Minireview

How diet and the microbiome shape health or contribute to disease: A mini-review of current models and clinical studies

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Impact statement

The studies reviewed in this article combine diet in the context of disease progression or treatment with analysis of the microbiome. First, we present findings on how diet manipulation impacts the microbiome and disease pathogenesis in a broad variety of rodent models of disease. Then, we describe results from clinical trials that are using diet therapies to attempt to shift the microbiome and treat disease symptoms. Finally, we discuss what these studies have taught us about the influence of the microbiome of disease and health states and highlight the evidence suggesting that dietary modulation of the microbiome is an emerging therapeutic option for a variety of different diseases.

Abstract

The human gut microbiome is a complex ecosystem of commensal microorganisms that help to shape host development and health. Host diet directly influences not only the composition, but also the function of the microbiome. In turn, the microbiome impacts the health of the host through production of metabolites from ingested food. Studies of this host-microbe relationship have recently enhanced our understanding of disease development and pathogenesis, and are now being targeted to combat disease symptoms and promote health. For example, dietary shifts to a high-fat, high-sugar "Western diet" drives microbiome dysbiosis in several disease models, which correlates with disease severity. Reintroduction of fiber, increased antioxidants, or decreases in fat and sugar intake helps to restore microbial balance to a healthier composition and often improves disease parameters. Analyses of microbiome-produced metabolites emphasize that understanding how diet shifts the function of the microbiome may be of critical importance for therapeutic targeting of the host-microbe relationship to promote health. In this mini-review, we discuss what is known about the three-way relationship between diet, the microbiome, and disease utilizing animal models, as well as the findings from human clinical trials of dietary therapeutics.

Keywords: Diet, microbiome, disease, inflammation, immunonutrition, genetics

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Introduction

The human gut microbiome is host to a mix of bacteria, archaebacteria, fungi, and viruses that play important roles in the development, function, and defense of the digestive tract. Mass colonization of the microbiome begins during birth, and the composition is influenced by factors such as mode of birth, genetics, environment, and diet.[1] Recently, environment has been shown to be dominant over host genetics in determining the core gut microbiome composition in humans.[2] People with distinctly different ancestral genetics, but a common place of residence, share significant similarities in composition. Over 20% of inter-person variability can be explained by factors such as diet, drugs, and anthropometric measurements.[2]

The organisms in the microbiome consume the same food the host consumes, so it is no surprise that diet impacts microbe composition. Long-term dietary habits, specifically consumption of protein and animal fat versus carbohydrate consumption, are major determinants in shaping the core microbial composition.[3] Rapid and drastic changes in dietary habits can elicit detectable shifts in subsets of microorganisms within 24 h to effectively utilize the new nutrient composition; however, these changes are not thought to be permanent and require continued consumption of the diet for maintenance.[3–5] Over time, the dietary composition in developed countries has changed from a diet rich in low-fat, high fiber foods to a processed, high-fat (HF) diet prototypical of a Western diet. This has

manifested in significant changes in fecal microbiome composition and gene expression, suggesting that the microbiome co-evolves with the diet of the host to maximize nutrient utilization.[5–7] Indeed, one of the earliest realized mutualistic benefits of commensal microbes was the digestion of complex polysaccharides so host cells can salvage energy and nutrients from otherwise indigestible foods.[8] Several studies have looked into this phenomenon and have been covered in recent reviews.[9,10]

Dietary-induced changes in the gut microbiome composition in early life can have lasting impacts on immune function.[11–14] The development and composition of the gut microbiome have also been shown to play a role in training and maintaining a healthy immune system.[13,15,16] Alterations to the microbiome may be a major contributor to the pathogenesis of several acute and chronic diseases. Evidence of the influence of both host diet and microbiome on health and disease in every organ system is rapidly increasing. In response, integrative animal models of both acute and chronic diseases are being developed to provide insights into the interaction of multiple risk factors seen in human patients. Understanding the influence of diet on disease may lead to new, non-invasive therapeutic options.

In this mini-review, we will focus on what is known about the three-way relationship between diet, the microbiome, and disease from animal models, and the findings from human clinical trials of dietary therapeutics designed from the data obtained from these animal models. Although pre-, pro-, and synbiotics have also been shown to influence both the microbiome and disease susceptibility/progression, these agents have already been extensively reviewed.[17] Micronutrients (vitamins and minerals) are also important dietary components, and there is growing interest in how they influence the composition of the microbiome. A recent review has covered the importance of micronutrients in shaping the composition of the microbiome and how deficiencies in micronutrients can be detrimental to host health.[18] Therefore, macronutrients will be the main dietary components of focus of this mini-review.

