, propionate, acetate) profile (Costabile et al. 2010, Healey et al. 2018, Baxter et al. 2019). Interestingly, the consumption of ITF-rich vegetables during 3 weeks (with an estimated intake of 15 g/day) also increased the proportion of *Bifidobacterium* genus in healthy adults (Hiel et al. 2019). In addition, the volunteers consuming ITF-rich vegetables showed improvements in food behavior such as a greater satiety and reduced desire to eat sweet or salty.

In children with overweight or obesity, 16 weeks of oligofructose-enriched inulin (8 g/day) decreased bacterial richness, associated with an increase of *Bifidobacterium* and *Collinsella* genera and decreased *Ruminococcus* (Nicolucci et al. 2017). This prebiotic-based intervention improved body fat, the level of interleukine-6, and the triglycerides content in children. Twelve weeks of supplementation with the same prebiotic administer in similar amount increased *Bifidobacterium* and the C-peptide, and was accompanied by a tendency to improve the gut barrier permeability in children with type 1 diabetes (Ho et al. 2019).

In obese adult women, 3 weeks of ITF supplementation increased the *Bifidobacterium* and *Faecalibacterium,* both genera were inversely correlated with the serum LPS, a marker of metabolic endotoxemia (Dewulf et al. 2013). qPCR analysis revealed that ITF especially increased the species *B. longum, B. adolescentis,* and *B. pseudocatenulatum,* and decreased the fecal SCFA, acetate and propionate (Salazar et al. 2015). In a larger cohort, 12 weeks of ITF supplementation (6 g oligofructose + 2 g inulin from chicory root) in adults with overweight/obesity also stimulated the growth of *Bifidobacterium,* whereas food-related behavior was improved with a lower hunger, desire to eat, and prospective food consumption (Reimer et al. 2017). A multicenter placebo-controlled trial performed in obese individuals also confirmed the increased proportion of *Bifidobacterium* genus by ITF associated with ITF-rich vegetables after 3 months (Hiel et al. 2020). This was accompanied by an increase of *Catenibacterium* genus and a decreased proportion of *Desulfovibrio* and *Roseburia* genera. Compared to placebo, the prebiotic induced greater weight loss and additionally decreased diastolic blood pressure, AST, and insulinemia. However, this study identified medication as an important factor to consider during prebiotic-based intervention since metformin use compromised most of the gut microbiota changes and metabolic improvements linked to prebiotic intervention. In a subcohort, ITF did not alter fecal SCFA content but reduced fecal calprotectin, a marker of gut inflammation (Neyrinck et al. 2021). All this data support the increase of *Bifidobacterium* genus as a specific signature of ITF intake. However, the amplitude of *Bifidobacterium* changes, as well as the impact on the host metabolism can vary between the studies and between the individuals involved in a same protocol.

2.2 Galacto-Oligosaccharides

Prebiotic galacto-oligosaccharides, GOS, are polymers of galactose with a terminal glucose monomer. In elderly people, administration of β-GOS mixture (5.5 g/day) enhanced the growth of *Bacteroides* and *Bifidobacterium* and resulted in a higher production of anti-inflammatory cytokine IL10, as well as a lower synthesis of proinflammatory cytokine IL1β, compared to placebo group (Vulevic et al. 2015). The same dose administered for 12 weeks in type 2 diabetes (T2D) individuals had no significant effects on both clinical outcomes or bacterial abundances compared to placebo (maybe due to confounding factors such as medication or an important heterogeneity) (Pedersen et al. 2016). A higher dose of GOS (15 g/day) in overweight or obese people led to an increase of *Bifidobacterium*, without any improvement of metabolic markers (Canfora et al. 2017). This suggests that changing the microbial composition in favor of bifidobacteria growth is not automatically associated with beneficial effects on human metabolism.

