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REVIEW

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Dietary fiber and prebiotics and the gastrointestinal microbiota

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ABSTRACT

The gastrointestinal microbiota has an important role in human health, and there is increasing interest in utilizing dietary approaches to modulate the composition and metabolic function of the microbial communities that colonize the gastrointestinal tract to improve health, and prevent or treat disease. One dietary strategy for modulating the microbiota is consumption of dietary fiber and prebiotics that can be metabolized by microbes in the gastrointestinal tract. Human alimentary enzymes are not able to digest most complex carbohydrates and plant polysaccharides. Instead, these polysaccharides are metabolized by microbes which generate short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate. This article reviews the current knowledge of the impact of fiber and prebiotic consumption on the composition and metabolic function of the human gastrointestinal microbiota, including the effects of physiochemical properties of complex carbohydrates, adequate intake and treatment dosages, and the phenotypic responses related to the composition of the human microbiota.

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Introduction

The human gastrointestinal microbiota—one of the most densely populated microbial communities on earth—contains highly diverse microbial communities that provide metabolic, immunologic, and protective functions that play a crucial role in human health.[1-3] The gastrointestinal microbiota is influenced by a number of factors including genetics, host physiology (age of the host, disease, stress, etc.) and environmental factors such as living conditions and use of medications.[3-7] Increasingly, diet is recognized as a key environmental factor that mediates the composition and metabolic function of the gastrointestinal microbiota.[8] Indeed, consumption of specific dietary ingredients, such as fiber and prebiotics, is an avenue by which the microbiota can be modulated.

Dietary fibers, carbohydrate polymers which are neither digested nor absorbed, are subjected to bacterial fermentation in the gastrointestinal tract and thus impact the composition of bacterial communities as well as microbial metabolic activities, including the production of fermentative end products. Some dietary fibers can also be classified as prebiotic.[9] Prebiotics are defined as "selectively fermented ingredients that result in specific changes, in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefit(s) upon host health."[10] This review discusses the impact of consumption of dietary fibers and prebiotics on the gastrointestinal microbiota, including the role of the ingredients' physiochemical properties and dose, as well as the phenotypic responses related to the composition of the resident microbiota.

The role of diet, fiber, and prebiotics on the gastrointestinal microbiome

The capacity of diet to modify the gastrointestinal microbiota of humans and other mammals has been extensively studied indicating that the composition of the diet, habitual dietary intake, and acute dietary changes all impact the microbial communities within the gut. Among mammals, the microbiota of herbivores, omnivores, and carnivores are compositionally and functionally distinct.[11] Specific to humans,

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habitual dietary patterns are associated with the composition of individual's gastrointestinal microbiota, but significant changes in macronutrient and fiber intake also can rapidly induce changes.[12] Pronounced shifts in bacterial diversity and production of microbial derived fecal fermentative end products have been demonstrated in as little as 24 hours in humans switching between an agrarian diet rich in fiber (> 30 grams/day) to a meat-based diet that was essentially devoid of fiber.[13]

Dietary fiber intake is notably different across industrialized and unindustrialized parts of the world—Westernized diets are characterized by their high content of animal protein, fat, sugar, and starch, and low fiber content while the diets of inhabitants of unindustrialized rural communities in African countries, such as Burkina Faso,[14] and Tanzania,[15] provide up to seven times more fiber due to increased intake of fibrous plants. On average, adults consume between 12–18 grams/day of dietary fiber in the United States,[16] 14 grams/day in the United Kingdom,[17] and 16–29 grams/day in Europe.[18] Cross-sectional studies of human populations across the globe reveal that greater dietary fiber intake is associated with increased gastrointestinal microbial community diversity.[19] Preclinical studies have demonstrated a causal role of fermentable fiber consumption on microbiota diversity, whereby, mice fed diets that are devoid of fermentable fibers develop depleted microbiota diversity over a few generations.[20] In addition, intervention studies in humans have demonstrated that dietary fiber and whole grain intake increase gut bacterial diversity.[21,22] Low-fiber intake in Western societies is purported to be a driver in the depletion of the human gastrointestinal microbiota and subsequent increases in chronic non-communicable diseases, such as obesity, cardiovascular disease, type 2 diabetes, and colon cancer.[23]

