Gastroenterology Report, 8(2), 2020, 85–89

doi: 10.1093/gastro/goz072
Advance Access Publication Date: 20 January 2020
Review

REVIEW

Beneficial and detrimental effects of processed dietary fibers on intestinal and liver health: health benefits of refined dietary fibers need to be redefined!

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Abstract

Consumption of processed foods—which are generally composed of nutritionally starved refined ingredients—has increased exponentially worldwide. A rise in public health awareness that low fiber intake is strongly linked to new-age disorders has spurred food manufacturers to fortify processed foods with refined dietary fibers (RDFs). Consumption of whole foods rich in natural fibers undoubtedly confers an array of health benefits. However, it is not clear whether RDFs extracted from the whole plant, kernel, and fruit peels exert similar physiological effects to their naturally occurring counterparts. Recent studies caution that RDFs are not universally beneficial and that inappropriate consumption of RDFs may risk both gastrointestinal and liver health. Herein, we briefly summarize the beneficial and detrimental effects of RDFs on digestive health and discuss the contribution of metabolites derived from microbial fermentation of RDFs in driving such positive or negative health outcomes.

Key words: gut microbiota; fermentation; IBD; metabolic syndrome; liver cancer

Introduction

Dietary fibers (DFs) are plant-derived complex carbohydrates (aka polysaccharides). The monosaccharides in these polymers are linked via β (1→4) glycosidic bonds that cannot be broken by host enzymes but digested by the gut microbes present in the distal gut [1]. Based on their solubility, the DFs are categorized into two types: soluble and insoluble. Soluble DFs are easily accessible for microbial fermentation, whereas gut microbes barely degrade insoluble DFs. Relative to humans, ruminant gut bacteria are more effective in digesting these complex carbohydrates, as they express a myriad of carbohydrate-active enzymes (CAZymes). Through fermentation of DFs, gut microbes extract essential nutrients, including carbon and energy and the host gets to expose to an array of fermentation-derived metabolites, which fine-tune both metabolic and immune health [2]. The most abundant metabolites derived from microbial fermentation of soluble DFs are short-chain fatty acids (SCFAs). These SCFAs, namely acetate (C2), propionate (C3), and butyrate (C4), are generated at millimolar levels—in an approximate 60:20:20 millimolar ratio, respectively—in the

Submitted: 2 September 2019; **Revised:** 14 November 2019; **Accepted:** 5 December 2019

distal gut [3]. It is not surprising that their dysregulated production can precipitate chronic illnesses such as metabolic syndrome [4], liver cancer [5], hydronephrosis [6], and inflammatory bowel disease (IBD) [7].

The spectrum of nutritious compounds in whole grain is diverse. However, ultra-processing (aka refining) of whole grains primarily removes the outer layer that is rich in essential micro- and macronutrients, including fiber. As a corollary, the refined wheat flour contains mainly starchy endosperm but lacks fiber, trace minerals, and vitamin-rich germ and bran. In our modern food practices, a significant portion of our daily diet is occupied by refined components, which are increasingly considered to be detrimental to health [8]. The effect of ultra-processed food on human health has been elegantly reviewed elsewhere [9]. Both soluble and insoluble DFs provide many health benefits. Despite such endorsed health claims, the data from national consumption surveys indicate that <10% of the American population meet the recommended intake of DFs [10]. Many types of structurally distinct refined dietary fibers (RDFs)—such as inulin (a polymer of fructose) and pectin (a polymer of galacturonic acid)—are being incorporated by food manufacturers in a variety of processed foods with the intent to enhance their health benefits and narrow the fiber-intake gap.