The studies reviewed in this article combine diet in the context of disease progression or treatment with analysis of the microbiome. First, we present findings on how diet manipulation impacts the microbiome and disease pathogenesis in a broad variety of rodent models of disease. Then, we describe results from clinical trials that are using diet therapies to attempt to shift the microbiome and treat disease symptoms. Finally, we discuss what these studies have taught us about the influence of the microbiome of disease and health states and highlight the evidence suggesting that dietary modulation of the microbiome is an emerging therapeutic option for a variety of different diseases.

Rodent models

Rodent models are widely used as pre-clinical disease models. In order to replicate human disease characteristics, these animals either undergo genetic manipulations or are treated with chemical agents. While these methods often create mouse lines with phenotypes mimicking clinical features of the disease reported in human patients, the models often do not recapitulate all aspects of human disease, especially diseases that are multifactorial in nature. As the role of the microbiome in influencing multiple organ systems becomes clearer, implications of its dysfunction in a variety of diseases are increasing. Here we will discuss the current study of diet-induced microbiome dysfunction in a variety of different disease models, as well as the testing of dietary treatments targeted at relieving microbiome dysfunction to improve disease phenotypes.

Gastrointestinal diseases

The gastrointestinal tract, the major site of food digestion and the home of the gut microbiome, is the most obvious organ to be readily influenced by changes in dietary composition. The mucus layer is an important structural component of the intestinal barrier that separates the epithelial layer from the environment, potential pathogenic threats, and commensal microbes. The Western diet (WD) has been shown to slow the production of the inner colonic mucus layer and increase its permeability in mice, and these changes are concurrent with microbial dysbiosis.[19]

Like the WD, a high-salt diet (HSD) induces a shift in the microbiome, with an increased *Firmicutes* to *Bacteroidetes* ratio and decreased abundance of the butyrate producing species *Lactobacillus*.[20,21] HSD-fed mice had increased susceptibility to both DSS (dextran sodium sulfate) and DNBS (2,4-dinitrobenzene sulfonic acid)-induced colitis, and this phenotype was absent in germ-free mice indicating that it is microbe-dependent.[21] Dietary heme had a similar effect in altering microbiome composition as a HSD; it decreased α-diversity, decreased microbial butyrate production, and increased susceptibility to DSS colitis.[22]

A more comprehensive approach to determining the impact of dietary components on intestinal health and the microbiome was performed in mice fed an extensive panel of defined diets consisting of various concentrations of macronutrients (protein, fat, and host digestible and indigestible carbohydrates) followed by induction of colitis by DSS.[23] This study revealed that increased protein concentration potentiated DSS colitis severity and mortality, while host indigestible carbohydrates (fiber) decreased colitis severity.[23] Of the proteins tested, casein had the greatest effect on disease severity, with animals consuming a high-casein diet losing twice as much weight as their low-casein diet fed counterparts.[23] Weight loss was accompanied by increased concentrations of fecal lipocalin-2 (Lcn-2), increased TNF-α and IL-6 secretion from colon explants, more severe colon histopathology, and increased intestinal permeability.[23] This phenotype was determined to be microbiota-dependent because germ-free mice fed a high-casein diet did not experience increased susceptibility to DSS.[23] Culture-independent sequencing of 16S rDNA revealed reduced phylogenetic diversity in the fecal microbiome of high-casein diet fed mice, with increases in the relative abundance of *Bacteriodetes* and decreases in *Firmicutes*.[23] There was also an increase in microbial density in the gut. These findings indicate that protein can have dramatic effects on intestinal health through increasing

microbial density, decreasing microbial diversity and decreasing intestinal barrier function to result in a greater susceptibility to intestinal inflammation.

Conversely, this study demonstrated that diets containing high levels of the host indigestible carbohydrate psyllium reduced DSS colitis severity and maintained microbiome composition.[23] High dietary consumption of psyllium decreased weight loss by 9- and 2-fold on days 4 and 7 of DSS administration, and was associated with decreased fecal Lcn-2 levels, colonic TNF-α and IL-6 secretion, reduced colon histopathology, and decreased intestinal permeability.[23] Only a portion of this protection was determined to be microbiota-dependent, as germ-free mice fed a high-psyllium diet had only a moderate decrease in disease severity as compared to controls.[23] A psyllium-rich diet helped to maintain a diverse fecal microbiota profile and did not allow for an increase in microbial density.[23] When combined into a single diet, casein and psyllium concentration best explained DSS severity in a linear model, and this held true in a humanized-gut microbiota model, showing conservation between mouse and human microbiota.[23]