Dietary fiber

Dietary fiber is a broad term, and thus the impact of fiber consumption on the gastrointestinal microbiota will vary based on the type of fiber consumed. Dietary fibers, as defined by the Codex Alimentarius Commission in 2009,[24] are "carbohydrate polymers with ten or more monomeric units, which are neither digested nor absorbed in the human small intestine and belong to the following categories: (i) edible carbohydrate polymers naturally occurring in foods as consumed, (ii) edible carbohydrate polymers which have been obtained from food raw materials by physical, enzymatic, or chemical means and which have a beneficial physiological effect demonstrated by generally accepted scientific evidence, and (iii) edible synthetic carbohydrate polymers which have a beneficial physiological effect demonstrated by generally accepted scientific evidence." There is some flexibility in the definition of fiber, whereby national authorities may make the decision to include carbohydrates with three to nine monomeric units instead of restricting the definition to only include carbohydrates that are ≥ 10 monomeric units in length. In Australia, Brazil, Canada, China, Europe and New Zealand, the definitions of fiber includes nondigestible carbohydrates with greater than three monomeric units.[24,25]

Dietary fibers are heterogeneous, and thus different classifications are utilized to describe them, including, origin, chemical composition, and physicochemical properties with additional subcategorization based on the degree of polymerization (e.g. chain length). Importantly, each of these properties can also impact microbial fermentation. With regard to origin, plant-based fibers can be separated into fibers derived from cereals and grains, fruits, vegetables, nuts, and legumes. However, it is important to note that the fibers present in different types of plants will also have variable chemical compositions, as well as physicochemical properties.[26-28] For example, bananas contain resistant starch and inulin-type fructans, while apples are a source of pectin. Thus, diets rich in plant-based foods provide many different types of dietary fibers thereby supporting a more diverse microbiota composition.[29,30]

The physicochemical characteristics of fibers include fermentability, solubility, and viscosity, and these properties influence not only fermentation, but also the therapeutic effects of consumption.[27] Insoluble fibers, such as cellulose, are generally poorly fermented by gut microbes, but their presence in the diet increases gut transit rate and thus reduces the amount of time available for colonic bacterial fermentation of non-digested foodstuff.[31] Psyllium is also a non-fermentable fiber; however, its high solubility and viscosity results in unique therapeutic effects including improved glycemic control and reduced blood cholesterol levels.[27,32] Fibers that are highly fermentable while also possessing high solubility and viscosity include β-glucan and pectins.[27] These fibers are

naturally found in the diet in whole grains such as oats and barley (β-glucan) and fruits such as apples (pectin).[26,28] Slowed glucose absorption and binding of bile acids—the mechanisms underlying the physiological benefits of psyllium, β-glucans, and pectin —are also purported to impact the gastrointestinal microbiota. Non-viscous, soluble fibers that are readily fermented by gastrointestinal microbiota include inulin, resistant maltodextrins, resistant starch, polydextrose, and soluble corn fiber.[33-35] Inulin-type fructans are naturally found in agave, artichokes, asparagus, bananas, chicory root, garlic, onions, leeks, and wheat.[36] While varying botanical origins and degree of polymerization of inulin-type fructans has been shown to impact fermentation profiles in humans,[37,38] evidence for physiological benefits of inulin-type fructans in clinical studies are limited. Rodent studies, however, have demonstrated that consumption of inulin-type fibers differentially reduces body weight, blood cholesterol and blood glucose concentrations.[39-41]

In addition to the degree of polymerization, the solubility of complex carbohydrates impacts the location of fermentation within the human gastrointestinal tract. Soluble fibers, such as short-chain fructooligosacchaides (FOS) and pectin are metabolized by bacteria more proximally in the gastrointestinal tract (e.g., the ileam and ascending colon) while fibers that are less soluble, such as cellulose, can be partially fermented in the distal colon where transit time is slower, and bacterial densities are higher.[42] Recently, it was shown that fibers with varying chain lengths and solubility differentially impact the composition of the cecal microbiota of mice—diets supplemented with 5–10% cellulose, an insoluble fiber, had significantly different microbial community compositions than mice consuming 10% FOS or inulin, soluble fibers.[43] The impact of fermentable fibers in the diet, or microbiota assessable carbohydrates (MACs),[20] has been extensively studied. Indeed, it is this last category of dietary fibers that encompasses the term prebiotic.

