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The Role of the Gut Microbiota in the Relationship Between Diet and Human Health

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Abstract

The interplay between diet, the gut microbiome, and host health is complex. Diets associated with health have many similarities: high fiber, unsaturated fatty acids, and polyphenols while being low in saturated fats, sodium, and refined carbohydrates. Over the past several decades, dietary patterns have changed significantly in Westernized nations with the increased consumption of calorically dense ultraprocessed foods low in fiber and high in saturated fats, salt, and refined carbohydrates, leading to numerous negative health consequences including obesity, metabolic syndrome, and cardiovascular disease. The gut microbiota is an environmental factor that interacts with diet and may also have an impact on health outcomes, many of which involve metabolites produced by the microbiota from dietary components that can impact the host. This review focuses on our current understanding of the complex relationship between diet, the gut microbiota, and host health, with examples of how diet can support health, increase an individual's risk for disease, and be used as a therapy for specific diseases.

INTRODUCTION

Diet has direct effects on host physiology as well as indirect effects mediated by the microbiota and its metabolome (**Figure 1**). Direct long-term dietary effects on host physiology can be positive or negative depending on the diet. For example, a diet rich in fiber and unsaturated fatty acids, such as the Mediterranean diet, is associated with a decreased risk for cardiovascular disease (CVD) and metabolic syndrome (1–3). Conversely, a diet low in fiber and high in saturated fats and refined carbohydrates, termed the Western diet, is associated with an increased risk for obesity and CVD (4–6). Diet can also be used as a treatment for certain diseases. For example, first-line treatment for celiac disease is a gluten-free diet (7), and exclusive enteral nutrition (EEN) is an effective therapy for Crohn's disease (8, 9).

There is growing evidence, mostly in animal models, that the gut microbiota impacts host health. Many of the same diseases that are known to be associated with diet, such as obesity, metabolic syndrome, and CVD, have also been associated with alterations in the gut microbiota. The microbiota and associated microbial metabolites are altered by both diet and host physiology; however, the causative role of the microbiota in many diseases, including those mediated by diet, is still being elucidated.

This review explores the relationship between diet, the gut microbiome, and host health. Although we use specific diets to describe this relationship as examples, we do not discuss all diets that impact the gut microbiome and host health. The review is organized as follows. It first provides an overview of the gut microbiome (general concepts and dietary fiber), followed by a summary of diets that promote health and their impact on the gut microbiome (Mediterranean diet, vegetarian diet, intermittent energy restriction/ketogenic diet). Diets associated with disease and their impact on the gut microbiome (Western diet) are discussed, and the article concludes by discussing diets for the treatment of disease and their impact on the gut microbiome [EEN, modified EEN/elimination diet, a diet low in fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs), and the gluten-free diet].

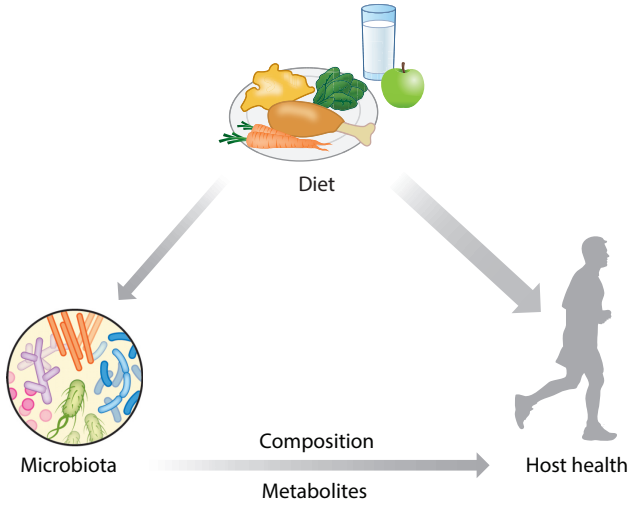

Figure 1

Relationship between diet, the gut microbiota, and host health. There is well-documented evidence that diet can have a substantial direct effect on host physiology and health. However, growing evidence suggests that diet may also have an indirect effect by altering gut microbiota composition and/or its production of metabolites that, in turn, have an impact on host physiology.

Gut Microbiome: General Concepts

The gut microbiota is a highly complex microbial community. The greatest biomass is in the colon, although more proximal regions of the gastrointestinal tract contain distinct microbial communities (10). In addition to bacteria, the gut microbiota contains viruses, fungi, Archaea, and microeukaryotes. Although most research has focused on bacteria, there is growing evidence that these nonbacterial components may also play a role in health and disease (11). The initial inoculation by the microbiota occurs at birth. Many factors have been shown to influence the composition of the infant gut microbiota, such as the modality of birth (caesarian section versus vaginal delivery), diet (breast versus formula feeding), and the use of antibiotics (12). The microbiota rapidly diversifies during the first few years of life (13, 14) and plays an important role in development of the immune system (15), including protection against bacterial overgrowth and pathogenic microbes (15). In adults, the microbiota is involved in the regulation of intestinal and systemic hormonal function (16), the modification and elimination of specific toxins/drugs (17), regulation of bone density (18), and optimization of intestinal barrier function (19), among others.

Microbiota composition and function are impacted by multiple factors, including host genetics and physiology, environmental exposures, and age, as well as diet (20–22). In mice and humans, the microbiota exhibits rapid (within 24 h) alterations in response to diet (20, 23).