Gut microbes inhabiting the gastrointestinal tract live in harmony with the host in a symbiotic relationship. The gut microbiota (GM) help in the proper development of gut-associated lymphoid system, protect against enteropathogens via colonization resistance, and also provide a source for vitamin K and biotin. Specifically, the major metabolites SCFAs can serve as fuel for colonocytes. Recent research indicates that GM is fundamentally involved in our gastrointestinal and metabolic health. The composition of healthy gut microbiome is not precisely defined [11]; however, having greater species diversity and richness is largely considered beneficial for human health. High microbial diversity not only protects against pathogenic microbes, including viruses, but also serves as a major source of diverse enzymes to degrade the complex carbohydrates and maintain a rich chemical library of metabolites in the gut microenvironment. Three main classes of enzymes—(i) glycoside hydrolases (GHs), (ii) carbohydrate esterases (CEs), and (iii) polysaccharide lyases (PLs), which are commonly referred to as CAZymes [12]—are involved in degrading the complex carbohydrate in the gut. While the host (human) expresses approximately 17 CAZymes, the repertoire of CAZymes expressed by GM is far larger [12, 13]. The updated comprehensive details on enzymes belonging to the CAZymes group are available in the Carbohydrate-Active Enzymes database (http://www.cazy.org). Between the two dominant phyla of GM, i.e. Firmicutes and Bacteroidetes, Bacteroidetes express relatively more carbohydrate-processing GH and PL enzymes than Firmicutes [14].

DFs are among the primary source of nutrition and energy for most of the gut bacteria; therefore, they influence the richness of the bacterial species and their proliferation in the gut. Adequate consumption of fermentable DFs stimulates the expansion of under-represented but beneficial gut bacteria such as *Bifidobacterium* and *Akkermansia muciniphila*. Recent research has explicitly shown that a shift in the microbial community and metabolites derived from the fermentation of DFs execute DF-induced effects on gastrointestinal and metabolic health. Herein, we summarize the beneficial and detrimental effects of RDFs on intestinal and liver health.

RDFs: what are they?

DFs are naturally rich in fruits, vegetables, whole grains, legumes, and nuts. Given that low fiber intake—in part due to regular consumption of processed foods—can affect digestive, cardiovascular, and overall health adversely over time, food companies incorporate RDFs into food products during manufacturing. The added fiber could be: (i) extracted (e.g. inulin, which is mainly extracted from chicory root through hot-water extraction), (ii) enzymatically modified (e.g. oligofructose, derived through partial enzymatic hydrolysis), or (iii) semi-synthetic (e.g. methylcellulose, derived from chemically treated wood pulp) [15–17]. Based on the food application, manufacturers employ different methods to isolate DFs, such as blanching, milling, dry or wet processing, and enzymatic or microbial treatment. For example, enzymatic treatment in combination with micronization of rice bran produces fine fiber powder with enhanced solubility, low water- and oil-holding capacity [18], and increased absorption of bile acids and lipids in the gut. All methods used in the isolation and processing of DFs are directed towards improving its stability, enhancing the application in functional food development, and health benefits. However, whether such fiber-enriched food products deliver the expected health benefits is severely under-studied, specifically during GM dysbiosis.

DFs in modulating intestinal and metabolic health: beyond SCFAs

DF-rich food sources such as fruits, vegetables, and whole grains contain both insoluble and soluble types of DFs. Not only the metabolites derived from bacterial fermentation of DFs, but also the physico-chemical properties of DFs are beneficial for overall health. For example, insoluble DFs such as cellulose and hemicellulose benefit metabolic and intestinal health by promoting satiety, accelerating the gastric transit—which in turn influences the absorption of macronutrients present in the diet [19]—and increasing the fecal bulk. Highly viscous DFs such as β-glucan and pectin lower blood cholesterol by limiting the reabsorption of bile acids.

Bacterial fermentation of soluble DFs leads to the production of bioactive metabolites such as SCFAs, which are considered to be one of the potential mediators of beneficial effects associated with soluble DFs [20]. Our recent study demonstrated that the beneficial effects of DFs could be independent of SCFAs. Specifically, we found that dietary inulin-induced protection against diet-induced obesity was dependent on interleukin (IL)-22-mediated restoration of colonic health [21]. Collectively, consuming DF-rich foods can improve health in many ways, such as limiting bile reabsorption, providing advantageous bioactive metabolites—via microbial fermentation—and strengthening the intestinal barrier, which in turn protects against an array of microbiota-mediated inflammatory challenges.

DFs: a key determinant of gut-microbiome composition and metabolic activity

Although many environmental factors, including dietary protein, fat, and host immune and metabolic health status, impact the composition of GM, the influence of DFs is very profound. Soluble DFs (aka fermentable dietary fibers, FDFs) such as inulin and pectin are readily accessible for microbial fermentation, whereas insoluble DFs like cellulose resist bacterial fermentation. FDFs are akin to staple food for the GM and, by fermenting FDFs, gut microbes acquire their carbon source and energy for

their survival and proliferation. Therefore, FDFs are considered to be a bifidogenic factor and a critical modulator of microbial communities and their metabolic activity. The shift in GM composition due to diets low in FDFs is linked to poor intestinal and metabolic health [21, 22].