Prebiotics

Not all fibers can be classified as prebiotic; however, most prebiotics can be classified as dietary fibers.[9] Consumption of prebiotics is a dietary strategy by which the gastrointestinal microbiota can be modified for health benefit. Prebiotics were originally defined in 1995 by Gibson and Roberfroid as "a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improves host health."[44] At the time of the original definition, culture-based methods were almost exclusively used for studying the microbiota, and bifidobacteria and lactobacilli were the primary commensals targeted in prebiotic feeding studies. In 2004, the definition of prebiotic was updated to add three criteria: 1) resistant to gastric acidity and hydrolysis by mammalian enzymes and gastrointestinal absorption; 2) fermented by intestinal microbiota, and 3) selectively stimulate the growth and/or activity of intestinal bacteria associated with health and wellbeing.[45]

Over time, advances in molecular methods, independent of culture-based approaches, revealed denser and more diverse bacterial communities than those originally studied. Accordingly, in 2010, the prebiotic definition was revised to "a selectively fermented ingredient that allows specific changes, both in the composition and/or activity of the gastrointestinal microbiota that confers benefits."[10] The updated definition expanded the language on the number bacteria—from one or a limited number of bacteria to specific changes in the microbiota—and the location—from the colon to the entire gastrointestinal tract.

As our understanding of the impact of diet on the microbiota continues to evolve, there has been continued discussion on the need to expand the definition even further. Recently, Bindels and colleagues proposed that a prebiotic should be defined as "a nondigestible compound that, through its metabolization by microorganisms in the gut, modulates composition and/or activity of the gut microbiota, thus conferring a beneficial physiological effect on the host."[46] Their proposed definition identifies the ingredient as the causative agent for changes in the microbiota. It also excludes the restrictive language related to selectivity and specificity while maintaining the need to identify a beneficial physiological effect. This helps to pave the way for investigation of bacteria other than those historically studied (e.g., bifidobacteria and lactobacilli). For example, butyrate-producing bacteria, such as *Faecalibacterium prausnitzii,* and *Akkermansia muciniphila*, a mucin degrading bacterium, have both been associated with beneficial health effects, including reduced inflammation and improved gut barrier function, respectively.[47] As our understanding of the role of the

microbiota in host health continues to expand, it is likely this definition will continue to evolve.

Microbial fermentation

Advances in molecular and computational methods have expanded our understanding of how diet influences gastrointestinal microbiota composition and function. Metagenomic sequencing, for example, has revealed that the gastrointestinal microbiota contains approximately 150 fold more genes than that of the human genome.[48] Intriguingly, human enzymes are not able to digest most fibers and prebiotics; indeed, less than 20 glycosidases have been identified in the human genome as enzymes involved in digestion of dietary polysaccharides.[49] The metabolization of dietary polysaccharides by the gastrointestinal bacteria is an example of the symbiotic relationship between the host and the microbiota. Furthermore, this relationship provides an avenue for dietary modulation of the microbiota because microbial growth and metabolism depend on substrate availability, e.g., the type of dietary fiber or prebiotic consumed by the host.

Humans enzymes are capable of degrading only a few glycosidic linkages present in a subset of carbohydrates, including starch polysaccharides, via the action of pancreatic and salivary amylase, and the disaccharides sucrose and lactose via the brush border disaccharidases, sucrase and lactase.[49] Although the ability to digest lactose does vary across the globe and lactase activity can decrease across the lifespan. Carbohydrates that escape digestion by human enzymes are substrates for bacterial fermentation within the gastrointestinal tract. Bacteria vary widely in their ability to metabolize dietary glycans. The human diet, when rich in different types and numbers of fruits, vegetables, whole grains, nuts, and legumes provides an abundant source of plant polysaccharides that contain different types of glycosidic linkages. In general, the more complex the polysaccharide, the more glycosidase are necessary to metabolize it.[50] Some bacteria possess many different enzymes that allow them to metabolize dozens of different complex carbohydrates, while other microbes are only able to utilize one or a few different polysaccharides. For example, *Bacteroides thetaiotaomicron* and *B. ovatus*, bacteria found in the human microbiota, are capable of metabolizing more than a dozen different types of glycans.[50,51]

