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Using the Human Gastrointestinal Microbiome to Personalize Nutrition Advice: Are Registered Dietitian Nutritionists Ready for the Opportunities and Challenges?

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KNOWLEDGE OF THE GASTROintestinal (GI) microbiome, including its metabolic potential, provides the opportunity for registered dietitian nutritionists (RDNs) to offer more personalized nutrition advice for our clients. The GI microbiome is the entire community of microbes, which includes bacteria that live within the GI tract. In GI conditions, an opportunity may exist to reduce symptom severity by manipulating the bacteria present in the gut. In metabolic conditions, individual features of the microbiome may explain why individuals respond differently to standardized nutritional interventions.

The microbiome has been described as the "forgotten organ," with 10^{14} cells, more than 10 times the total number of human cells, and with 3.3 million nonredundant genes.[1] Nonredundant genes all perform different biochemical functions. So far, more than 1,000 separate species of microorganisms have been identified within the GI tract.[2] The microbiome is dominated by bacteria but also includes *Archaea* (many of which, in the gut, are methane producers), fungi, and viruses.[3] The genetic potential within the microbiome is vast, although significant redundancy occurs, with many bacteria sharing a substantial number of genes,[4] meaning the bacteria carry out some similar functions. The microbiome can be thought of as an ecosystem, with many bacteria working in harmony, whereby many end-metabolites from one bacterium can be used as a substrate by another bacterium. The GI microbiome has largely developed a "mutualistic" relationship with the host and has genes not possessed by humans; for instance, genes to break down fiber and produce vitamin K.[5] The microbiome ferments substrates that humans cannot and, in the process, produces biologically active metabolites. For example, the short-chain fatty acid butyrate is commonly released when dietary fiber is metabolized by the microbiome. Butyrate is then used as an energy source for colonocytes and plays a regulatory role affecting transepithelial fluid transport,[6] decreasing inflammation[7] and oxidative stress,[8] and strengthening epithelial tight junctions[9] and increasing intestinal motility.[10] The GI microbiome has a bidirectional relationship with the endocrine system as it secretes and produces hormones, including those involved in appetite regulation, and the microbiome is in turn affected by the host's endocrine system.[11]

Each individual has a unique microbiome, which will alter over his or her lifespan. The composition and diversity of the microbiome is affected by a variety of personal and lifestyle factors, including diet,[12,13] exercise,[14] weight, overall health status, antibiotic[15] and probiotic usage, other medications,[15] geographical location,[16] stress, age,[16] and sex.[17] However, long-term diet is believed to be the environmental factor with the most significant impact on the microbiome.[18] Epidemiological evidence shows that African children eating a diet high in complex carbohydrates had a significant enrichment of Bacteroidetes and a depletion of Firmicutes in comparison with Italian children eating a Western diet. In particular, the African children had a greater abundance of *Prevotella* and *Xylanibacter*, which are capable of breaking down complex carbohydrates.[12] In a randomized crossover 5-day dietary intervention in which participants solely ate either animal products or plant products, a change in microbiome was observed.[13] In the animal product–based diet, an increase in bile acid–tolerant bacteria and a reduction in those with the ability to break down complex carbohydrates occurred.

Within the GI tract, the density and the types of bacteria and other

microorganisms varies.[19] In comparison, the small intestine is less populated, and the evidence available suggests that small intestinal bacteria are more prominently involved in carbohydrate fermentation.[20] The colon is one of the most densely populated bacterial communities on earth.[4] In general, the colon bacteria can be divided into two main ecosystems: the luminal bacteria and mucosa-associated bacteria. Because they are easy to sample, the colonic luminal bacteria are well characterized. Luminal bacteria typically interact less with the host immune system than do mucosa-associated bacteria; instead, they metabolize many compounds, such as short-chain fatty acids, that are able to interact with the host epithelium. They are responsible for metabolizing many carbohydrates and amino acids and synthesizing essential vitamins used by the host.[4] Whereas colonic luminal bacteria can be investigated in a stool sample, investigating mucosa-associated bacteria requires biopsy sampling.[21] Making characterization of these bacteria more difficult is the fact that the preparation before the biopsy can have negative effects on the bacterial community present in the colon. The mucosa-associated bacteria, which are a much smaller population, directly interact with the immune system.[22] Further research is warranted to determine how the mucosal microbiome might play a role in health and disease, specifically in inflammatory bowel disease. Although good evidence exists that diet affects luminal bacteria,[18] no studies have looked at the effect of diet on mucosa-associated bacteria. Most studies collect fecal specimens, which are easily obtainable, limiting the invasiveness of the procedure.[23] Glucose breath testing could be used to identify an excess concentration of bacteria in the upper small intestine. It works on the principle that there should be no fermentation of glucose, because it is absorbed in the upper small intestine before it comes in contact with large numbers of bacteria. However, this test is unable to identify the type of bacteria present.