The impact of dietary fibers on intestinal disease is not black and white, however. Additional studies indicate that the impact of fiber on intestinal health and the microbiota is context dependent and can be modified by other components of the diet or other factors. For example, supplementation of a WD with a low concentration (1%) of oligofructose-enriched inulin was sufficient to restore inner mucus layer density in a microbiota-dependent manner.[19] Additionally, supplementation of a chow diet with high levels of inulin (20%) modestly protected mice from acute DSS colitis.[24] However, there are discrepant findings on the impact of inulin in purified diets. One study found a custom refined diet supplemented with inulin (5–15%) had no significant effect on disease activity,[23] while similar levels of inulin supplementation of a purified diet in a different study demonstrated that inulin exacerbated DSS colitis activity, resulting in severe gut pathology.[24] Unfortunately, these studies did not report the impact of the inulin-supplemented purified diets on the microbiome, so it is unclear if the enhanced disease activity is due to differences in purified diet composition or facility-dependent alterations in microbiome composition.

Obesity, cardiovascular disease, metabolic syndrome, and diabetes

The link between obesity and diet is one that is well established and often obesity is a major risk factor for the development of other diseases.[25] The link between obesity and the microbiome, and how we can manipulate this to improve outcomes, is a growing field of study. A clinical study of lean and obese monozygotic and dizygotic twin pairs revealed that obesity is associated with decreased bacterial diversity, phylum-level changes in abundance, and altered bacterial gene expression resulting in changes in metabolic function.[26] This concept of dysbiosis in the context of obesity has led to the interrogation of dietary supplements as a means to restore the microbiome and improve the health of obese subjects.

Soluble fiber supplementation of HF diet-induced obesity in mice induced remarkable changes in not only microbiome composition, but also host health and immune functions.[27,28] Dietary fiber supplementation decreased fat accumulation, excessive weight gain, and associated parameters of metabolic syndrome.[27,28] It also increased energy expenditure without increasing food intake.[27] Interleukin-22 production by innate lymphoid cells was restored, and there were marked increases in intestinal epithelial health.[28] All of these changes were attributed to restoring both the abundance and the diversity of the gut microbiome.[27,28]

Oolong tea has long been touted as having anti-obesity properties without much research to back these claims. Recently, purified polyphenols found in oolong tea were found to decrease weight gain and improved microbiome diversity in a human flora-associated mouse obesity model.[29,30] Beneficial bacterial genera characterized to produce butyrate and acetate were also significantly increased by polyphenol consumption.[29] Using the Kyoto Encyclopedia of Genes and Genomes (KEGG), pathways for amino acid biosynthesis, carbon metabolism, and ATP-binding cassette transporters were found to be significantly upregulated.[29,30]

A mixture of fish and krill oil added to a HF diet was demonstrated to relieve many aspects of obesity and positively alter the gut microbiome.[31] Weight gain, fatty liver index, total cholesterol, triglyceride, and low-density lipoprotein levels were all reduced in the HF diet group supplemented with fish and krill oil, as compared to their unsupplemented counterparts.[31] The microbiome composition was also was altered by the HF diet and was shifted by the oil supplementation towards a "normal" microbiota observed in the chow-fed control group.[31]

Cardiovascular disease (CVD) is the leading cause of death in the United States, with a cause strongly linked to diet and lifestyle choices. In 2011, a link between diet, the microbiome, and CVD was made with the identification of the microbially derived metabolites trimethylamine (TMA) and trimethylamine N-oxide (TMAO).[32] Production of TMA and TMAO is microbe dependent, as germ-free and broad spectrum antibiotic treated mice do not have detectable circulating levels of either of these metabolites.[32] Dietary choline, phosphatidyl choline, and resistant starches have all been implicated in driving the production of TMA by gut microbiota.[32,33] Vascular dysfunction, a preclinical step in CVD development, was observed in a WD-fed mouse model and was shown to be driven by gut dysbiosis.[34] Suppression of the microbiome by a broad-spectrum antibiotic cocktail reversed arterial stiffness and endothelial dysfunction.[34] Chronic usage of broad-spectrum antibiotics is not a sustainable therapeutic option, so other avenues are being explored. Direct chemical inhibition of microbial TMA production in atherosclerotic lesion prone Apolipoprotein $E^{-/-}$ mice has been shown to inhibit macrophage foam cell formation, atherosclerotic lesion development, enhanced platelet responsiveness, and thrombus formulation.[35,36] Dietary mannan

oligosaccharides (MOS) have been shown to have similar effects on atherosclerosis phenotypes.[37] Supplementation with 1% MOS decreased atherosclerotic lesions by up to half, decreased plasma total cholesterol, and increased fecal bile acids.[37] This effect was not due to changes in weight, food intake, or fecal cholesterol excretion, but may be related to MOS-induced increases of cecal *Bacteroides ovatus*.[37]