The microbial conversion of complex polysaccharides to monosaccharides involves various biochemical pathways, which are mediated by the enzymatic activities of microbes. The main bacterial fermentative end products of complex carbohydrates are SCFAs, namely acetate, propionate, and butyrate, and gases (H_2, and CO_2). SCFAs are an important indicator of bacterial fermentation in the colon. The concentration of SCFAs changes throughout the length of the gastrointestinal tract, with the highest concentrations in the proximal colon and diminishing concentrations in the distal colon, the region of the gastrointestinal tract with the greatest density of microbes.[52]

Among the SCFAs, butyrate is the key energy source for colonocytes and enterocytes. Propionate also can be utilized locally through conversion into glucose by intestinal gluconeogenesis[53] or diffuse into the portal vein to be utilized as a substrate for hepatic gluconeogenesis.[52] Between 90 and 99% of SCFAs are absorbed in the gut or used by the microbiota.[54] However, a small amount of SCFAs, primarily propionate and acetate, are found in peripheral circulation. Acetate is the most abundant SCFA found in circulation and has been shown to cross the blood-brain barrier.[55,56] SCFAs influence gastrointestinal epithelial cell integrity, glucose homeostasis, lipid metabolism, appetite regulation, and immune function.[57]

Dietary consumption of fiber and prebiotics modulates the microbiota

Fermentation of undigested carbohydrates by bacteria depends on the physiochemical properties the carbohydrate, as discussed above, as well as the fiber dosage, and the bacterial community composition on the individual consuming the fiber. Bacteria possess carbohydrate-binding modules and an extensive set of enzymes, including glycoside hydrolases, glycosyltransferases, polysaccharide lyases, and carbohydrate esterases that allow for the hydrolysis of a wide variety of fibers.[58,59] Therefore, having a variety of dietary fibers (e.g., cellulose, hemicelluloses, pectins, gums, fructans, etc.) and resistant starches in the diet that contain a range of monosaccharide units and α- and β-linkages is more supportive of a varied gastrointestinal microbial community compared to a diet that has a less diverse substrate load (e.g., refined diets).[60,61]

Polysaccharide chain length or the degree of polymerization and branching of the fiber influences the ability of bacteria to utilize it as an energy source. Many bacteria can ferment short chain FOS, and *Bifidobacterium, Bacteroides, Faecalibacterium,*

Lactobacillus, and Roseburia can ferment oligofructose in vitro; however, relatively few can utilized long-chain fructans.[62,63] Bacterial species within the same genera also have varying abilities to degrade fiber sources. For examples, *B. bifidum* can grow on FOS in vitro, but not inulin.[64,65] Branching of fiber molecules also differentially impacts the location of fermentation within the gastrointestinal tract. Clinical studies using breath hydrogen as a marker of fermentation illustrate this because microbial fermentation is the only source of hydrogen production in the human body and 14% of total hydrogen produced in the gut is perfused into the lungs.[66] For example, short-chain FOS is fermented within 4 hours[67]; agave inulin, a highly branched fructan begins to be fermented four hours postprandially and peaks within 6 hours,[37]; and chicory inulin, a long-chain linear fructan, has peak fermentation 8 hours postprandially.[38]

Consumption of dietary fiber promotes extensive metabolic interactions among bacterial species present in the gastrointestinal microbial community. Therefore, there is considerable potential for indirect stimulation of the growth of other microbes within the community through the utilization of by-products of other community members. This process is called cross-feeding; whereby, the products produced from fermentation of a polysaccharide by one bacterial species provide substrates for growth of other bacteria present in the community. Thus, dietary modulation of the human gastrointestinal microbiota via fiber or prebiotic consumption can result in metabolic consequences that are different from results of single culture based experimentations that assess bacterial growth on isolated substrates. For example, dietary consumption of fructans has been shown to result in increased butyrate concentrations even though the primary increases in bacteria following fructan consumption do not directly metabolize butryate.[34,62] Bifidobacteria and lactobacilli, the main utilizers of fructans, are lactic acid bacteria, which produce lactate and acetate as their major fermentation end products when grown in pure culture. The likely cause of this phenomenon is that the lactate and acetate produced by bacteria metabolizing fructans as an energy source is then used by many other bacteria, including *Eubacterium, Roseburia*, and *Faecalibacterium*, that produce butyrate.[68,69] Therefore, cross-feeding is one mechanism that underlies differential results of single culture in vitro experimentation as compared to co-culture in vitro experimentation or in vivo studies.