Gut Microbiome: Dietary Fiber

High levels of dietary fiber are common to many diets that have been shown to be beneficial to human health. Fiber generally refers to nondigestible complex carbohydrates from plants (24). Fiber is generally classified based on solubility and fermentability, although it can also be classified by structure, viscosity, and food source (25, 26). Soluble fiber dissolves in water and can be fermented in the colon by the microbiota to generate short chain fatty acids (SCFAs). Insoluble fiber does not dissolve, adds bulk to stool, and is less likely to be fermented; however, some types of insoluble fiber, such as resistant starch, can be fermented by gut microbes in the colon (27). Fiber-rich diets have been associated with a reduction in all-cause mortality, body weight, diabetes, cholesterol, and blood pressure (28). Recent randomized control trials (RCTs) have demonstrated that whole grains significantly reduce plasma levels of lipopolysaccharide-binding protein, tumor necrosis factor alpha (29), interleukin 6 (IL-6), and C-reactive protein (30). This suggests both an improvement in gut barrier function (reduced lipopolysaccharide-binding protein) and a reduction in inflammation (reduced tumor necrosis factor alpha, IL-6, and C-reactive protein) (29, 30). Some beneficial effects of dietary fiber may involve the gut microbiota. High-fiber diets are generally associated with increased microbiota diversity in humans (31–33); however, a recent RCT found that microbiota diversity, which is generally lower in disease states than in healthy controls, was unchanged following a high-fiber diet intervention where there was also a lack of consistent alteration in immune function between subjects, although there was an increase in carbohydrate-active enzymes (34). Conversely, in a gnotobiotic mouse model, the consumption of a low-fiber diet leads to an increase in the abundance of mucin-degrading bacteria, with a resultant reduction in mucus thickness and barrier function (19).

One source of fiber that has been particularly well studied in humans is soluble inulin-type fructans (ITFs), which are found naturally in plants, particularly wheat and onion, and are isolated from chicory for prebiotic applications (35–37). Multiple studies have evaluated the impact of ITFs on health, the microbiota, and the metabolome with varying results. ITFs have been shown to reduce hunger and desire to eat (38) along with ameliorating constipation (39). However, in another study, ITFs also led to a significant increase in frequency of moderate flatulence (40). Multiple studies have found increases in *Bifidobacterium* levels following ITF supplementation

(38–41); however, other microbiota effects varied by study. Some of these effects include an increase in *Faecalibacterium* and corresponding reductions in *Coprococcus*, *Dorea*, and *Ruminococcus* (40); an increase in *Anaerostipes* and a corresponding reduction in *Bilophila* (39); and an increase in *Anaerostipes* and *Bacteroides* with corresponding reductions in *Blautia*, *Oscillibacter*, and *Ruminococcus* (41). Although inulin has not been found to have an effect on fecal (39–41) or plasma (41) SCFA levels, there were alterations in a number of plasma metabolites, including tyrosine and glycine, that corresponded with improvement in fasting insulin following inulin supplementation (41).

Another well-studied type of fiber in humans is inulin propionate ester (IPE), which is designed to deliver propionate to the colon (41). IPE supplementation leads to a wide array of metabolic effects including a significant reduction in IL-8 (41), weight gain, and the distribution of intra-abdominal adipose tissue (42), as well as increased insulin secretion (43). The impact of IPE on intrahepatocellular lipid content has also been studied, with RCTs yielding conflicting findings (43, 44). IPE has been demonstrated to significantly increase the relative abundance of *Bacteroides uniformis* and *Bacteroides xylanisolvens* with corresponding reductions in *Eubacterium ruminantium* and *Blautia obeum* (41).

Causative evidence for the gut microbiota–mediated effects of dietary fiber on host biology has been based primarily on animal models. Studies in mice models have shown that microbiota-derived SCFAs promote immune tolerance via augmentation of regulatory T cells that have been shown to reduce numerous inflammatory diseases including colitis (45, 46) and asthma (47). SCFA production is also involved in promoting goblet cell differentiation and mucus production, which are critical to maintaining epithelial cell health and preventing bacterial translocation (25, 48). Finally, SCFAs have been shown to regulate numerous pathways affecting the development of obesity in mouse models, in part through the activation of the G protein–coupled receptor GPR41 (49). Conversely, diets low in dietary fiber have been shown to have deleterious effects on the microbiota. Lower-fiber diets decrease SCFA production (11) and have been shown to lead to a progressive and irreversible reduction of bacterial diversity over successive generations in mice (50). This may, in part, explain the reduced diversity of the human gut microbiota in industrialized countries (51). Additionally, activation of glycoside hydrolases focused on mucus glycan degradation leads to a reduction in colonic barrier function in a gnotobiotic mouse model (19).

Despite strong mechanistic evidence in animal models, data regarding mechanisms by which dietary fiber impacts human health, either directly or mediated by the gut microbiota, are limited. In the relatively small RCTs that have been conducted, changes to the microbiota and metabolome differed between studies. This could be due to the fiber source and/or dose, how these studies were designed and performed, or intersubject variability in humans. Nevertheless, some human studies have revealed interesting effects of dietary fiber, including a 3-day consumption of dietary fiber in the form of barley kernel–based bread that led to improved glucose metabolism associated with an alteration in the *Prevotella/Bacteroides* ratio in responders. This phenotype was transferable to gnotobiotic mice inoculated with human feces and was associated mechanistically with hepatic glycogen storage (52). Despite evidence that dietary fiber supports health of the host, further research will be required to better characterize the operative mechanisms in humans before specific therapeutic strategies can be designed.