Metabolic syndrome can be a precursor to diseases such as heart disease, stroke, and diabetes. A HF diet consumption initiates several phenotypes of metabolic syndrome, such as: increased body weight, increased insulin resistance, and increased serum levels of lipids.[38] The gastric microbiome of HF diet-fed mice displayed significant increases in *Firmicutes* and *Proteobacteria*, and decreases in *Bacteroidetes* and *Verrucomicrobia* prior to the onset of changes in the intestinal microbiome composition.[38] In a rat model, a diet with excess fat or sucrose (fructose and glucose) drove insulin resistance and impaired glucose tolerance through different mechanisms.[39] The excess fat diet increased *Enterobacteriales* and *Escherichia coli* levels, whereas sucrose supplementation did not.[39] Additionally, the excess fat diet leads to increased systemic inflammation, and the sucrose diet did not, suggesting a role for fats in shifting the microbiome to drive inflammation in a metabolic syndrome model.[39]

Supplementing HF diet-fed mice with chitin oligosaccharide, a cellulose-like polysaccharide, attenuated some phenotypes of metabolic syndrome.[40] Long-term chitin supplementation of a HF diet stopped the decline in glucose tolerance, suppressed mRNA expression of regulators in lipogenesis, gluconeogenesis, and adipocyte differentiation, and positively influenced the microbiome composition.[40] *Bidobacterium, Lactobacillus, Akkermansia,* and *Bacteroides* levels were all restored when the HF diet was supplemented with chitin.[40] Similar effects were observed in a HF diet fed rat model with blueberry powder supplementation; insulin sensitivity was improved alongside mucosal health markers and microbiome composition, and pro-inflammatory cytokine gene expression was decreased.[41]

Type II diabetes mellitus (T2DM) onset is often preceded by metabolic syndrome, and is also associated with significant changes to the microbiome that include decreased short-chain fatty acid (SCFA) production. In a two part study, human subjects with T2DM were randomized to groups receiving either the standard of care (education and dietary recommendations) or the standard of care and placed on a high-fiber diet.[42] The subjects that consumed a high-fiber diet had a higher rate of achieving adequate glycemic control (hemoglobin A1c $<7\%$), had rapid reductions in fasting glucose, had a greater reduction in body weight, and displayed a better blood lipid profile.[42] Gut microbiota from subjects pre- and post-intervention were transplanted into germ-free mice to investigate the causal connection between fiber intake and the observed improvements in glycemic control.[42] Mice receiving microbiota from post-intervention high-fiber diet subjects displayed significant reduction in fasting and post-prandial glucose levels, mirroring their donor counterparts.[42] They noted significant changes in genes used for carbohydrate utilization in the high-fiber group, and this resulted in the increased production of the SCFA butyrate.[42] This butyrate production stimulated the increased production of glucagon-like peptide-1 and peptide-YY that stimulate insulin production, creating a link between the diet intervention and improvements in glycemic control.[42] Similar outcomes were reported in a T2DM rat model, with pumpkin polysaccharide supplementation improving insulin tolerance, decreasing serum glucose and total cholesterol levels.[43] Consumption of the pumpkin polysaccharide also impacted the gut microbiota, increasing key microbial species and enhancing SCFA production.[43]

Obesity, CVD, metabolic syndrome, and T2DM are closely related diseases, where there are overt changes in metabolism and blood lipid and cholesterol profiles. Therefore, it is not surprising that HF, WDs have been shown to induce or exacerbate phenotypes of these diseases in mouse models, or that a common treatment, increased fiber intake, alleviates symptoms.

Cancer

The gut microbiome plays an important role in immune development and function, as well as regulation of global inflammation. Characterization of immune-mediated cancer drivers and modifiers is a field of study that has exploded in recent years. Increasing host immune system function to target cancer cells is a promising avenue for antineoplastic therapies that are currently being explored in clinical trials. In cancer patients, the microbiome is often altered, suggesting a link between tumorigenesis and gut dysbiosis-induced inflammation.

Many host factors contribute to tumor formation, one of those factors being genetic aberrations, both germline and somatic. Mutations leading to microsatellite instability in the TGF-β receptor gene are one of the most common genetic perturbations in inflammatory bowel disease (IBD)-associated colorectal cancer (CRC) patients.[44] Mice deficient in TGF-β signaling via *Smad3* knockout had increased microbial transcription of lipopolysaccharide (LPS) genes, and decreased in butyrate production from *Lachnospiraceae* bacterium A4, resulting in an increased inflammatory response.[44] Multiple species of bacteria associated with polyamine production, which is associated with cancer, were also increased.[44]