While cross-feeding may be beneficial to some bacteria, nutrient competition and changes in pH that occur due to metabolite production can inhibit the growth of other microorganisms in the community. Bacterial fermentation of polysaccharides results in the production of acidic fermentation end products, primarily lactic acid and SCFAs, that reduce the colonic pH, which in turn impacts the composition of the microbial communities present in the gastrointestinal tract. Normal human colonic pH values are between pH 5.5 and 7.5. In vitro fermentation experiments utilizing human fecal samples to model the colon reveal that a reduction in pH from 6.5 to 5.5 significantly alters the bacterial community—more acidic conditions better support growth of butyrate-producing Firmicutes, such as *Roseburia* spp., while reducing the proliferation of the acid sensitive *Bacteroides* spp.[70,71]

Although the gastrointestinal microbiota can be effected by fiber and prebiotic consumption, individual responses can vary. These phenotypic responses are related to a combination of host genetics,[7] adequate dosages of the dietary polysaccharide of interest,[72,73] and the unique microbiota composition of the individual.[74] Thus, "responders" and "non-responders" to dietary modulation of the microbiota via specific fibers may be linked to inadequate dosages and/or lack of bacteria that can ferment the supplemented fiber(s). For example, consumption of 2.5 grams/day of short-chain FOS[72] or galactooligosaccharide (GOS)[73] did not increase bifidobacteria, but doses of 10 grams/day were adequate to induce a bloom in bifidobacteria in the gastrointestinal microbiota. Furthermore, individuals without detectable levels of bifidobacteria failed to respond to consumption of up to 7.5 grams/day agave inulin.[34] Responses are also dependent on fiber intake in the context of the entire diet; for example, dietary fiber per kilocalorie has been shown to be positively related to both *Bifidobacterium* spp. abundances and fecal butyrate concentrations.[34] Intriguingly, the composition of an individual's microbiota and the presence of keystone species also influences fiber fermentation. In one well-controlled feeding study, individuals without *Ruminococcus bromii* present in their microbiota had a reduced capacity to ferment the supplemented resistant starch, resulting in 20–30% fermentability compared to 100% fermentability in those with *Ruminococcus bromii*.[74]

State of the science

Clinical studies on the impact of fiber or prebiotic consumption on the composition and function of the human gastrointestinal microbiota provide examples of varied responses related to consumption of different types of fibers in the context of the complex milieu of the gastrointestinal tract (Table 1). Briefly, clinical studies conducted in adolescents or adults free of gastrointestinal diseases that utilized molecular methods to assess ≥ two microbes and fermentative profiles and were published in the last 5 years (2011–2016) were identified by searching PubMed and Google-Scholar databases using combinations of keywords including "fiber," "fibre," "prebiotic," "human," "microbiota," and "microbiome." These clinical trials reveal that GOS, inulin, xylooligosaccharide, and arabinoxylan oligoscaharides induced blooms in *Bifidobacterium* spp. while, soluble corn fiber and polydextrose stimulated more diverse changes in microbes in the Bacteroidetes and Firmicutes phyla. Molecular approaches that aimed to assess the community composition of the human microbiota follow GOS,[73] agave inulin,[34] and resistant starch type 4[36] consumption revealed that consumption of these fibers, in adequate doses, primarily selectively enriched *Bifidobacterium* spp. and resistant starch type 2[36] enriched *Eubacterium*. Although other minor shifts in bacterial community composition were present, these results support the designation of GOS and inulin as prebiotic fibers. Microbial metabolism results were highly variable, with the same fiber inducing changes in SCFAs concentrations depending on the clinical population. Alternatively, polydextrose and soluble corn fiber[33] broadly induce changes among several taxa in the Firmicutes and Bacteroidetes phyla with subsequent reductions in fecal butyrate, phenol and indole concentrations.