DIET, HEALTH, AND THE GUT MICROBIOME

Diet can be a modality for disease prevention. Dietary interventions are standard secondary and tertiary prevention strategies for certain diseases and include low glycemic index foods for diabetes (53), salt restriction for heart failure (54), and calorie restriction for obesity (55). Although these are examples of avoiding specific dietary constituents that are known to promote disease, a more generalized approach involves well-rounded diets with multiple constituents known to

promote health. Examples of diets with direct positive effects on host health include the Mediterranean and vegetarian diets, both of which are rich in polyphenols (1, 56) and low in red meat, saturated fats, and processed foods. Diet may also have indirect effects on health mediated by the gut microbiota. Impacts of diet on the gut microbiota and health have been demonstrated through mechanistic studies in animal models, although studies in humans are largely correlative. Additionally, there is a growing body of evidence that effects of diet on the gut microbiota in humans are more personalized—that is, dependent on the specific subject and correlated with anthropometrics, starting microbiome composition, and host genetics, among others (20, 57–59). Such effects may support a role for personalized nutrition to treat disease and/or promote human health (59).

Mediterranean Diet

The Mediterranean diet is a well-balanced diet characterized by diverse food groups high in nuts, vegetables, fruits, and olive oils, with moderate amounts of fish, poultry, and wine, along with limited consumption of processed and red meats (60). Many of the components are high in dietary fiber. It continues to gain popularity among medical and nonmedical personnel because of its diverse food groups, accessibility, and health benefits. More data have been published describing the direct impact of the Mediterranean diet from nutritional constituents on human health than the interplay between the Mediterranean diet and the gut microbiota, although there is growing interest in the latter (**Figure 2**).

A multitude of favorable metabolic changes have been demonstrated with the Mediterranean diet, including improvements in insulin sensitivity (5, 61), anti-inflammatory and antioxidant effects (1, 3), reductions in plasma cholesterol and low-density lipoprotein (LDL) (5), and reductions in CVD (2, 3) and all-cause mortality (62). Some of the observed health benefits associated with the Mediterranean diet are thought to be specific dietary constituents, one of which is polyphenols (1–3, 56). Polyphenols are a heterogeneous group of naturally occurring phytochemicals found in a variety of food groups, such as cereals, nuts, vegetables, fruits, and certain beverages including red wines and teas (63, 64). Polyphenols act on a variety of biochemical pathways to influence physiology. Resveratrol, a polyphenol found in red wine and berries, has been demonstrated to increase insulin sensitivity and promote cellular longevity through sirtuin 1 in both animal models (65, 66) and humans (67). Other polyphenols, such as saponins, have been demonstrated to decrease glucose transport across the brush board in the small intestine and also delay gastric emptying of glucose (64).

Another class of dietary nutrients thought to play an important role in the beneficial effects of a Mediterranean diet are unsaturated fatty acids, a type of lipid with at least one carbon to carbon double bound. Unsaturated fatty acids are components of phospholipids that make up cell membranes (68) and are found in many foods including oils, nuts, seeds, and plant-based products (69). A landmark study evaluating the impact of the Mediterranean diet on mortality in patients with CVD risk factors found a significant reduction in major cardiovascular events in those who consumed a Mediterranean diet supplemented with either nuts or olive oil compared to a control group (60). Unsaturated fatty acids can be further categorized as monounsaturated fatty acids (MUFAs), which contain a single double bond, or polyunsaturated fatty acids (PUFAs), which contain two or more double bonds. A low-fat diet supplemented with PUFAs has been shown to reduce waist circumference, blood pressure, triglycerides, and prevalence of metabolic syndrome (70).

Human studies examining the impact of a Mediterranean diet on the gut microbiota have found varying effects. Increased abundance of *Bifidobacterium* has been found in multiple studies (71, 72). In one of these studies, *Enterococcus*, *Prevotella*, and *Bacteroides* were also increased (72). Another study found increased abundance of *Faecalibacterium prausnitzii*, *Roseburia*, and *Lachnospiraceae* (5), with a corresponding decrease in *Ruthenibacterium lactatiformans*, *Flavonifractor*