2.3 β-Glucans

In patients with high risk of metabolic syndrome, 4 weeks of supplementation with barley β-glucans lowered the plasma total cholesterol (Velikonja et al. 2019). Barley β-glucans also decreased the microbial diversity and increased the production of propionic acid. The prebiotic properties of a novel insoluble fiber chitin-glucan CG, composed by branched β-1,3/1,6 glucan that is linked to chitin via a β-1,4 linkage, were also investigated in healthy humans (Rodriguez et al. 2020b). After 3 weeks of supplementation, CG decreased the relative abundance of *Dorea* and increased the butyrate-producing bacteria belonging to *Roseburia* and *Eubacterium* genera.

2.4 Arabinoxylans

Arabinoxylans (AX) are the most abundant non-digestible carbohydrates present in wheat. An intake of 15 g/day of AX during 6 weeks reduced the gut microbiota diversity in overweight individuals and stimulated the production of total SCFA (Salden et al. 2018). Unfortunately, no changes in metabolic markers (cholesterolemia, triglyceridemia, glycemia, or insulinemia) were observed. Similar results (i.e., bifidogenic effects without metabolic improvements) were obtained after 4 weeks of arabinoxylan oligosaccharides (AXOS) supplementation in overweight people (Kjolbaek et al. 2020).

2.5 Resistant Starch

Resistant starch (RS) is a type of dietary fiber that can be divided into many sub-types (RS1 physically inaccessible, RS2 starch conformation), RS3 retrograded,

RS4 chemically modified or RS5 starch lipid complex), also considered as prebiotics (Gill et al. 2021). In healthy adults, 8 days of RS2-enriched wheat (14-19 g/day) intake altered the overall composition of gut microbiota assessed by β-diversity indices and reduced the α-diversity, a marker of bacterial diversity (Hughes et al. 2021). Compared to baseline, *Ruminococcus, Gemmiger, Faecalibacterium, Roseburia,* and *Bifidobacterium* increased after RS2-enriched wheat supplementation. Interestingly, after 1 week of intervention, some metabolic processes were improved following a challenge with a breakfast containing RS2-enriched wheat (postprandial glucose and insulin response) (Zhang et al. 2019). A higher dose during 4 weeks (40 g/day high amylose RS2) reduced visceral subcutaneous and intra-abdominal fat and promoted early-phase insulin, GLP-1, and acetate production. In contrast to the previous study, RS2 intake did not alter α-diversity. However, it increased the genus Ruminococcaceae_UCG-005 and decreased 15 other bacterial genera. In normotensive and overweight or obese adults, plasma concentration of trimethylamine-N-oxide (TMAO), a biomarker of cardiovascular disease risk and dependent of intestinal microbiota, was higher after a high-RS versus low-RS diet in the context of low carbohydrates intake (Bergeron et al. 2016). Administration of RS3 during a phase of weight maintenance following weight loss improved fasted plasma glucose compared to subjects who did not receive RS (Johnstone et al. 2020). The addition of RS during weight maintenance caused distinct changes by targeting bacterial groups mainly belonging to the genera *Roseburia, Ruminococcus,* and *Faecalibacterium.* It is important to take into consideration that the structure of this dietary fiber is crucial for its impact on the gut microbiota in humans since chemically modified RS with small structural differences induce different specific effect such as the stimulation of different SCFA production (propionate versus butyrate) (Deehan et al. 2020).

To conclude, few human studies investigated the impact of dietary fibers on both the gut microbiota and the metabolic alterations observed in several physiological or pathological conditions. The main issue reported in these first studies is the lack of benefits obtained in humans, particularly for metabolic health, when compared with beneficial effects of dietary fibers supplementation in preclinical models. Some studies explained these disappointing data by an important inter-individual response to dietary intervention targeting the gut microbiota within the studies, leading to the difficult interpretation of results.

3 Can the Gut Microbiome Predict the Efficacy of Dieting in Humans?

Identification of predictive traits for the anticipation of diet-based effects on weight loss is a matter of study in which the gut microbiome emerges as an important factor to take into consideration (see Fig. 1).