Fiber, such as resistant starches, has been shown to be a powerful stimulator of gut microbial growth and diversification with potential for use therapeutically. In a genetically driven mouse model of colorectal polyposis, a dietary fiber mixture significantly increased SCFA-producing bacteria, SCFA levels in the stool, and levels of the butyrate receptor in the epithelium.[45] All of these changes accompanied a decrease in polyposis.[45] In pancreatic cancer xenograft mice, supplementation with engineered resistant starch (ERS) significantly hindered tumor growth, with increased growth and diversity of the gut microbiome, which was suppressed by the xenograft.[46] The ERS-stimulated microbiome also elicited changes in SCFA production.[46] *In vitro*, ERS supplementation of pancreatic cancer cells decreased

ERK1/2 and mTOR activation, which correlated with a decrease in cellular proliferation.[46] This shows that ERS can elicit direct changes on cancer cells, and this may be aided *in vivo* by bacterial metabolism of ERS and transport of end products through the blood to the site of the tumor.

Neurological diseases

The brain is separated from the rest of the body by the blood–brain barrier and was not traditionally thought to be influenced by the gut or the microbiome. Recently, the intestinal microbiome has been implicated in both the normal function and disease states of the brain via indirect and direct action on the nervous system.[47] In an experimental autoimmune encephalomyelitis (EAE) preclinical multiple sclerosis mouse model, differences in survival and pathology score were seen between groups fed two different standard chow diets.[48] The two diets elicited changes in microbiome composition, and the level of the genus *Lactobacillus* was inversely correlated with EAE severity.[48]

Maternal obesity is associated with increased risk of neurodevelopmental disorders in offspring. In a maternal HF diet mouse model, offspring displayed impaired reciprocal social interactions, sociability, and preference for social novelty; reminiscent of autism spectrum disorder (ASD).[49] Comparison of the gut microbiota of offspring from high-fat diet fed mothers (MHFD) to those from regular diet fed mothers (MRD) by 16s rRNA sequencing uncovered marked differences in analysis of unweighted UniFrac distances (assessment of the presence or absence of operational taxonomic units).[49] Co-housing MHFD mice with MRD mice corrected social deficits exhibited in single-housed MHFD mice, and microbiome profiles normalized between the two sets of mice.[49] Similar social deficits of MHFD mice were observed in germ-free mice, and microbiota transplantation from MRD mice also corrected social deficits in the germ-free mice.[49] Decreased abundance of *Lactobacillus reuteri* was identified as the cause of social deficits, as supplementation of MHFD mice with this species ameliorated this phenotype.[49] This is hypothesized to be due to *L. reuteri* increasing the reduced number of oxytocin-expressing cells in the hypothalamus of MHFD mice.[49]

In a juvenile rat model, a diet containing prebiotics, lactoferrin, and milk fat globules (test diet) was shown to increase fecal *Lactobacillus* spp. which positively correlated with the altered expression of serotonin receptors and c-fos gene expression in multiple brain regions.[50] In an open field behavioral test, rats fed the test diet displayed reduced levels of anxiety.[50] Within these three studies of different neurological diseases, *Lactobacillus* spp. correlated with neurological health, suggesting a role for this bacterial genus in brain development and health.

Immunity and infections

The microbiome is a key factor in the training and maintenance of the host immune system, and perturbations in the microbiome are linked to a wide variety of immune-mediated diseases.[51] The maternal microbiome greatly influences the developing offspring's immune system both during pregnancy and lactation.[52] Maternal consumption of a high fiber diet led to a decrease in *Firmicutes* bacteria and an increase in SCFAs.[52] *Bacteroidetes*, which are thought to be the main producers of SCFAs, were absent in the offspring microbiome, yet SCFAs were significantly increased in their plasma, suggesting the microbially derived metabolites from the mother's microbiome are transmitted to the offspring.[52] The offspring of high-fiber fed mothers had higher frequencies of thymic and peripheral T_{reg} cells and increased autoimmune regulator (AIRE) expression.[52]

In a sepsis model, mice fed a high-fiber diet displayed increased survival over normal- and low-fiber fed mice.[53] Bacterial 16s rRNA sequencing revealed increases in the relative abundance of *Akkermansia* and *Lachnospiraceae*, both of which are associated with metabolic health.[53] High-fiber diet fed mice also exhibited decreased: circulating pro-inflammatory cytokines, neutrophil infiltration in the lungs, and hepatic inflammation.[53] These effects were correlated with *Akkermansia* enrichment, as treatment with antibiotics suppressed the fiber-induced increase in bacterial abundance and negated the protective effect of the diet against sepsis.[53]