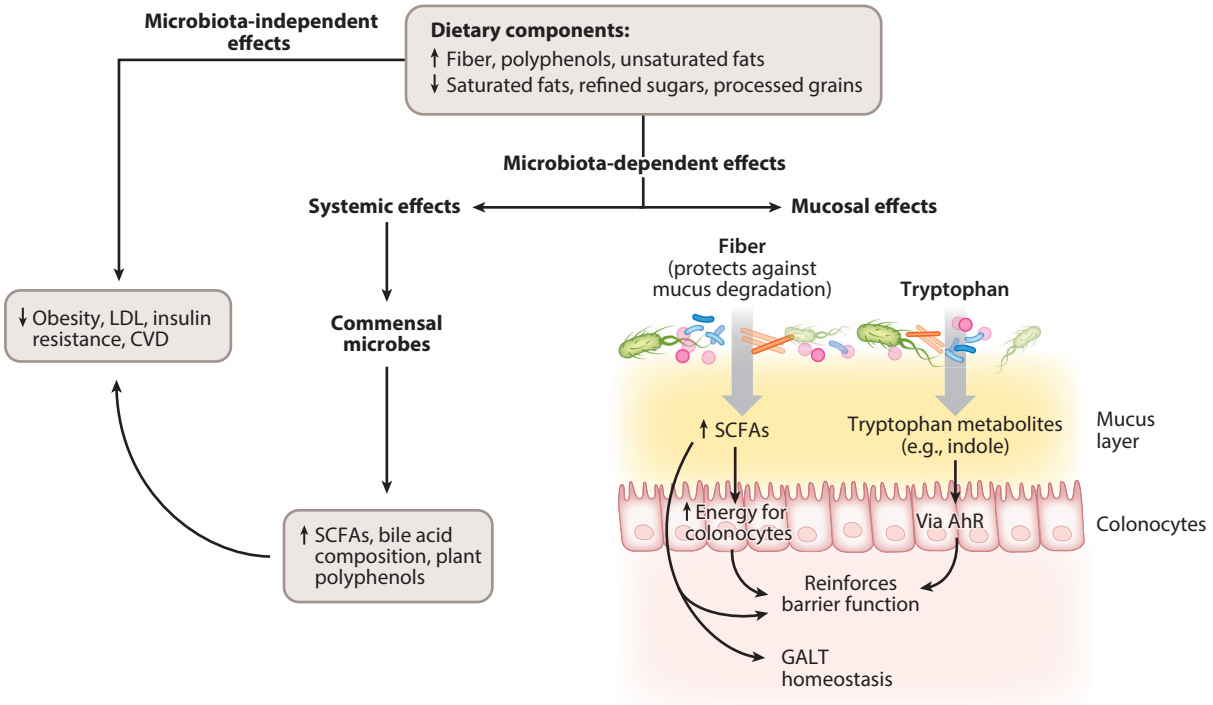

Figure 2

Impact of a healthy diet on the gut microbiota and host. There is strong evidence supporting the impact of a healthy diet on reducing the risk for disease that likely does not involve the gut microbiota. For example, specific health-promoting dietary components such as fiber and polyphenols, along with a reduction in harmful dietary components such as saturated fats and processed grains, have a multitude of effects on health, including reduced obesity, LDL, insulin resistance, and CVD. By contrast, there are currently limited data in humans supporting a direct causal link by which diet promotes health through the microbiota. Nevertheless, there are growing intriguing data in animal models showing a cause-and-effect relationship between diet and host health via the gut microbiota. Some salient examples include the fortification of barrier function through the gut microbiota production of SCFA from fiber and tryptophan metabolites acting on the AhR; protection of the mucus layer with fiber acting as a nutritional substrate for microbiota; SCFAs augmenting regulatory T cells, which support immune tolerance and GALT homeostasis; and systemic effects of microbial metabolites including the effects of SCFAs, bile acid composition, and plant polyphenols on obesity, cholesterol, insulin, and CVD. Abbreviations: AhR, aryl hydrocarbon receptor; CVD, cardiovascular disease; LDL, low-density lipoprotein; GALT, gut-associated lymphoid tissue; SCFA, short chain fatty acid.

plautii, *Parabacteroides merdae*, *Ruminococcus torques*, and *Ruminococcus gnavus* (5). Other studies have found increases in *Lactobacillus* (71) and Firmicutes (73). Specific components of the Mediterranean diet have individually been found to alter gut microbiota composition. For example, walnut consumption was associated with an increase in the relative abundance of *Roseburia*, *Eubacterium eligens* group, *Lachnospiraceae*, and *Leuconostocaceae* (74). In that study the relative abundance of *Lachnospiraceae* was inversely correlated with blood pressure and lipid profile (74). The MUFA oleic acid was associated with an increase in the *Clostridiales* vadin BB60 group (74). PUFAs have been shown to significantly increase *Bifidobacterium* (75, 76), *Lactobacillus* (76), and *Roseburia* (76).

Some of the strongest evidence for microbiota-mediated impacts on host health are through microbial metabolites. One example is microbial metabolism of tryptophan, an essential amino acid found in a variety of foods, including poultry, fish, dairy products, and grains (77), which are commonly found in the Mediterranean diet. Tryptophan can be metabolized by the microbiota into small molecules that can serve as ligands for the aryl hydrocarbon receptor (AhR),

which stimulates glucagon-like peptide 1 (GLP-1) secretion from enteroendocrine cells (77, 78). In both animal models and human studies, metabolic syndrome is associated with a reduction in both AhR ligands and GLP-1 release, along with impaired intestinal barrier function in animal models (78). Interestingly, the beneficial effects of microbiota-dependent tryptophan metabolism are not isolated to the gut but have also been demonstrated to promote neural progenitor cell terminal differentiation into mature neurons (79) and reduce central nervous system inflammation in a mouse model (80). Another example of the microbial-mediated impact of diet is the increase in microbiome gene representation associated with SCFA production on a Mediterranean diet (5); this is consistent with reported increases in fecal SCFAs (73). However, the association between a Mediterranean diet and systemic levels of trimethylamine *N*-oxide (TMAO), a biomarker of seafood intake, is an example of issues that need to be resolved when determining the role of the gut microbiota in the health benefits of a Mediterranean diet. Although the consumption of seafood reduces the risk for CVD (81), studies on the gut microbiota in both animal models and humans suggest that the production of trimethylamine (TMA) by the microbiota with its subsequent conversion to TMAO accelerates CVD in mice and is a biomarker for CVD in humans (82, 83). A more thorough discussion is provided below.

Vegetarian Diet

A vegetarian diet generally consists of vegetables, fruits, grains, legumes, and nuts, with the possible addition of eggs and dairy products (84). Many of the food groups generally described in a balanced vegetarian diet also fall within the Mediterranean diet, including foods rich in fiber, unsaturated fatty acids, and polyphenols. Due to the exclusion of red meat consumption, there is a reduction in animal-derived saturated fatty acids. Indeed, a vegetarian diet has been associated with a reduction in acylcarnitine metabolites and L-carnitine (84), metabolites that have been associated with CVD (85, 86). These factors help to explain some of the health benefits associated with a vegetarian diet, which include reduction in cholesterol and weight (87).