A plethora of studies have demonstrated that GM dysbiosis negatively influences overall health. Dysbiosis is a relative and vaguely defined term. A reduced alpha diversity, which represents a loss in bacterial-species richness within an organism, is considered as dysbiosis [23]. Our recent study broadens this criterion by incorporating the following key signatures of GM dysbiosis: (i) increase in total bacterial load, (ii) overrepresentation of Proteobacteria, (iii) selective shift in microbial species, (iv) enrichment of under-represented bacterial species (e.g. *Clostridia* spp.), and (v) atypical elevation of microbial-derived metabolites [5, 7]. With the knowledge that the gut harbors a complex community of trillions of microbes and FDFs are a fundamental energy source for those microbes, current research aims to exploit such a dependence of GM on FDFs to correct dysbiosis and associated health complications. In this effort, many prebiotics have been commercially developed as nutritional supplements to promote the growth of specific groups of bacteria, which are believed to be beneficial for human health. However, recent research cautions that prebiotic fibers might not be universally beneficial for health [5, 7].

Microbial-derived metabolites dictate the effect of DFs on host health

Though the association of disrupted GM composition with human health and disease has been explored extensively, very few studies have gone beyond their 'strong association' to provide proof-of-concept on how a shift in microbial communities impacts chronic health conditions. We [5, 7] and others [8, 24] have found that the host health is adversely impacted by the inappropriate type and quantity of metabolites, which are produced by dysbiotic gut bacteria. For example, elevated levels of SCFAs have been shown to fuel the metabolic syndrome in dysbiotic mice [4] and induce inflammation in the renal system [6]. Moreover, we found that elevated levels of caecal butyrate exacerbated chronic colitis in mice [7]. Likewise, a study that examined the effect of butyrate on barrier dysfunction by using epithelial monolayers from patients with ulcerative colitis demonstrated that butyrate worsens inflammation-induced barrier dysfunction in primary epithelial monolayers [24].

With few exceptions, all FDFs feed gut bacteria and then the host via gut metabolites derived from fermentation. The principal products of gut microbial fermentation are SCFAs, namely acetate (C2), propionate (C3), and butyrate (C4). Among all three SCFAs, butyrate, which is the main source of energy for colonocytes, is being considered as a potential therapeutic molecule to attenuate intestinal inflammation. While there is a wealth of scientific data demonstrating multiple benefits of SCFAs on intestinal health [25–28], several studies, including ours, show that persistent elevation of SCFAs in the distal gut lumen could do more harm than good to both colonic and metabolic health [4, 5, 7, 24, 29–33]. On a similar note, an FDF-induced shift in GM composition is not universally beneficial. Inulin, a commonly used prebiotic fiber to demonstrate the beneficial effects of FDFs on health, stimulates the growth of *Bifidobacterium*, which possesses notable bile-salt hydrolase (BSH) activity. Relative to other bacterial genera, *Bifidobacterium* and *Lactobacillus* are the most efficient in generating secondary bile acids due to a higher expression of genes encoding for BSH enzymes [34, 35]. Secondary bile acids, such as deoxycholate and lithocholate, are toxic to host cells and have been reported to promote cancer [36].

Refined fermentable fibers, commonly present in processed food, induce hepatocellular carcinoma in dysbiotic mice

Though the mammalian genome does not encode most of the enzymes required to digest complex carbohydrates, we receive many fermentation-derived metabolites with the help of symbiotic bacteria residing in the gut. Between the two most abundant bacterial phyla, the bacterial species from the Bacteroidetes express a large repertoire of FDF-degrading enzymes [13]. Accordingly, Bacteroides species can digest diverse DFs, including pectin, galactomannan, laminarin, xylan, arabinogalactan, β-glucans, alginate, and xyloglucan [37–40]. However, a few Bacteroides species, e.g. *B. vulgatus*, are unable to digest inulin-like fructans [41]. Inulin-type fructans are mainly fermented by the *Bifidobacterium* [42].