Clostridium difcile (*C. diff*) is an opportunistic pathogen that thrives in dysbiotic gut microbiomes. In a mouse model of antibiotic-induced *C. diff* infection, microbiota-accessible carbohydrate (MAC)-deficient diets perpetuated the typically 12 day long infection to greater than 30 days.[54] Reintroduction of MACs into the diet at 36 days post-infection suppressed the infection burden and *C. diff*-mediated inflammation.[54] Antibiotic treatment and *C. diff* infection significantly altered the microbiome composition as determined by 16s rRNA profiling and principle component analysis.[54] MAC supplementation helped shift the microbiome to a composition similar to the pre-infection state.[54]

Caloric restriction is a strategy that has been shown to modulate the immune system, and presents a new approach to combat infections. The responsiveness of the immune system declines with age, and this leaves open an opportunity for an infection, such as influenza (the flu), to manifest. In an aged mouse model, caloric restriction was shown to normalize the virally increased levels of the pro-inflammatory cytokine IL-1α caused by infection with influenza virus.[55] This was accompanied by increases in *Proteobacteria* and *Verrucomicrobia* abundance.[55] A principal component analysis revealed that diet restriction status had a greater influence on microbiome composition than infection status or age of the animal, suggesting this may be a new approach to combat infections.[55]

Infections can manifest in different organs depending on the invading bacteria or virus, suggesting that different diets are effective for different infections. As design of dietary therapies to combat infections progresses, it will be important to consider whether stimulating the microbiome (e.g. fiber supplementation during *C. diff* infections), or trying to subdue the microbiome (e.g. caloric restriction during a flu infection) will achieve the desired outcome.

Human studies

With the increasing amount of evidence from animal studies that host diets influence the microbiome and disease pathogenesis of a multitude of diseases, many patients and their families have become interested in using diet therapies for symptom management. Diet therapy is seen as a favorable adjunct therapy because it is less invasive and perceived to have less side effects than many other therapeutic options. Diet is also something that patients can feasibly modulate with guidance from their physician and a dietitian or nutritionist. Therefore, much effort is currently focused on testing the efficacy of dietary modulation for disease symptom management. In this half of the minireview, we will cover current clinical trials testing the effects of dietary modification on a range of different diseases.

Gastrointestinal diseases

Carbohydrate restriction diets are one of the current trends in treating symptoms of gastrointestinal diseases based on the concept that restriction of dietary components readily utilized by the microbiome may decrease microbial stimulation or propagation of inflammation. The low FODMAP (fermentable oligo-, di-, mono- saccharides and polyols) diet limits processed foods, carbohydrates, and fermentable items to try to decrease microbial fermentation. In a cohort of non-celiac gluten sensitive (NCGS) subjects and healthy controls, adherence to a combination of a low FODMAP and gluten-free diet significantly reduced gastrointestinal symptom rating scores, Bristol stool scores, and the number of duodenal intraepithelial lymphocytes.[56] Microbiome analysis of NCGS subjects revealed clear shifts in composition to approximately the microbiome of their non-gluten sensitive counterparts.[56]

The low FODMAP diet is also commonly used to try to relieve symptoms of irritable bowel syndrome (IBS). In a small study, approximately 50% of subjects responded to the low FODMAP diet as defined by $\geq$50% decrease in IBS symptom severity scores.[57] Responders tended to be younger than non-responders, and responders had higher levels of *Bacteroides fragilis, Acinetobacter, Ruminiclostridium, Streptococcus,* and *Eubacterium*, and lower levels of *Clostridia*, *Actinomycetales*, *Anaerotruncus, Clostridiales*, and *Shigella/E. coli* prior to dietary intervention.[57] Using these selected bacterial markers, a response index value was calculated for each subject; subjects with a response index greater than 3 were five times more likely to respond, suggesting these bacterial markers can be used as prognostic markers to determine whether an individual will respond to dietary modulation prior to intervention.[57] These clinical findings were replicated in a larger, randomized, placebo-controlled trial, where a greater proportion of patients following a low FODMAP diet reported "adequate symptom relief" as compared to those in the sham diet group.[58] This was accompanied by significantly lower IBS-SSS (IBS Severity Scoring System) scores, a higher proportion of patients achieving the MCID (minimal clinically important difference; reduction in total IBS-SSS score of $\geq$50), and lower severity scores for a number of symptoms.[58] An assessment of perceived quality of life using the SF-36 and IBS-QOL surveys revealed that patients adhering to the low FODMAP diet had a better perceived quality of life.[58] Analysis of microbiome composition showed some differences to the prior study, demonstrating a decrease in *Bidobacterium* absolute (by qPCR analysis) and relative (by 16S rRNA sequencing) abundance among patients following the low FODMAP diet as compared to the sham diet.[58] However, there were no significant differences in alpha- (Chao index) or beta- (Bray Curtis dissimilarity index) diversity between the low FODMAP and sham diet groups.[58]