The vegetarian diet has also been associated with alterations in gut microbiota composition including an increase in alpha diversity (29, 88). Specifically, a vegetarian diet has been associated with an increase in the relative abundance of the SCFA-producing taxa *Akkermansia* (84), *F. prausnitzii* (88), *Eubacterium rectale* (88), and *Eubacterium biforme* (88). *Akkermansia* has been demonstrated to help maintain the integrity of the epithelial barrier and epithelial energy balance within the colon of animal models (89). It is possible that changes to the microbiota associated with the vegetarian diet influence human health, but additional data are needed in humans to support a direct causal relationship.

Intermittent Energy Restriction and Ketogenic Diets

Intermittent energy restriction (IER) diets involve alternating periods of caloric restriction and unrestricted caloric intake. IER has been associated with increased compliance, reduction in triglycerides, LDL, and weight (90), along with a reduction in oxidative stress and inflammatory markers (91). IER is composed of a variety of different dietary paradigms, the most well studied of which are time restricted eating and intermittent fasting. Time restricted eating limits food consumption to a 9–12-h window daily in which ad libitum feeding can occur (92), whereas intermittent fasting restricts calories consumption generally to 2–3 days per week alternating with days of ad libitum food intake (93). To date, there are modest but growing data on the effects of IER diets in humans, although most studies have been conducted using animal models.

In mice, time restricted eating has been demonstrated to protect against metabolic diseases even if time restricted eating is occasionally interrupted (e.g., weekends) and when high-fat,

high-fructose, or high-sucrose diets are consumed (92). In humans, time restricted eating has been demonstrated to reduce weight (94), blood pressure (95, 96), and cholesterol (95) while improving insulin sensitivity (96). However, a larger trial found a significant reduction in lean mass with time restricted eating but no weight loss (97). Intermittent fasting ameliorated disease progression and reduced the levels of IL-17-producing T cells while increasing the levels of Treg cells in a mouse model of multiple sclerosis (MS) (98). However, the same investigators conducted a small pilot RCT in humans comprised of relapsing and remitting MS participants randomized to either intermittent fasting or an ad libitum control diet and found no difference between diets (98). Although time restricted eating and intermittent fasting are the most-studied IER diets, many variations of IER have been employed (93). For example, a study in humans found that continuous energy restriction (in this case, a continuous 25% reduction in caloric intake) and IER (in this case, two days of 75% calorie restriction followed by five days of no calorie restriction) resulted in similar weight loss between the two groups (99).

The microbiota has also been associated with IER diets. In a mouse model of diet-induced obesity, time restricted eating restored key microbiota and altered the stool metabolome (100). There was also a diurnal effect of time restricted eating on the gut microbiota whereby there are high levels of Firmicutes during feeding that decrease during fasting and correspond with an increase in Bacteroidetes and Verrucomicrobiota. These microbiota effects resulted in increased alpha diversity during feeding and a subsequent decrease during the fasting (100). Similarly, in a mouse model of MS, intermittent fasting increased alpha diversity and resulted in higher levels of *Lactobacillaceae*, *Bacteroidaceae*, and *Prevotellaceae*; these microbiome effects were associated with amelioration of disease progression (98).

The current literature in humans suggests that IER is likely effective for weight loss, although there could be negative effects on lean muscle mass. Mouse data suggest that IER may have benefits for several other clinical conditions, some of which may be mediated by the gut microbiota; however, these require further investigation and validation in human subject studies.

Ketogenic diets are designed to induce a shift in metabolism and typically involve very low-carbohydrate and high-fat consumption, leading to an increase in circulating ketone bodies and a shift in energy demands. This diet is highly effective treatment for drug-resistant epilepsy in children (101). More recently, ketogenic diets have been studied for use in the treatment of obesity; however, in a small pilot study in humans a ketogenic diet resulted in a small increase in energy expenditure but did not increase loss of body fat (102). In fact, a recent study found that a plant-based low-fat diet significantly lowered energy intake compared to an animal-based ketogenic low-carbohydrate diet over a two-week period during which human subjects consumed the diets ad libitum (103). Microbiota changes have also been linked to the consumption of a ketogenic diet, including decreased *Bifidobacterium* levels in humans (104). Beta-hydroxybutyrate, a major ketone body produced during ketogenesis, was found to directly inhibit *Bifidobacterium* growth and was associated with a reduced level of intestinal T helper 17 (Th17) cells in a mouse model (104). Mouse studies have shown that the gut microbiota is essential for the antiseizure effects of ketogenic diets, which is specifically modulated by *Akkermansia* and *Parabacteroides* and correlated with levels of amino acid γ-glutamylation (105). Despite these promising findings, there is still much to be explored regarding the interplay between ketogenic diets, the microbiota, and health outcomes.

WESTERN DIET, DISEASE, AND THE GUT MICROBIOME

Diet can also have a negative impact on health. A Westernized diet is one example of this where the increase in calorically dense and ultraprocessed food rich in saturated fat, high in salt, high in processed carbohydrates, and low in fiber is correlated with the rapidly increasing incidence