The beneficial effects of the prebiotic fiber inulin on metabolic health are well documented. However, we did not observe such inulin-induced beneficial effects in a subset of toll-like receptor five deficient mice (*Tlr*5KO), which display spontaneous metabolic syndrome in a microbiota-dependent fashion. Surprisingly, a subset of *Tlr*5KO mice developed hepatocellular carcinoma (HCC) upon being fed an inulin-containing diet for 6 months [5]. No incidence of HCC was found in mice receiving a diet containing cellulose, which is largely not accessible to GM in both rodents and humans due to the absence of cellulolytic bacteria. Lack of HCC in mice fed with a similar amounts of inulin incorporated in a grain-based chow diet—which represents minimally processed whole foods—emphasizes that the consumption of RDFs fortified in processed foods could be detrimental to human health.

Structurally distinct DFs differentially modulate intestinal health

FDFs are well tolerated by healthy individuals and consuming an adequate amount of FDFs can provide numerous health benefits. Contrarily, a subset of IBD patients experience poor tolerance to certain types of fiber, including inulin-type fructans commonly present in the FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) [43, 44]. In our recent study [7], we showed that two structurally distinct FDFs (inulin and pectin) behave oppositely in the inflamed gut (Fig. 1), which emphasizes the complexity of fiber intolerance in IBD patients. To understand the fundamental mechanisms of why inulin aggravated intestinal inflammation, we analysed both the composition and the metabolic products of the GM in cecal contents, which revealed that inulin specifically promoted the expansion of γ-Proteobacteria, a well-known opportunistic pathogen, and an abundance of butyrate when compared to mice fed pectin and cellulose as a DF source. Further, oral feeding of tributyrin, the triglyceride form of butyrate, exacerbating colonic inflammation affirmed that elevated butyrate could be detrimental during heightened colonic inflammation triggered via loss of IL-10 function. Exacerbated colitis in the inulin-fed group was also associated with augmented IL-1β activity, where inhibition of the nucleotide-binding oligomerization domain (NOD)-like receptor protein 3 (NLRP3) by genetic, pharmacologic, or dietary means diminished colitis. Collectively, our study partly explains why limiting or avoiding foods that contain high FDFs—or consuming a low-FODMAP diet—improves clinical

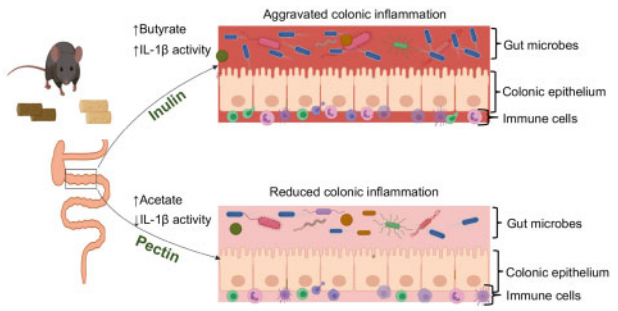

Figure 1. Dietary fiber pectin, but not inulin, protects against colonic inflammation. The image depicts the distinct effect of fermentable dietary fiber on colonic inflammation induced via loss of IL-10 signaling. All changes are relative to control-diet (cellulose)-fed mice. A ratio of IL-1β to IL-1Ra, an endogenous antagonist of IL-1β, is presented as IL-1β bioactivity. IL-10, interleukin 10; IL-1β, interleukin-1 beta; IL-1Ra, interleukin-1 receptor antagonist.

complications in IBD patients. Remarkably, pectin used in this study improved colonic inflammation. Collectively, accumulated data suggest that not all DFs are created equally or ferment uniformly, and do not provide similar effects on host gastrointestinal health.

Conclusion

The vital role of the GM in maintaining overall metabolic and immune health urges research to constitute a strategy to maintain a healthy GM composition. The phrase 'dietary fiber' adds many values to packaged food. Without exception, consuming DFs naturally present in whole foods is beneficial for overall health, but whether RDFs are equally beneficial for health is largely unexplored. The notion of eating more fiber has spurred food manufacturers to fortify nutritionally deprived processed food with RDFs. This approach certainly narrows the gap of adequate fiber intake that is commonly found in the Western world, but it can have negative consequences on gastrointestinal and liver health.

Funding

This work was supported by grants from the National Institutes of Health [R01CA219144] to M.V.-K. V.S. is supported by a Career Development Award [ID# 597229] from the Crohn's & Colitis Foundation (CCF).

Conflicts of interest

None declared.

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