IBD is a chronic inflammatory disease with multiple contributing factors to onset and pathogenesis, including host diet and microbiome. In treatment-naïve Crohn's disease patients, their microbiome is dysbiotic with increased abundance of *Enterobacteriaceae*, *Pasteurellacaea*, *Veillonellaceae*, and *Fusobacteriaceae*, as well as decreased *Erysipelotrichales*, *Bacteriodales*, and *Clostridiales* levels.[59] These changes in microbial composition strongly correlated disease status.[59] In an effort to combat these changes as well as disease symptoms, dietary protocols that eliminate specific food classes thought to perturb the microbiome have been formulated.[60] The specific carbohydrate diet (SCD) restricts processed foods, many types of carbohydrates, and some dairy products, and has been successful in attenuating IBD symptoms in pediatric populations. After 12 weeks on the SCD, a pediatric cohort of IBD patients had significant decreases in disease activity index scores and C-reactive protein levels.[61] Analysis of microbiome composition prior to and after SCD revealed dysbiosis prior to intervention and significant changes post-intervention, but these microbial shifts were not consistent between subjects.[61]

In patients with non-alcoholic fatty liver disease (NAFLD), carbohydrate restriction rapidly and significantly decreased very-low-density lipoprotein triglycerides, fasting plasma triglyceride concentrations, and liver fat content without significant changes in subject weight.[62] Whole genome shotgun sequencing of fecal samples revealed that carbohydrate restriction caused rapid changes in microbiome composition after just one day of intervention.[62] As anticipated, species of carbohydrate-degrading bacteria were decreased, resulting in decreased carbohydrate fermentation, as determined by reductions in fecal SCFA concentrations.[62] Pathways involved in folate biosynthesis were significantly upregulated in the gut microbiome, and pathways involved in starch and sucrose metabolism were significantly decreased.[62] Folate is a common fermentation product of *Streptococcus* and *Lactococcus.* These bacterial genus were increased over the study period and have been linked to improved liver fat metabolism, connecting the diet-induced changes in the microbiome to liver improvements.[62]

Restriction of all or a specific subset of carbohydrates appears to be a promising therapeutic strategy to treat gastrointestinal diseases. Carbohydrates are a primary source of energy for bacteria, so these diets may be eliciting their effects by decreasing bacterial growth and/or function, allowing for a cellular reset of disease symptoms; however, more research needs to be performed to determine the

mechanisms by which carbohydrate restriction alters the microbiome to promote gastrointestinal health.

Obesity, CVD, and metabolic syndrome

Caloric restriction is a traditional method to combat obesity, but the primary outcome measured is typically weight loss, not microbiome composition or other measures of health. When these additional parameters were included in studies, dramatic changes were observed in intestinal microbiome composition, intestinal barrier function, and production of microbial metabolites. A four-week, very-low calorie diet (VLCD, 800 kcal/day) induced significant weight loss in a cohort of obese women, as well as induced changes in microbiome composition, and decreased gut paracellular permeability.[63] Microbial composition changes were not consistent among the subjects though, lending no insight on which microbes may be mediating these improvements.[63] In another caloric restriction study, reductions in choline and L-carnitine (substrates for microbe-derived TMA and TMAO), but not TMAO itself, were significantly associated with decreased body weight and waist circumference, suggesting a link between gut microbiome function and host body weight.[64] In obese but otherwise healthy adults, whole-grain wheat and whole-grain rye consumption did not remarkably change microbiome composition, but resulted in modest changes of fecal butyrate and improvement in gastrointestinal symptoms, such as stool frequency and bloating.[65]

In a two-year study comparing obese patients with and without metabolic syndrome, adherence to either a Mediterranean or low-fat diet significantly altered microbiome composition only in subjects with metabolic syndrome. In these patients, the diets reversed the microbial dysbiotic patterns.[66] In a fecal transplant study, transplantation from a lean vegan donor to obese metabolic syndrome patients resulted in shifts in microbiome composition mimicking that of the vegan donor in some patients.[67] Functional analysis revealed no changes in TMAO production as assessed in the peripheral blood though, and there were also no changes in abdominal aortic ^{18}F-fluorodeoxyglucose uptake and *ex vivo* cytokine production by peripheral blood mononuclear cells.[67] This suggests a single transplantation of a "healthier" microbiome is not sufficient to drastically alter some functional outputs of the gut and vascular inflammation.[67]

In a study of mildly hypercholesterolemic adults, supplementation of diet with fermented plant extract for 10 weeks significantly decreased body weight, fat, and mass index over a placebo.[68] They also showed significant reductions in total cholesterol and low-density lipoprotein cholesterol in the plasma.[68] Analysis of the microbiome showed that beneficial bacteria *Bidobacterium* spp. and *Lactobacillus* spp. were significantly increased and harmful bacteria such as *E. coli* and *Clostridium perfringens* were decreased.[68]

While characterizing and re-balancing, the microbiome was the first step in understanding the connection between the microbiome and CVD, and these studies highlight the need for deeper investigations. The discovery that plasma TMAO levels correlates with increased risk of CVD highlights the connection between bacterial function and host disease risk and to better understand how to take advantage of this.