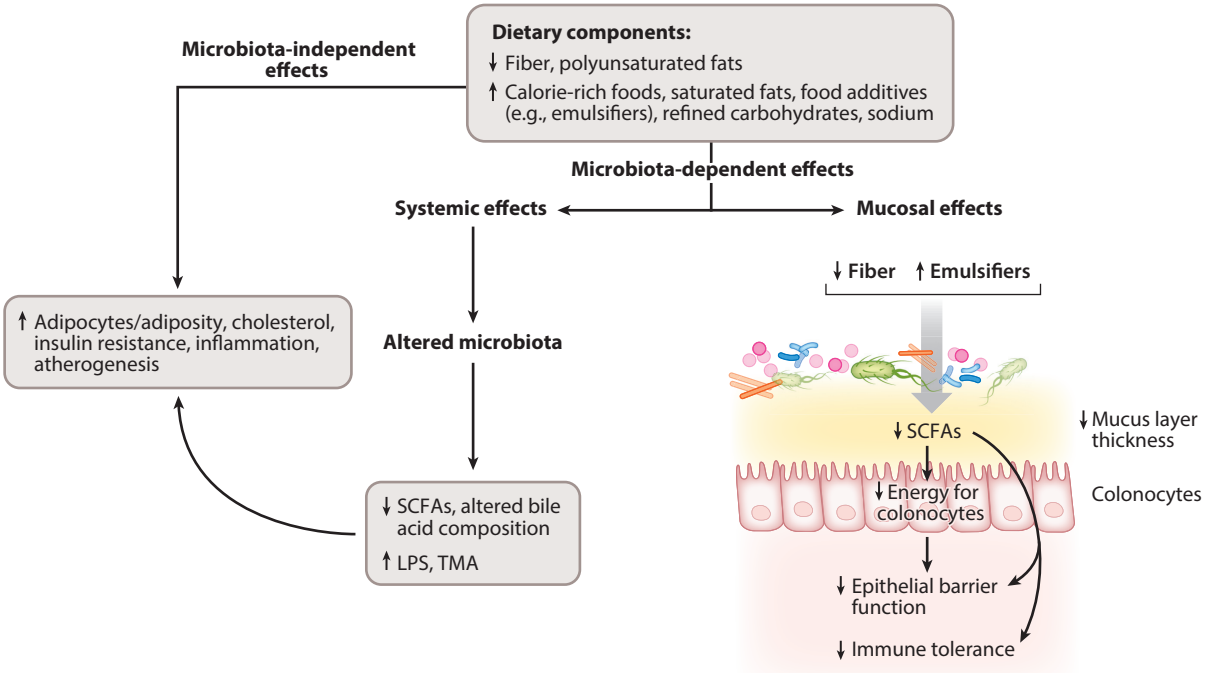

Figure 3

The Western diet, gut microbiota, and human disease. Increased proportions of dietary components such as saturated fats and refined carbohydrates, along with a reduction in health-promoting components such as fiber and unsaturated fatty acids, are directly associated with the development of disease independent of the gut microbiota, including increased adiposity, cholesterol, insulin resistance, inflammation, and atherogenesis. Nevertheless, results from studies in animal models provide evidence that these diets may also promote disease through the gut microbiota. Salient examples of gut microbiota–dependent effects of an unhealthy diet include decreased mucus layer thickness from increased emulsifiers and decreased fiber, decreased SCFA production resulting in decreased immune tolerance and decreased epithelial barrier function from decreased energy sources for colonocytes, and systemic effects of microbial metabolites. Additionally, a reduction in SCFA, altered bile acid composition, and increased LPS and TMA have systemic effects, including increased adiposity, cholesterol, insulin resistance, inflammation, and atherogenesis. Abbreviations: LPS, lipopolysaccharide; SCFA, short chain fatty acid; TMA, trimethylamine.

of obesity, metabolic syndrome, and CVD in industrialized nations (106). These effects are likely due to both gut microbiota-independent and -dependent factors (107) (**Figure 3**).

The Western diet is characterized by high levels of calorie-dense animal meats, refined grains, and sugars along with reduced levels of fruits and vegetables (108, 109). The Western diet has been associated with an increased risk for proinflammatory states, CVD, metabolic syndrome, diabetes, obesity, and certain malignancies (4–6). It is well described that saturated fats can cause a rise in plasma cholesterol levels (110), although the relationship is likely much more complex than this given the heterogeneity of this class of compounds. It has been demonstrated that certain saturated fats can increase LDL, such as palmitate, while others, such as stearate, do not impact LDL levels (111). Diets low in saturated fats but higher in PUFAs demonstrate a significant reduction in CVD, similar to the effect size seen with statin therapy; however, diets low in saturated fat diets but higher in refined sugars and carbohydrates do not reduce CVD rates (112). Increased consumption of calorically dense foods is a major factor linked to increased risk of obesity (107), which has increased in the United States from 30.5% in 1999–2000 to more than 40% in 2017–2018 (113). Individual components of the Western diet have independently been associated with

long-term weight gain, including unprocessed and processed meats, potato chips, potatoes, and sugar sweetened beverages (6). The increased consumption of highly processed carbohydrates may play a particularly important role in the development of metabolic disease by shifting energy partitioning toward deposition in adipose tissue through hormonal effects involving insulin (114). In addition to its association with obesity and metabolic syndrome, a Western diet, specifically processed and unprocessed meats, has been linked to colorectal adenomas in both humans and animal models (115–117). Proposed mechanisms of colorectal adenoma development include reductions in dietary antioxidant consumption (116) and lipid peroxidation (117). Interestingly, non-nitrosylated and nitrosylated heme iron, which are found in unprocessed and processed red meat, respectively, have been associated with advanced distal and proximal adenoma risk, respectively (116).

A Western diet is typically low in dietary fiber, which has a significant impact on the microbiota (50). Populations consuming a Western diet have higher levels of *Bacteroides* compared to those consuming a more agrarian diet higher in fruits and vegetables who have higher levels of *Prevotella* (20, 51, 118). This shift has even been observed in subjects immigrating from southeast Asia to the United States (119). In addition to lower levels of whole foods containing dietary fiber, a Western diet is characterized by high levels of additives derived from food processing, such as synthetic emulsifiers. In mice, these emulsifiers have been shown to alter the gut microbiota, reduce mucus barrier thickness, and promote intestinal inflammation and metabolic disease (120). A recent RCT seeking to extend these findings to humans during a short-term dietary intervention in healthy subjects found that dietary emulsifier supplementation decreased microbiota diversity, SCFA production, and free amino acids. Specifically, there was a decrease in *F. prausnitzii* and *Ruminococcus* levels, with a corresponding increase in levels of *Lachnospiraceae* and *Roseburia*. Finally, even during a short-term intervention, there was a reduction in colonic mucus thickness in some, but not all, subjects (121).