The differential effects of consumption of the fibers (Table 1) is driven by their chemical structures. GOS are generally composed of galactose polymers linked by β-1,6 bonds and β-1,4 linkage to the terminal glucose, and a DP between 2 and 10.[75] Agave inulin is a linear and branched fructose chain linked by β-2,1 and β-2,6 linkages, and a DP between 25 and 34.[76] Resistant starch type 2 and 4 are both composed of glucose monosaccharides linked by α-1,6 glycosidic bonds, resistant starch type 4 has additional cross-linkages by phosphorylation.[35] Soluble corn fiber is corn starch fraction rich in 1,6-glycosidic bonds.[77] Polydextrose contains both α- and β-linked 1,2, 1,3, 1,4, and 1,6 glucose monomers.[78] Each fiber's distinct molecular structure provides a partial explanation for the differential effects of consumption of the human gastrointestinal microbiota.

Conclusions

Host-microbe interactions are undeniably complex with the balance of benefit and harm depending on many dietary and microbial factors. Technological and computational advances over the past decade have allowed researchers to gain a better understanding of the composition and function of the trillions of microbes that reside in the gastrointestinal tract, and there is mounting evidence of an interrelationship of diet, the gastrointestinal microbiota, and human health. Herein, the impact of specific dietary fibers and prebiotics on the human gastrointestinal microbiota composition and function was reviewed including the role of ingredients' physiochemical properties, dosages, and phenotypic responses related to the composition of the resident microbiota.

Human, animal, in vitro, and computational research are all necessary to continue to move the field forward as each type of investigation has limitations. In human research, randomized, controlled trials are the gold standard approach, and crossover studies with washout periods should be utilized when feasible and appropriate. Care must be taken to monitor study participant compliance to the dietary intervention. Use of stable isotopes to label foods is a fidelity measure that should be incorporated whenever possible. Clinical trials are expensive and frequently generate extensive databases that are under-utilized. As such, computational modeling and bioinformatics approaches should also be undertaken to extend our understanding of these data sets.

Animal experiments, including gnotobiotic studies, are useful to determine mechanisms and can be used to complement clinical research findings. Limitations, however, include the physiological difference of preclinical models compared to humans. Notably, rodents are cecal fermenters and practice coprophagy. Single housing of animals and wire bottom cages can be utilized to reduce coprophagy. It is also important to consider the translation of dosages used in animal studies to human consumption values. Rodent trials frequently supplement

Table 1. Dietary fiber and prebiotic studies published in the last 5 years in adolescents and adults free of gastrointestinal diseases that assessed microbiota composition and function. Abbreviations: RCT, randomized controlled trial; GC, gas chromatography; SCFA, short-chain fatty acids; FISH, fluorescent in situ hybridization; DGGE, denaturing gradient gel electrophoresis; NMR, nuclear magnetic resonance spectroscopy.

