Dietary Macronutrients in Modulating Gut Microbiota

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Over the past two decades a plethora of studies have identified broad-spanning associated links between the gut microbiota and systemic health and disease risk. The responses of the gut microbiota to sensitive factors are considered to be a valuable tool to exploit and develop new strategies to promote human health. Among these influential factors, dietary factors, including micro- and macro-nutrients, are the most influential in shaping and modulating the human gut microbiota.

Gut Microbiome Nutrition Health Diet

1. Carbohydrates

Carbohydrates are the predominant energy source for the human body and play an important role in modulating and shaping the gut microbiota. Here, the evidence for how different types of dietary carbohydrates modulate the microbiota at their genus level, the F/B ratio, and the microbial community diversity was summarized.

Plant-derived carbohydrates that escape digestion in the upper digestive tract are classified as dietary fiber and their structure, along with other undigested nutrients, influences the extent to which they are fermented by the large intestinal microbes. In animal models, the Western-style diet, with relatively lower fiber content, has been shown to reduce the abundance of *Bifidobacterium*, and the diversity of gut microbiota [1]. A chronic lack of dietary fiber could reduce the diversity of gut microbiota [2].A pre-hispanic Mexican diet (high fiber) has been shown to alleviate gut dysbiosis in the rats fed with a sucrose-enriched high-fat diet, as evidenced by reducing the Firmicutes to Bacteroidetes ratio (F/B ratio) and increasing the abundance of *Lactobacillus* sp. [3]. In a preclinical trial, humanized mice were fed a diet rich in fiber and later introduced a feed with low-quality fiber to perturbate their gut microbiome [4]. However, re-introduction of fiber by feeding a plant polysaccharide-rich diet with neutral detergent fiber content of 15% by weight did not restore the microbial composition and diversity in the tested animals. Moreover, this perturbation was observed to continue over multiple generations [4][5]. In clinical trials, studies have consistently demonstrated that high-fiber diet intervention, e.g., whole grain cereal, inulin and fructo-oligosaccharide (1:1) mixed fiber, soluble corn fiber, barley kernel-based bread, increases the fecal abundance of several beneficial microbiota, such as *Bifidobacterium* sp. [6][7][8], *Lactobacillus* sp. [8], *Akkermansia* sp. [9][10], *Fecalibacterium* sp. [10], *Roseburia* sp. [10], *Bacteroides* sp. [10][11], and *Prevotella* sp. [12][13]. Moreover, fiber-enriched diets reduce the F/B ratio [11][14] and improve gut microbial diversity [10][12][14]. The relative proportion of Bacteroidetes was reported to be lower in obese people compared with that in lean people [15]. The Bacteroidetes proportion increased on a carbohydrate-restricted low-calorie diet for one year and responded to weight loss [15]. Furthermore, the gut

microbiome of obese patients was found to show an increase in beneficial members of *Prevotella*, *Parabacteroides distasonis*, and *Fecalibacterium prausnitzii* after consumption of high-complex carbohydrate diet (low-fat, 28% fat) for one year [16].

Arabinoxylans (AX), arabinoxylan-oligosaccharides (AXOS), and xylo-oligosaccharides (XOS) are commonly found in wheat and are classified as prebiotics, as they specifically increase the pool of beneficial microbiota, including *Bifidobacterium* and *Lactobacillus* [17][18][19][20][21][22][23][24][25]. In a dietary intervention, an AX-enriched diet increased the abundance of *Bifidobacterium* sp. in adults with metabolic syndrome and lowered microbial diversity [17]. AXOS, consisting of arabinoxylooligosaccharides and XOS, can be obtained by enzymatic hydrolysis of AX [26]. AXOS and XOS were shown to increase *Bifidobacterium* sp. and/or *Lactobacillus* sp. [25] in healthy adults [18][19][20][21][22][23] and children [24].