High levels of animal protein in Western diets have been linked to increased risk for several diseases, including atherosclerosis, heart failure, obesity, and type 2 diabetes mellitus through the metabolism of phosphatidylcholine, choline, and L-carnitine by the gut microbiota (122–124). These compounds are converted by microbes to TMA, which is then converted to TMAO by flavin-containing monooxygenase in the liver (86, 125). Multiple human studies have demonstrated an association with TMAO and increased thrombosis and CVD risk (122–124, 126, 127). In mouse models, circulating TMAO increased endothelial damage while decreasing endothelial cholesterol removal and platelet hyper reactivity, which are known to promote atherogenesis and atherothrombosis (122–124). Given the implications of TMAO in mice models, this metabolite has garnered significant attention in human health.

However, the association between diet, the gut microbiota, TMAO, and CVD is complex. Seafood is rich in TMA and TMAO but is cardioprotective (128), and fish oil has been demonstrated to offset the negative effects of TMAO, such as insulin sensitivity and adipocyte inflammation, in mouse models (129). A recent RCT found no difference in plasma TMAO levels in healthy individuals randomized to a six-month dietary intervention of either a Mediterranean diet or control diet (130). Despite robust associations with disease risk in humans and compelling mechanistic evidence in animal models, the role of the gut microbiota and TMAO in disease requires additional study.

DIETARY TREATMENT FOR DISEASE AND THE GUT MICROBIOME

In addition to supporting host health or increasing predisposition for disease, diet can be used to treat disease. Among the numerous diets available, we provide three types of diets as examples:

EEN for the treatment of Crohn's disease, a type of inflammatory bowel disease; a low FODMAP diet for the treatment of irritable bowel syndrome (IBS); and a gluten-free diet for the treatment of celiac disease.

Exclusive Enteral Nutrition

EEN is a completely liquid diet that can be used as a therapy to treat inflammatory bowel disease (IBD), particularly Crohn's disease (8, 9). Proposed mechanisms of action include correction of nutritional deficiencies that are often associated with Crohn's disease, direct anti-inflammatory effects of EEN (131, 132), and the exclusion of yet-to-be-determined components of a whole food diet that play a role in Crohn's disease pathogenesis. The efficacy of EEN is reduced if some level of whole food consumption is introduced (133). EEN has been demonstrated to not only induce remission but also promote significant rates of mucosal healing (134).

Although alterations in the gut microbiota have been described with the use of EEN, they are not completely consistent with current notions about the potential positive effects of the gut microbiota on human health. The consumption of EEN leads to a reduction in alpha diversity (8, 9), as well as the abundance of *F. prausnitzii* (8, 9, 134), *Roseburia* (134), and the *Bacteroides/Prevotella* group (8). EEN-induced remission in Crohn's disease patients was associated with increased levels of the mucin degraders *R. gnavus* and *R. torques*, which do not produce butyrate (134); indeed, butyrate levels are also significantly reduced on EEN (8). Many of the gut microbiota impacts of EEN are likely due to the absence of dietary fiber in EEN (135). Although the mechanisms are poorly understood, the positive effects of a fiber-free EEN diet in the treatment of Crohn's disease are based on strong clinical evidence. More mechanistic information is needed to characterize the mechanism by which an EEN diet is effective in treating Crohn's disease.

Modified Exclusive Enteral Nutrition and Elimination Diets

Although EEN is regularly used as a treatment for Crohn's disease, especially in the pediatric population, adherence can be difficult given the tolerability. Multiple diets have been investigated as alternative dietary therapeutics for Crohn's disease. One example is the whole food Crohn's disease exclusion diet, which is a staged diet that eliminates certain foods including dairy, animal fat, emulsifiers, artificial sweeteners, packaged/canned foods, baked goods, frozen/canned fruits and vegetables, ready-to-serve sauces, alcohol, and deep-fried foods. It has required daily mandatory foods including chicken, eggs, apples, potatoes, and bananas along with allowed daily and weekly foods. In the second stage, the list of allowed foods increases to include whole grain bread, canned tuna, and most fruits and vegetables (136). When the Crohn's disease exclusion diet was combined with a partial enteral nutrition diet as a modality to enhance tolerability of the latter, corticosteroid-free remission rates were higher at 12 weeks compared to EEN combined with an unrestricted whole food diet (136). A sustained reduction in C-reactive protein and calprotectin was also observed (136). The Crohn's disease exclusion plus partial enteral nutrition diet led to increased levels of Clostridia and a corresponding decrease in Proteobacteria (136). Overall, this study provides evidence for the value of selective exclusion of specific components of a whole food diet as a therapeutic modality for the treatment of chronic, immunologically mediated intestinal inflammatory disease processes, supporting the notion that certain components of a Western diet may promote a proinflammatory response as an environmental factor involved in the pathogenesis of IBD. The role of the gut microbiota in the efficacy of this and other exclusion diets for the treatment of IBD remains to be determined.