Fiber	Design	Population	Measures	Microbiome changes	References
Arabinoxylan-oligosaccharies, 2.2 g	3-wk, RCT, crossover, 3 wk wash outs	20 F, 20 M	FISH GC	Increased *Lactobacilli* and *Bacteroides* Increased butyrate	Walton et al., Nutr J 2012[79]
Arabinoxylan oligoscaharides, 3 and 10* g	3 wk, RCT crossover, 2 wk washout	30F, 33M 18–85 yr BMI 23.3 +/− 3.2 kg/m^2	FISH GC	Increased *Bifidobacterium** Increased acetate, propionate, butyrate*, lower pH*	Francois et al., BJN 2012[80]
Arabinoxylan oligoscaharides, 5 g/d	3 wk, RCT crossover, 2 wk washout	11F, 18M (8–12 yr)	FISH GC	Increased *Bifidobacterium* Decreased isobutyric acid and isovaleric acid	Francois et al., JPGN 2014[81]
Whole grains (> 80 g/d vs < 16 g/d); 26 g/d total dietary fiber vs. 16 g/d total dietary fiber	6 wk crossover, 4 wk washout	21F, 12M 40–65 y BMI 20–35 kg/m^2	FISH GC	No significant changes	Ampatzoglou et al., J Nutr 2015[82]
Galactooligosaccharides (5.5 g/d)	RCT, crossover, 10 weeks	25 F, 15 M (65–80y)	FISH NMR	Increase *Bifidobacterium* spp, *Bacteroides* spp, Increased lactate, glutamate, ornithine and caproic acid concentrations	Vulevic et al. BJN, 2015[83]
Agave inulin (5.0 and 7.5* g/d)	3 wk, RCT, crossover, 1 wk washout	15F, 14 male; 20–36 y BMI 20–29 kg/m^2	MiSeq GC	Increased *Bifidobacterium* decreased *Ruminococcus**, *Lachnobacterium, Desulfovibrio*,	Holscher et al, J. Nutr, 2015[34]
Inulin + oligofructose, 16 g/d	12 wk, RCT	30 F 18–65 y BMI > 30 kg/m^2	PCR-DGGE q-PCR GC	Increased *Bifidobacterium longum, Bifidobacterium pseudocatenulatum and Bifidobacterium adolescentis* Decreased total SCFA, acetate and propionate	Salazar et al., Clin Nutr 2014[84]
Inulin + partially hydrolyzed gaur gum, 15 g/d	3-wk, RCT	32 F 18–65 yr	PCR GC	Decreased *Clostridium spp*, no changes in SCFA	Linetzky et al., Nutr Hosp, 2012[85]
Xylo-oligosaccharide (XOS), 5 g Inulin-and-XOS mixture, 3 g inulin + 1 g XOS	4 wk, parallel arm, RCT	34F, 26M 18–24 yr BMI 18.5–27 kg/m^2	qPCR GC	XOS: Increased *Bifidobacterium*, Increased butyrate, propionate, and decreased acetate, p-cresol, and pH XOS + Inulin: increased total SCFA and propionate, and butyrate	Lecerf et al., BJN 2012[86]
Xylooligosaccharide, 1.4 and 2.8* g/d	8 week, RCT, crossover, 2 wk washout	21 F, 11 M 21–49 yr mean BMI: 24.1 and 25.6 kg/m^2	pyrosequencing	Increased *Bifidobacterium, Bacteroides fragilis** No effect on pH, SCFA, or lactic acid	Finegold et al., Food Funct 2014[87]
Polydextrose (8 g/d)	3 wk double-blind, controlled, crossover, 3 wk washout	16F, 15M 22–52 yr BMI 19–25 kg/m^2	FISH, DGGE, qPCR GC NMR	FISH analysis: decreased *C. histolyticum, lactobacilli/enterococci* qPCR: increased *C. histolyticum, R. intestinalis, C. leptum* DGGE: increased diversity No significant changes in SCFA No changes in fecal metabolites (SCFA, BCFA, biogenic amine, succinate)	Costabile et al., BJ Nutr 2012[88] Lamichhane et al., J. Ag Food Chem 2014[89]
Polydextrose, 21 g/d Soluble corn fiber, 21 g/d	3 wk, RCT, crossover	21M 21–28 y 20–34 kg/m^2	Whole genome sequencing GC	Increased Bacteroidetes:Firmicutes Ratio Increased *Parabacteroides* Decreased *Eubacterium, Ruminococcus, Roseburia, Dorea* Decreased bacterial butyrate metabolism genes Decreased fecal butyrate, phenol, and indole	Holscher et al., AJCN 2015[33] Vester-Boler et al., BJN 2011[90]
Soluble corn fiber, 10, and 20* g/d	RCT, crossover; 4-wk	28 F (11–14 y)	MiSeq GC	Increased *Parabacteroides, Bifidobacterium**, *Dialister** Decrease: *Anaerostipes, Dorea**, *Ruminococcus* Decreased fecal pH, numeric increase in SCFA	Whisner et al., J. Nutr (2016)[91]

(*Continued on next page*)

Table 1. (*Continued*)