The rationale that individualized response to dietary intervention can be dependent on the gut microbiota came from the observation that non-digestible carbohydrates can produce marked changes in the gut microbiota, these changes

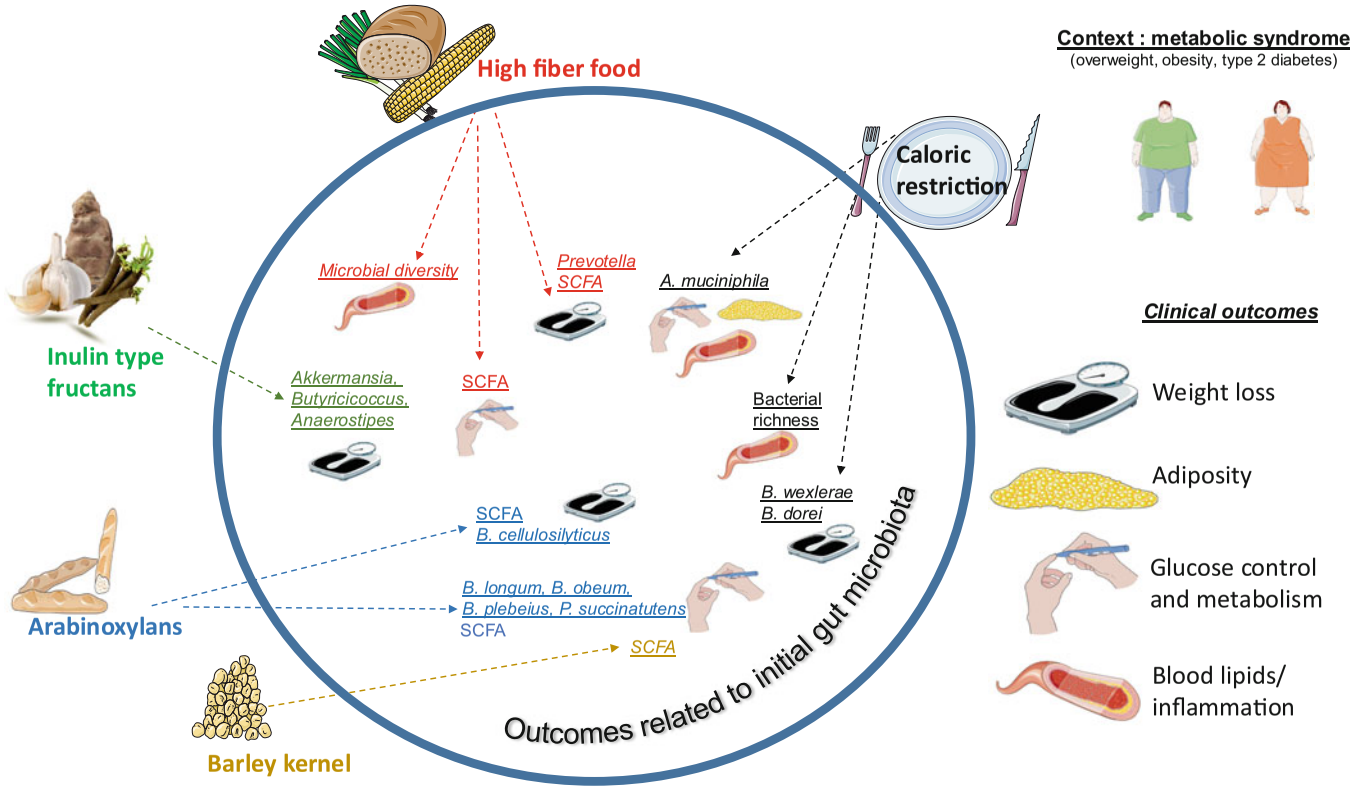

Fig. 1 The gut microbiota is an important factor predicting the metabolic improvements in obese individuals. The figure highlights the gut microbiota characteristics at baseline (richness, presence of specific bacteria, enterotypes, short-chain fatty acids (SCFA) profiling linked to a variable response toward dietary interventions. Metabolic improvements include body weight control, fat mass expansion, glucose homeostasis and blood lipids or inflammation. The type of nutritional intervention is linked to the metabolic outcomes and related characteristics of the gut microbiota

being dependent on its initial composition (Walker et al. 2011). For instance, supplementation with RS in overweight individuals showed that a large difference in the proportion of fecal RS can be found between participants suggesting that the initial microbiota composition can lead to inter-individual differences in microbial fermentation of RS and thus in microbial response. Consistently, a variable response of human microbiome was also observed in another study with RS supplementation, leading to the heterogeneous responses in butyrate concentrations (Venkataraman et al. 2016).