In vitro fermentation of galacto-oligosaccharides (GOS) [27] has been shown to increase *Bifidobacterium* sp. and *Lactobacillus* sp. [28]. A similar observation was reported in a dietary intervention study using GOS on a specific pathogen-free mice model [29]. In clinical trials, GOS at a dose range of 1.5 to 10 g/day when consumed for up to 12 weeks by healthy adults increased the fecal level of *Bifidobacterium* [30][31][32][33][34][35]. A similar dietary intervention in teenage girls (10–13 years old) showed that GOS supplementation at 5 or 10 g/day for three weeks increased *Bifidobacterium* sp. population [36]. In healthy elderly volunteers (65–80 years), administration of GOS at 5.5 g/day for 10 weeks increased *Bifidobacterium* and *Bacteroides* [34]. In addition to *Bifidobacterium* sp., an increase in the relative abundance of lactose-fermenting *Fecalibacterium* and *Lactobacillus* was observed when GOS was consumed by lactose-intolerant volunteers, suggesting that administration of GOS promoted a colonic environment that favors the digestion of lactose [35]. Due to its bifidogenic potential, GOS is included in infant formula to promote a healthy gut microbiome which is dominated by *Bifidobacterium* sp. [27][37][38][39][40][41]. Babies receiving an infant formula containing 4 g GOS/L led to an increase in the abundance of beneficial microbiota *Lactobacillus* and reduced *Clostridium* [27][41]. Lactose-containing baby formula specially formulated with GOS showed significant increases in *Bifidobacterium* and *Lactobacillus* [42]. In a clinical trial for healthy adults, raffinose-oligosaccharide was identified to positively modulate *Bifidobacterium*, and negatively modulate *Clostridium*, viz. *Clostridium histolyticum* and *Clostridium lituseburense* group [43]. In addition, the raffinose-oligosaccharide did not have any significant effect on the diversity of the gut microbiota [43].

Inulin-type fructans (including main dietary sources) have been shown to consistently promote Bifidobacteria. Animal studies have shown that inulin or inulin-type fructan (ITF) could alter gut microbial diversity [44][45], and *Bifidobacterium* sp. was further identified to be promoted by ITF in clinical trials [46][47][48][49][50][51]. Supplementation of ITF at 16 g/day to obese individuals for three months increased the abundance of *Bifidobacterium* [47][50] and *Fecalibacterium* [47], and reduced the abundance of detrimental microbiota of the genus *Bacteroides* [47]. At a lower level of inulin supplementation (10–12 g/day), individuals with mild constipation showed an increase in *Bifidobacterium* [48] or an increase in *Bifidobacterium* and *Fecalibacterium* in healthy adults [46]. In children (mean age 10 years), a similar dose of inulin (10 g/d) for three months only increased the abundance of *Bifidobacterium* but did not affect the level of *Fecalibacterium* or *Bacteroides* [49]. Another study in overweight or obese children (7–12 years, 8 g inulin/day for 16 weeks) showed an increase in *Bifidobacterium* and

decrease in *Bacteroides* [51]. Taken together, these studies highlight a range of factors—dosage, inulin type, and other dietary factors (e.g., total fiber intake)—that may contribute to the effectiveness of ITF in modulating key microbes.

Resistant starch is an important substrate for supporting gut health, as it is utilised by a range of beneficial gut microbes [52]. For instance, *Bifidobacterium* sp., *Fecalibacterium* sp., *Eubacterium* sp., and *Ruminococcus* sp. were significantly increased in healthy adults who consumed resistant starch (100 g/day, type 2/ type 4) for three weeks [53]. Individuals with metabolic syndrome demonstrated that resistant starch (type 2), when applied in conjunction with arabinoxylan, could modify gut microbiota towards a beneficial pool (with higher bifidobacterial concentration and less dysbiotic genera), and modified SCFA composition, which resulted in beneficial effects on colonic health and metabolic syndrome [17]. Moreover, a dietary intervention study using resistant starch as a non-digestible carbohydrate confirmed its function to substantially alter the composition of gut microbial species, including *Ruminococcus bromii*, *Eubacterium rectale*, *Collinsella aerofaciens*, and uncultured Oscillibacter group [54].

The intervention of butyrylated high-amylose maize starch was reported in a clinical trial to increase the abundance of the beneficial microbiota, such as *Lactobacillus* sp., *Clostridium coccoides*, *C. leptum* group, and *Ruminococcus bromii*, and reduce the abundance of *R. torques* and *R. gnavus* in the participants who had gut dysbiosis caused by red meat-increased O6-methyl-2-deoxyguanosine adduct level [55].