Finally, it should be noted that complete whole food diets with a focus on avoiding specific foods that cause inflammation have also been studied as therapeutics modalities to treat Crohn's

disease with limited success. Two of the more popular diets include the Mediterranean diet and the specific carbohydrate diet. A randomized outpatient dietary intervention in patients with mild-to-moderate Crohn's disease found moderately high rates of symptomatic remission with an improvement in quality of life associated with both diets but only limited objective evidence of reduced inflammation as quantified by fecal calprotectin and C-reactive protein (137). These results suggest that these two diets are less efficacious as IBD therapeutics relative to standard immunosuppressive therapies.

Low FODMAP Diet

Dietary fermentable carbohydrates exert osmotic effects within the intestine, which increase intraluminal water content in addition to generating colonic gas via fermentation from the microbiota (138). This can result in gastrointestinal-related symptoms such as gastric distension, bloating, and flatulence (138, 139). Given the impact of these specific dietary components, a diet low in FODMAPs has gained attention for the treatment of a variety of functional bowel disorders, such as IBS. The gut microbiota is fundamental to the mechanistic efficacy of this diet.

In functional gastrointestinal disorders, a low FODMAP diet has been demonstrated to reduce gastrointestinal symptoms, but symptoms recurred after discontinuation of the low FODMAP diet (139). A low FODMAP diet has been demonstrated to decrease histamine and the IBS severity score while increasing *p*-hydroxybenzoic and azelaic acids (140, 141). This diet has also been found to reduce *Bifidobacterium* levels (141) and increase Actinobacteria richness (i.e., number of species/taxonomic groups) (140). In patients with functional gastrointestinal disorders, a low FODMAP diet reduced the abundance of *Bifidobacterium* and increased the abundance of *Bilophila wadsworthia* (139). The low FODMAP diet likely exerts beneficial effects on gastrointestinal symptomatology by decreasing the concentrations of unabsorbed, osmotically active short chain carbohydrates in the intestinal lumen, which leads to a reduction in small intestinal water volume. Additionally, given that fewer of these carbohydrates reach the colon, there is a reduction in fermentation by the microbiota, resulting in decreased colonic gas production (141).

Gluten-Free Diet

Celiac disease is an autoimmune disease that presents in individuals with a genetic predisposition, such as *HLA-DQ 2* and *HLA-DQ 8*, following inappropriate immune response to gluten, a group of proteins found in grain products (142). Upon gluten exposure, a genetically predisposed individual will experience intestinal inflammation and loss of intestinal barrier function due to an inappropriate response to gluten-related antigens. Celiac disease commonly presents with gastrointestinal manifestations including malabsorption, steatorrhea, and abdominal pain, along with extraintestinal manifestations including dermatitis herpetiformis, iron deficiency anemia, metabolic bone disease, infertility, and liver disease (7). A gluten-free diet, which completely avoids consumption of the antigen, is the mainstay of treatment for celiac disease and can lead to resolution of both gastrointestinal and extraintestinal manifestations (142).

Untreated celiac disease is associated with dysbiosis (143–145) characterized by increased levels of *Escherichia coli* and *Staphylococcus* that return to normal after treatment with a gluten-free diet (143). Celiac disease has also been associated with shifts in the small intestinal microbiota, including a reduction in *Prevotella* and *Streptococcus*, which was ameliorated with gluten-free diet treatment (144). Patients on long-term gluten-free diets who had persistent symptoms were found to have higher relative abundances of Proteobacteria and lower relative abundances of Bacteroidetes and Firmicutes (145), further implicating the microbiota in both disease pathogenesis and dietary therapy. Although more research is required to further examine the relationship

between celiac disease and microbiota composition, emerging evidence from recent studies in animal models provides new mechanistic insights. *Pseudomonas*, a Proteobacteria with increased abundance in duodenal biopsies from patients with celiac disease, expresses elastase, which in the presence of gluten, induced more severe disease in a mouse model of celiac disease (146). In addition, dietary tryptophan can lead to the production of ligands for the AhR that plays an important role in mucosal homeostasis and can reduce disease in an animal model of celiac disease (147). Patients with active celiac disease demonstrated reduced AhR pathway activation and ligand production, suggesting possible therapeutic opportunities for the treatment of celiac disease at the intersection between diet and the gut microbiota. Although these mechanistic studies in animal models provide promising insights, further studies are needed to extend these findings to humans.

CONCLUSION

The importance of diet as an environmental factor that plays a role in human health and disease is indisputable, with certain dietary patterns that are generally health promoting, whereas others are associated with disease. Dietary interventions have also been developed to treat disease. The mechanisms by which diet regulates these responses have been well characterized for many diseases such as obesity, metabolomic syndrome, CVD, and celiac disease, to name a few. Given the impact of diet on the composition of the gut microbiota as well as the production of microbial metabolites, it is very plausible that the impact of diet on human health and disease may be due, in part, to gut microbiota-dependent mechanisms. Using several salient examples, we review the impact of diet on health and disease with an emphasis on the potential role of the gut microbiota. By contrast to the substantial body of literature on the direct effect of diet on human physiology, the impact of the gut microbiota is just emerging. This is undoubtedly due to the relatively recent advances in characterizing with precision the microbial environment made feasible through high-throughput DNA sequencing technologies along with advances in metabolomics and high-dimensional data analytics. Numerous descriptive associations have been made between diet and the gut microbiota in humans, but most mechanistic data on the impact on health and disease are currently based on data generated from animal models, and we have highlighted this fact in our review. The degree to which results in animal models are relevant to human biology remains to be determined, where the consistency of an observed response and the effect size is likely to be much larger in the former than the latter. The dramatic increase in the incidence of many inflammation-associated diseases is associated with the epidemic of obesity secondary to the Westernization of diet. Continued investigation of the intersection between diet and the gut microbiota is of critical importance as modifiable environmental factors that can be modulated to prevent and/or treat human disease.

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