Then, a linear model applied on three different obese cohorts (from Belgium, Finland, and Britain) based on dietary interventions for metabolic health indicated that the baseline abundances of several species (mainly Firmicutes members) can predict the overall responsiveness of the microbiota to the tested interventions (Korpela et al. 2014). In addition to these findings, a 6-month weight-reduction program with collection of dietary, physical activity, body weight, obesity-related host genotypes, and fecal samples identified the baseline gut microbiota as the most powerful individual factor for predicting the individual weight loss trajectories (Jie et al. 2021). In this last study, *Blautia wexlerae* and *Bacteroides dorei* were identified as the strongest predictors for weight loss when they were highly abundant at baseline. Obese/overweight individuals and some lean people composed the cohort, this allowed the authors to show that some species were enriched in obese subjects and their decreased abundance was associated with weight loss (*Coprococcus sp., Holdemanella biformis, Solobacterium moorei, Ruminococcus gnavus*, and *Clostridium sp.).* On the other hand, *Coprobacter* sp., *Bacteroides intestinalis, Akkermansia muciniphila, Alistipes obesi*, and *Tannerella* species were significantly enriched in lean individuals, and their increase during dieting was significantly associated with weight loss. In line with these observations, another study confirmed that initial abundances of some intestinal bacteria can drive the successful of dietary interventions (Dao et al. 2016). Higher basal abundance of *Akkermansia muciniphila* was associated with greater improvements of glucose control, blood lipids, or body composition after caloric restriction. In addition, low gene richness may also have predictive potential for the efficacy of nutritional intervention. Indeed, 6 weeks of energy-restricted high-protein diet followed by a 6-week weight-maintenance diet improved clinical phenotypes, but a less efficient improvement on the inflammatory markers was observed in obese or overweight subjects with lower gene richness (Cotillard et al. 2013).

The hypothesis that gut microbiome composition prior to intervention can influence the response to dietary intervention, and may predict weight loss or metabolic improvement, was reinforced with some data relative to glucose control (Zeevi et al. 2015). A high interpersonal variability in post-meal glucose was observed in an 800-person cohort and the use of personal and microbiome features enables accurate glucose response prediction (Zeevi et al. 2015). Moreover, the initial gut microbiota can influence the glycemic response to bread and the prediction of personal glycemic response-inducing bread can be done by using only the microbiome features (Korem et al. 2017). A recent study using multivariate methods to integrate 24 h-food records and fecal shotgun metagenomes in healthy human confirmed that similar foods can

induce different effects on microbiome, suggesting that the interactions between diet and microbiome are personalized (Johnson et al. 2019). In line with this finding, a recent study also highlighted a personalized immune response to a high-fiber supplementation in healthy adults (Wastyk et al. 2021). In this work, the authors identified three different clusters associated with distinct immunological trajectories in high-fibers consumers. The different immune response to high-fiber diet seems to be linked with baseline microbiota diversity, the higher diversity at baseline being observed in the group exhibiting the lower inflammation during the study.