A six-week dietary intervention study with 10% oligofructose in diet-induced obese rats increased the abundance of *Bifidobacterium* sp., *Lactobacillus* sp., and *Roseburia* sp. and decreased *Clostridium leptum* [56]. In healthy infants, the consumption of infant formula containing oligofructose (3 g/L eight weeks) increased the fecal levels of *Bifidobacterium* sp. [57].

In addition, a synthetic polymer of glucose, polydextrose (PDX) provides similar physiological effects as other dietary fibers and has shown prebiotic potential when tested in animals [58]. Dietary intervention with prebiotics has been shown to selectively stimulate the growth and/or activity of one or a limited number of intestinal bacteria associated with several physiological benefits on health. *Clostridium* clusters I, II, and IV and *Ruminococcus intestinalis* were further reported to be promoted by PDX (8 g/day) in clinical trials for healthy subjects aged 18–50 years during a three-week innervation [59].

Dietary carbohydrates have long been shown to modulate health-beneficial microbes in both humans and animals. A high-fiber diet increased the abundance of *Bifidobacterium* and reduced the ratio of Firmicutes/Bacteroidetes in humans and experimental animals. The prebiotic potential of GOS and other carbohydrates is well known and their supplementation has resulted in an abundance of *Bifidobacterium* sp., *Lactobacillus* sp., *Akkermansia* sp., *Fecalibacterium* sp., *Roseburia* sp., *Bacteroides* sp., and *Prevotella*. Arabinoxylan, resistance starch, and inulin type fructans modulate health-beneficial bacteria, such as *Bifidobacterium, Fecalibacterium,* and *Lactobacillus*. Oligofructose and polydextrose were also found to modulate many health beneficial bacteria, such as *Roseburia, Clostridium lepum,* and *Ruminococcus intestinalis*.

Studies have also shown the restorative function of certain carbohydrates on dysbiosis, observed in obese individuals, and hence such carbohydrates could be used as a therapeutic intervention for metabolic diseases.

2. Fat

A dietary pattern high in saturated and/or total fat is consistently shown to have adverse effects on intestinal microbiome. Fifteen clinical reports (including six randomized controlled interventional studies and nine observational studies) have shown that diets high in total fat and saturated fat have a negative effect on the richness and diversity of gut microbiota [60]. These findings were supported by carefully controlled feeding trials in rodents, which showed that diets containing fat ranging from 44% to 72% increased the F/B ratio of gut microbiota [3][61][62][63][64][65][66][67][68][69][70].

Although it has been indicated that the changes in the F/B ratio in gut microbiota are dependent on the intestinal region and the duration of ingestion [62], changes in the F/B ratio vary with the amount of fat in the diet. In rats, the consumption of a mixed HFD (range from 44%−72%) [61][62][63][64][65][66][67][68][69][70] increases the abundance of *Firmicutes* and decreases the proportion of *Bacteroidetes*, thereby leading to an increased ratio of F/B. These bacterial phyla viz. *Bacteroidetes* and *Firmicutes* are commonly known to predominate in the intestinal tract, however, with varying compositions. For example, the genetic obese ob/ob mice displayed fewer *Bacteroidetes* and more *Firmicutes* [61]. The same research team discovered that the obesity phenotype could be transmitted by gut microbiota transplantation in mice. The obesity increased the F/B ratio, and thereby increased the abundance of Firmicutes. After the colonization of “obese-microbiota”, the total body fat in mice significantly increased, and the capacity to harvest energy from the diet was increased as well, thus contributing to the pathophysiology of obesity [71]. However, the amount of dietary fat ranging from 20% to 40% would result in a F/B ratio decrease [72][73][74][75], or no significant changes in their ratio [16][74][76][77]. Furthermore, the gut microbial patterns in HFD-induced rat models showed an abundance of microbes of the order Clostridiales and a decrease in abundance of the microbes of the family Lachnospiraceae, possibly due to its association with body fat percentage [78]. The diminution of *Lactobacillus* population was suggested to be correlated with the high fat and its abundance displayed a negative correlation with body weight and fat mass [3][66][70][73]. In a recent randomized, controlled-feeding clinical trial, 40% fat consumption by healthy young adults was reported to be associated with unfavorable changes in gut microbiota, in that the intervention resulted in an increased abundance of detrimental species from the bacteria *Bacteroides* and *Alistipes*, the two species reported to be abundant in patients with Type 2 diabetes mellitus (T2 DM), and decreased abundance of beneficial bacteria of the genus *Fecalibacterium.* However, 20% of fat consumption showed a positive effect in terms of increasing gut microbiota *Fecalibacterium* sp. and *Blautia* sp. [74]. In people who have metabolic disease, obesity, and coronary heart disease, lowering fat intake to less than 35% fat for two years helped restore the gut microbiome [16][75][77]. The results of this study suggested that low-fat diet intervention for people depends on the degree of metabolic dysfunction, as no change was observed in people if they were not diagnosed with metabolic disease [74]. Furthermore, a sex-dependent effect on shaping the gut microbiota according to diet has been reported recently. Researchers observed a higher abundance of *Roseburia,*