Neurological diseases

The ketogenic diet is a HF, low carbohydrate, adequate protein diet that has been used for decades to treat refractory epilepsy in adolescent patients.[69] The mechanism of action in reducing epileptic episode frequency has still not been fully elucidated. In a study of epileptic and healthy infants, over 60% of epileptic infants had at least a 50% decrease in seizure frequency after consumption of a ketogenic diet.[70] At baseline, there were significant differences in microbiome composition between the epileptic and healthy subjects.[70] Pre-treatment, epileptic subjects had high abundances of *Proteobacteria* and *Cronobacter*, both of which decreased after the ketogenic diet.[70] There were also increases in *Bacteroides* abundance after treatment, which is thought to be beneficial and may be partially responsible for the favorable outcome of these patients on the ketogenic diet.[70]

Conclusions

This mini-review highlights the role of the microbiome in a wide range of diseases, and how the host diet can be manipulated to influence the microbiome and potentially change the course of diseases. These studies demonstrate that a poor diet, such as the WD that is deficient in fiber and high in fat, can create a dysbiotic microbiome by shifting the microbial balance compared to that observed in healthy microbiomes. Reintroduction of important components, such as fiber and antioxidants, into the diet can stimulate the growth of health-associated microbiomes that produce metabolites which help alleviate disease symptoms. It is also becoming clear more needs to be learned about the specific types of dietary components and the context of supplementation to result in health benefits. This is highlighted by the opposing effects of fermentable fiber supplementation on intestinal inflammation,[23,24] suggesting that other factors, such as overall diet composition or microbiome composition, may influence the net effect of these dietary supplements. In future dietary studies, profiling microbiome composition as well as function may be a more informative output of how both diet and drug interventions are influencing disease and host health.

Historically studies of the microbiome have been mainly concerned with bacterial composition—who is there—but more recently studies have shifted towards determining bacterial function—what they are doing. Function may be a more informative way to quantify the "health" of ones microbiome, as several studies demonstrate a positive clinical effect of a dietary intervention that results in patient-specific shifts in microbiome composition. Many bacterial strains have similar macronutrient utilization preferences and metabolic outputs, so two patients experiencing similar health benefits but different changes in microbiome composition may still benefit from the same changes in microbial metabolism. Another example of how functional

studies can be used to better understand the diet-microbiome-disease interplay is with the changes seen after increased consumption of resistant starches (fiber). In many disease models discussed in this mini-review, resistant starches improve the diversity of the microbiome and are associated with a decrease in disease activity.[19,27,28,45,46,52–54] Resistant starches have also been shown to increase microbial production of TMA, a metabolite associated with increased risk of CVD.[32–34] So while stimulating the growth of some beneficial bacteria, resistant starches may also be increasing production of a harmful metabolite by these same microbes. Analysis of bacterial metabolic outputs may help to better define the "beneficial" bacteria and provide a more mechanistic target that can be the focus for developing new therapeutics.

A limitation of many current studies is that analyses only look at one component of the microbiome—the bacteria. The human microbiome is not only host to bacteria, but also viruses, fungi, and archaea that can all be altered in disease states. In a study of HF-fed mice, 6 fungal taxa abundances were significantly altered along with 16 bacterial taxa.[71] This study revealed inter-kingdom structural and functional relationships, suggesting that the role of bacterial and fungal components of the microbiome may be interconnected.[71] In a T-cell driven colitis model, in addition to bacterial shifts, a population of prokaryotic viruses known as bacteriophages (phages) was also significantly altered and dysbiotic, suggesting phages may contribute to disease pathogenesis in colitis.[72]

Changing the pathogenicity and metabolic outputs of the microbiome could be as simple and affordable as altering host macronutrient consumption. For patients with known familial risk factors for chronic disease development, dietary guidelines that promote commensal bacterial growth and favorable microbial metabolite production by certain commensal bacteria could be a promising preventative measure. While there have been great strides made towards prescribing diets as adjunct therapy, there are still broad gaps in knowledge on mechanism of action. Not all studies include microbiome profiling in the analysis of diet efficacy, but the studies discussed in this mini-review indicate that microbes have an important role to play in disease pathogenesis and the efficacy of dietary interventions.

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