Microbial enterotypes have also been proposed as a tool for predicting weight loss during a nutritional intervention. For instance, subjects with a high *Prevotella/Bacteroides* (P/B) ratio had improved enzymatic capacity for fiber digestion and glucose metabolism after 3 days of barley kernel-based bread, compared to subjects with a low P/B ratio (Kovatcheva-Datchary et al. 2015). This suggests that *Prevotella* plays an important role in the barley kernel-induced improvement in glucose metabolism. Other studies showed a link between *Prevotella* abundance in the human gut microbiota and weight loss when consuming fiber-rich diet in healthy or overweight subjects (Christensen et al. 2019; Hjorth et al. 2019). Interestingly, subjects with high P/B ratio were more susceptible to weight loss on a diet rich in fiber, compared with subjects with low P/B ratio (Hjorth et al. 2019). These observations underline that the P/B ratio could be an important biomarker within personalized nutrition for weight management (Hjorth et al. 2019). Another study confirms that P/B ratio can predict weight change in overweight people after 4 weeks of AXOS supplementation, but suggests that few species from *Bacteroides* genus, owing to AXOS-degrading capacity, would predict body weight changes (Christensen et al. 2020). The authors found association between *B. cellulosilyticus* and metabolic changes in overweight subjects consuming AXOS. The inter-individual response of gut microbiome to AXOS supplementation was also observed in healthy adults (Chung et al. 2020). The authors reported a different gut microbiota response to AXOS in individuals with higher levels of *Prevotella* at baseline compared to whom with lower abundance of this genus. However, no changes in SCFA production or metabolic markers were observed. In addition, AXOS supplementation in overweight people also induced a variable response in terms of propionate production (Nguyen et al. 2020). Propionate response was predictable through baseline composition of gut microbiota and after 6 weeks of intervention, propionate responders and non-responders differed in their microbiome response to AXOS.

In line with the importance of some bacteria as drivers of response to dietary response, Zhao et al. highlighted that a set of SCFA-producing bacteria, promoted by dietary fibers, was crucial for improving host glycemic control (Zhao et al. 2018). Interestingly, when these SCFA producers were present in greater abundance, T2D participants had better improvement in hemoglobin A1c levels. Another study demonstrated a different metabolic response to inulin supplementation in mice inoculated with stool samples from different obese donors with different gut microbiota characteristics (bacterial richness, level of *Bifidobacterium sp.*) (Rodriguez et al. 2020a). Interestingly, the gut microbiota from obese individuals

who exhibited a beneficial response to inulin in terms of BMI improvement was characterized by greater abundance of *Akkermansia* and *Butyricicoccus* and lower level of *Anaerostipes.*

In addition, it is also unanswered if long-term consequences from dieting in terms of weight loss maintenance would also be influenced by the gut microbiota. A recent study compared the impact of healthy dietary guidelines, Mediterranean, and Mediterranean/high polyphenols diet on the weight control of abdominally obese or dyslipidemic participants, their gut microbiome composition but also the regain of the weight loss after the intervention (Rinott et al. 2021). In this study, the Mediterranean/high polyphenols diet was the only dietary strategy inducing a significant change in microbiome composition during the 6 months of weight loss phase. Interestingly, by administering autologous fecal material transfer collected at the end of 6-months intervention and for additional 8 months, the authors observed that participants from Mediterranean/high polyphenol group had an attenuated weight regain, waist circumference, and a reduced insulin rebound compared to a placebo administration. This suggests that the maintenance of an "optimal" microbiome composition obtained by dietary intervention can help to also preserve the weight loss and metabolic improvements obtained after the nutritional program.

4 Conclusion and Perspectives

In conclusion, few human studies investigated the impact of dietary fibers on both the gut microbiota and the metabolic alterations observed in several physiological or pathological conditions. The main issue reported in these first studies is the lack of benefits obtained in humans, when compared with beneficial effects of dietary fibers supplementation in preclinical models. This can probably reflect an important inter-individual variation in response to the dietary fibers, due to the baseline gut microbiota composition, but also the presence of several confounding factors to take into account in the interpretation of the clinical studies, these factors being strictly controlled in preclinical experiments (similar diet, activity, housing. . .). In summary, it seems that the gut microbiota contains critical information for identifying the optimal health outcome toward dietary intervention and the gut microbiota characteristics may thus be used in the future for personalized food-related recommendations. Predicting how the gut microbiome will respond to a dietary intervention and identifying all the confounders susceptible to influence the metabolic response to intervention is the future challenge in personalized nutrition.

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