Holdemania, and *Desulfovibrio* in men with metabolic syndrome (MetS) than in women with MetS after three years of consumption of the low-fat diet, which led to a detrimental effect in men rather than women [79].

Researchers have also explored the role of saturated and unsaturated fat on the modulation and diversity of gut microbiome. Patterson et al. (2014) [80] showed that different types of dietary fats increased overall gut microbiota diversity but were not significantly different from each other in a mouse model. In a dietary intervention study, the mice fed with palm oil, rich in saturated fatty acid, resulted in a decrease of the Bacteroidetes population, and the changing trends in gut microbiota compositions have been confirmed to be positively correlated with the development of obesity. Similar research found that saturated fat (HFD-containing palm oil) intake (45% fat) induced an elevated F/B ratio in a mice model and has a more stimulatory effect on the development of obesity than mice fed unsaturated fat (olive oil or safflower oil) [81]. The saturated dietary fat altered conditions for gut microbial assemblage by promoting changes in host bile composition, resulting in dysbiosis that can perturb immune homeostasis [72]. In contrast, one of the saturated fats, medium-chain fatty acids, has shown antibacterial effects [82]. Olive oil, high in unsaturated fatty acids, increased commensal bacteria, the populations of *Bacteroidaceae*, in the cecum compared with palm oil, flaxseed oil, and fish oil [80]. Flaxseed/fish oil, when administered together with a low-fat diet, imparted a bifidogenic effect on the host intestinal microbiota composition by increasing the levels of *Bifidobacterium* [80]. *Akkermansia* and *Bifidobacterium* were also considered to be associated with prebiotic consumption and they were reported to show a decreasing trend under the influence of HFD [3][83]. Enteral supplementation with polyunsaturated fatty acids (PUFA) was associated with decreased abundance of detrimental bacteria (e.g., *Streptococcus* sp. and *Escherichia* sp.), greater bacterial diversity in premature infants with an enterostomy [84]. It was also reviewed from the clinical studies that a diet rich in monounsaturated fatty acids decreased total bacterial numbers, whereas a diet rich in polyunsaturated fatty acids had no effect on the richness and diversity of gut microbiota [60].

In summary, both quantity and type of fat in the diet can modulate the F/B ratio and affect both detrimental and beneficial microbes in the gut. In particular, saturated fat consistently lowers health-beneficial microbes, such as *Bifidobacterium* and *Fecalibacterium*, whereas unsaturated fat increases the abundance of *Akkermansia* and *Bifidobacterium* and reduces detrimental bacteria such as *Streptococcus* and *Escherichia* sp. Additionally, saturated fat can increase the F/B ratio and unsaturated fat can lower the F/B ratio, and thereby they could have varying effects on human health depending on the fat quality. Clinical studies to date suggest that a high-fat diet is detrimental to gut health, as it reduces the abundance of beneficial microbes, however this can be reversed if a diet lower in fat is followed.