Manipulating the microbiome to improve health status is becoming increasingly common. Three potential targets are replenishing beneficial microbes, increasing bacterial diversity, and reducing harmful microbes.[15] The potential for fecal microbial transplantation to treat clinical conditions is no longer confined to treating *Clostridium difficile*.[24] Research is also being undertaken for its role in ulcerative colitis, non–alcohol-induced fatty liver disease, and irritable bowel syndrome.[24] Probiotics, as either individual formulations or multispecies preparations or added to food, are widely consumed to gain the benefits from these beneficial bacteria.[25]

STUDYING THE MICROBIOME

Although culturing techniques were used in the past primarily to investigate the intestinal microbiome, most studies of its composition and diversity are now being done by using next-generation sequencing techniques that look at the bacterial DNA present in samples.[26] This type of analysis identifies which bacteria are present. However, simply identifying the bacteria present may not necessarily tell us what is happening in the GI tract. Other approaches, such as metagenomics, transcriptomics, proteomics, and metabolomics (collectively termed "omics"), can provide more information on what the bacteria are doing.[27] Metagenomic analysis aims to determine all gene sequences that are present in a sample. Transcriptomic evaluation attempts to characterize what (bacterial or eukaryotic) RNA is being expressed. Proteomic analysis looks at the proteins produced by the microbiome. Metabolomic studies determine what metabolites were produced as a result of cellular metabolism with urinary samples being collected. These samples are analyzed by using liquid chromatography/mass spectrometry, gas chromatography/mass spectrometry, or nuclear magnetic resonance. Although collecting all of this information would be ideal, because of the high cost and technical challenges associated with these approaches, undertaking them is not always practical.

A high cost is associated with next-generation sequencing analyses, but on a per sample basis, it is relatively affordable if conducted at an appropriate scale. These sequencing platforms, which were once only available at specialized sites, are now more accessible than ever before, and samples can be sent to service providers. Microbiome data may become available to incorporate into clinical practice in the near future.

Four studies highlight the opportunities to personalize nutrition based on the microbiome.[23,28-30] A pilot study published by Chumpitazi and colleagues[29] showed that the types of bacteria and their gene content in the colon could predict which children respond to a low fermentable oligosaccharide, disaccharide, monosaccharide, and polyol (FODMAP) diet. McIntosh and colleagues[30] found that a low-FODMAP diet reduced the histamine produced by the microbiome, which also may contribute to the reduction in pain experienced by irritable bowel syndrome (IBS) patients. Zeevi and colleagues,[23] in an 800-person cohort, set out to see whether features of the colonic bacteria could be incorporated into an algorithm for predicting postprandial blood glucose levels. The latter study in particular has significant ramifications for dietetic practice.

The algorithm developed by Zeevi and colleagues[23] to predict blood glucose levels incorporated traditional clinical measures used in diabetes management such as glycated hemoglobin and body mass index, as well as the types of bacteria found in the colon and the genes encoded by these bacteria. Using this algorithm, the authors were able to develop a model that could predict postprandial blood glucose levels after food intake with greater accuracy than by using carbohydrate counting. They found a variable postprandial response to different foods; for example, chicken liver caused a spike in blood glucose levels for some participants, whereas a much smaller increase in blood glucose levels was seen for other participants. In part, this was related to different responses to fat. Given the important role that GI bacteria play in fermenting complex carbohydrates and in metabolizing bile acids,[31] colonic bacteria present may influence blood glucose levels. Some of the features of the microbiome that affected postprandial blood glucose levels had already been identified, such as the association between *Bacteroides thetaiotaomicron* and obesity.[32] *B. thetaiotaomicron* uses starch and is able to degrade plant polysaccharides that humans are not able to break

down.[33] The effect of features of the microbiome may help to explain why different researchers and professionals can find evidence to support very different dietary patterns for the management of blood glucose levels.[34-37]