Fiber	Design	Population	Measures	Microbiome changes	References
Butyrylated high-amylose maize starch, 40 g/d	4 week, double blind, RCT, 4 week washout	10F, 13M mean age 62 yr	qPCR GC, HPLC	Increased SCFA Increased *Clostridium coccoides, Clostridium leptum, Lactobacillus* spp, *Parabacteroides distasonis* and *Ruminococcus bromii* Decreased *Ruminococcus torques* and *Ruminococcus gnavus, Ruminococcus torques* and *Escherichia coli*	Leu et al. BJN 2015[92]
Resistant starch, 22–29 g/d	3 wk, randomized crossover design	14 M	HITChip microarray	Resistant Starch: Increased *Oscillospira guillermondii, R. bromii, Sporobacter termitis, Clostridium leptum, C. cellulosi, Alistipes spp, E. rectale* Decreased Papillibacter cinnamivorans, microbiota diversity, and acetate, propionate, butyrate Non-starch Polysaccharides: Increased *Eggerthella, Collinsella, Corynebacterium, Bacteroides vulgatus* and *Prevotella oralis*	Salonen et al., ISME J 2014[93]
Non-starch polysaccharides, 30–55 g/d		27–73 yr BMI 27.9–51.3 kg/m^2	qPCR SCFA	Decreased: *C. leptum, C. cellulosi, Oscillospira* spp and *Sprorobacter* spp	

fiber at 5–20% weight/weight of feed and the translation of these doses in humans is often an unattainable amount. For example, 5% of the diet as fiber is at least 20 grams/day for adult humans. If the fiber of interest is highly fermentable, e.g., inulin-type fibers, this dosage is near the top of the tolerable limit for human consumption, and consumption at this level is likely to result in unpleasant side effects such as gas, bloating, and diarrhea.[94] Other fibers, such as polydextrose and soluble corn fiber, have been shown to be tolerable up to 50 grams/day in clinical trials.[95] Pigs provide an alternative preclinical model for studying the impact of fiber and prebiotic consumption as their gastrointestinal physiological is more similar to humans than rodents. However, challenges such as substrate availability can occur when there is limited ingredient availability. In all animal experimentation, defined diets rather than chow should be utilized to improve reproducibility of results among studies.

Future directions

Insights into how fiber, including those considered prebiotics, impacts the gastrointestinal microbiota are emerging; however, more research is needed to determine if modulation of the composition and function of the human gastrointestinal microbiota translates to health benefits in human populations. Large prospective studies are necessary to determine the directionality of the associations between perturbations in the microbiota and disease. Well-controlled clinical trials, optimally, complete feeding studies with single ingredient modifications utilizing crossover designs with washout periods, are needed to assess not only the impact of fiber on the gastrointestinal bacterial taxa, but also microbial metabolites and other physiological measures of health such as body composition, blood cholesterol, glycemia, and inflammation. When complete feeding trials are not feasible, crossover study designs are useful to account for the inter-individual make-up of the microbiota that contributes to a large portion of variability. When parallel arm designs are the most appropriate to assess other study outcomes, microbiome sample collection and analysis at baseline and over time will enable additional statistical analyses to account for variation and changes over time. The use of food frequency questionnaires and diet records or recalls are useful to assess the impact of other dietary factors that may be contributing to study outcomes. In addition, compliance logs to assess consumption of treatments are recommended. When possible, the use of stable isotopes to label fibers will further strengthen these investigations.

Animal models must also be utilized to investigate mechanisms. Research using gnotobiotics models is especially powerful, especially when animals are humanized through the use of fecal transplants. Ex vivo experimentation that simulates the gastrointestinal

tract is also informative because it provides a high-throughput approach. The collection, comparison, and integration of the vast data sets generated in human, animal, and in vitro studies should be further explored using data processing algorithms, such as machine learning. Machine learning approaches that integrate vast multi-omics data sets also allow us to extend our understanding of host-microbe interactions. In this era of rapid technological and computational advances, efforts should be made to move beyond simple characterization of the composition of the microbiota and toward functional activities of the microbiota through transcriptomics, metabolomics, and proteomics. Multidisciplinary approaches are needed, and research in the field of the human microbiome will require collaborations among scientists from various disciplines including nutrition, microbiology, physiology, immunology, and computer sciences to name a few.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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