3. Protein

Clinical and preclinical studies have suggested that the type and amount of protein in the diet has substantial effects on the gut microbiota.

Evidence from animal models suggests that the protein quality affects the composition of gut microbiota. For example, in a preclinical study, it was shown that the cheese whey proteins could act as growth factors for fecal

counts of *Lactobacilli* and *Bifidobacteria* compared with Caesin [85]. It was also shown that a whey protein-based diet reduced the abundance of *Clostridium* [86] in the gut. Mung bean protein was shown to reverse the HFD-induced F/B ratio in mice [87]. The mung bean protein also increased the abundance of the family *Ruminococcacea* in an HFD mice model. Based on this observation the authors hypothesized that the bile acid metabolism mediated by *Ruminococcacea* family members would have provided a health benefit in HFD mice [87]. In contrast to the evidence from plant-based protein interventions, diets containing casein increased fecal *Enterobacteriaceae* and decreased fecal *Lactobacilli* in piglets [88]. Furthermore, Bacteroidales and Clostridiales levels were higher in mice when fed a Western diet that contained high levels of meat and seafood [89]. It was also shown that animal-based protein could increase the sensitivity to intestinal inflammation via increasing the potential detrimental gut microbiota (viz. the genera of *Enterococcus*, *Streptococcus*, *Turicibater,* and *Escherichia*, and families Peptostreptococcaceae and Ruminococcaceaea) compared to mice consuming a plant-based protein [90]. A recent clinical study highlighted that casein and soy protein diets should be considered with caution because they appear to disturb normal gene expression in the rectal mucosa of overweight individuals [91]. The authors could not find any changes in microbial diversity or changes in the abundance of specific taxa but could find both beneficial and detrimental metabolites produced by specific microbes. Specifically, amino acid-degrading metabolites were higher, with a reduction in butyrate concentration that the authors found correlated heavily with specific bacteria of the genera *Clostridia, Oscilospira*, *Butyricimonas,* and *Odoribacter* [91].

Although it was suggested that the protein source had a large effect on bacterial community composition [90], other studies have shown that the quantity of proteins is also very important in its effect on gut microbial modulation. In one study [86], mice were fed with a low-fat diet (10% fat) or an HFD (45% fat) for 21 weeks, with either casein (20% kJ) or whey protein isolate (WPI) at 20%, 30%, or 40% kJ. The results of this study showed an increase in abundance of the phylum Proteobacteria and Actinobacteria in the gut microbiota for the experimental animal groups that received 20% WPI. When the protein was increased from 20% to 40% the results were opposite for the phylum Actinobacteria compared to that of the HFD group. A 70-day protein supplementation (a blend of whey isolate (10 g) and beef hydrolysate (10 g)) in a healthy athletes diet had a negative impact on gut microbiota, which resulted in a decreased level of the health-beneficial microbiota, viz. *Roseburia*, *Blautia*, and *Bifidobacterium longum,* and an increase in the microbiota of the phylum Bacteroidetes [92]. The control group, who received maltodextrin, did not show this effect. In addition, different cooking methods of protein could have different effects on gut microbiota. An in vitro study on human gut microbiota showed that the *C.hidtolyticum/perfringens* group, a common food borne pathogen that can produce enterotoxins, causing a wide range of pathologies, was observed in batch fermentations that contained fried meat compared to those containing boiled meat [93], thus suggesting that the cooking method and meat type can influence fermentation profiles within the human gut microbiota.

From the above discussion it is inferred that both the quality and quantity of protein can have effects on the composition and diversity of gut microbiota. Whey protein exerts a bifidogenic effect in HFD mice at a lower concentration and reverses this effect at a higher concentration. Mung bean protein helps to reverse F/B ratio in HFD mice model, and animal-based protein may increase the sensitivity to intestinal inflammation by increasing the potential detrimental gut microbiota. A blend protein supplementation in healthy adults has a negative effect on

beneficial microbiota, such as *Roseburia*, *Blautia*, and *Bifidobacterium longum*. Furthermore, it was shown that different cooking methods have different effects on the gut microbiota. More preclinical/clinical trials are required to conclude the effects of various protein supplementation on gut microbiota.

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