Irritable bowel syndrome is the second clinical area in which the microbiome has been shown to have the potential to predict response to dietary treatments.[28,29] The low-FODMAP diet restricts fermentable short-chain carbohydrates and has been shown to be effective in reducing symptom severity in 70% to 75% of adults.[30,38-41] Restricting FODMAP molecules reduces bacterial fermentation and the production of gas, which leads to luminal distension, causing pain in patients with visceral hypersensitivity.[42] However, predicting which patients will experience a reduction in pain, bloating, and either constipation or diarrhea has been difficult when following a low-FODMAP diet. A study of 33 children randomized in a crossover fashion to either a low-FODMAP diet or a typical American diet found that those children with more bacterial genes capable of breaking down carbohydrates at baseline were more likely to have a reduction in symptoms when following a low-FODMAP diet. This study measured the diversity and composition of the bacterial community; the presence of certain bacterial genes was predicted by using reference genomes.[29] Further research is required to see whether these findings of bacterial genes predicting dietary response can be replicated. McIntosh and colleagues investigated the effect of a high- vs low-FODMAP diet on symptom severity, the microbiome, and the metabolites it produces. After following a low-FODMAP diet for 1 month, no reduction in the diversity of the microbiome was seen, despite a decreased intake of prebiotic fructo-oligosaccharides and galacto-oligosaccharides. Because most participants in this study had diarrhea predominant IBS, any reduction in diversity caused by a reduction in prebiotics may have been offset by the beneficial effect on diversity caused by an increase in gastrointestinal transit time.[43] In the low-FODMAP diet, urinary histamine levels were either reduced in a small number of participants or remained constant. Histamine is a short-acting amine with an effect on cells of both the innate and adaptive immune system.[44] The reduction in urinary histamine could be attributable to less distension, subsequently causing decreased mast cell degranulation[45] or the effect of biologically active metabolites on mast cells. In animal models, bacterial metabolites such as ethanol have been shown to induce histamine release.[46,47] These findings need to be replicated.

PRACTICAL APPLICATIONS

Understanding the role that diet plays in shaping the microbiome provides more evidence that RDNs could use to help patients make healthy choices. The effect of fiber on increasing the diversity of the microbiome is another reason to encourage patients to not only increase their fiber intake but also to eat a wide variety of fiber sources. The fermentation of fiber by the microbiome involves many different biochemical reactions, with different bacteria having the ability to perform different steps. Incorporating a wider range of fiber sources provides a greater range of substrates for the microbiome, giving the opportunity for a wider range of bacteria to become established in the gastrointestinal tract. RDNs also could encourage the consumption of more fermented foods.[48]

Utilization of the microbiome in specific clinical situations has the potential to improve clinical outcomes not only in IBS, but also in diabetes management, cardiovascular disease, obesity, and potentially nonalcoholic fatty liver disease (NAFLD). A study by Zeevi and colleagues[23] suggests that metabolic or endocrine disorders may be a potential target for using the GI microbiome to personalize dietary interventions. NAFLD is the perceived 'next epidemic' of clinical concern, with an increasing number of patients suffering from this disorder. The microbiome of obese patients has lower diversity and has a decreased *Bacteroidetes/Firmicutes* ratio compared with lean individuals.[49] As yet, a distinct microbiome for NAFLD patients has not been identified. However, in a pediatric population with non–alcohol-induced steatohepatitis, increased levels of *Escherichia coli* were present, which can endogenously produce alcohol. These patients had elevated serum alcohol levels despite no alcohol intake.[50] Patients diagnosed with NAFLD also have an increased risk of developing cardiovascular complications.[51] Nutrition researchers and health professionals have struggled to identify suitable dietary interventions in this area. Although weight loss for NAFLD has been established as an effective treatment, the ideal macronutrient distribution has not been defined. Dietary intervention in NAFLD is one area that could particularly benefit from personalizing nutrition through incorporating features of the microbiome into its assessment. Bacterial metabolites produced by the GI microbiome are drained through the portal vein.[52] Thus, the liver is uniquely exposed to products of microbial metabolism. Altering the substrates used by the bacteria in the gut may alter the metabolites produced and may help to reduce liver damage. Zeevi and colleagues[23] found a clear negative association between liver alanine aminotransferase levels and some bacteria. Those individuals with less *Alistipes finegoldii* and *Bacteroides xylanisolvens* had increased alanine aminotransferase levels.[23] *A. finegoldii* has saccharolytic pathways breaking down sugars and produces succinic and acetic as end products.[2]

To incorporate findings from the GI microbiome into clinical practice will require RDNs to understand the microbiological findings that are being generated by specific patient cohorts through microbiome analysis. Although an increased knowledge and understanding of microbiology and biochemistry may be beneficial, RDNs will need to focus on relating this back to foods and dietary patterns consumed by individuals and populations to best translate this new tool into improved clinical outcomes. Therefore, not only will the RDN's knowledge of food composition be important, but so also will be recipe development to assist patients in being able to follow a personalized nutrition regimen.

RESEARCH IMPLICATIONS FOR RDNs

Future dietary and microbiological research will require a dynamic multidisciplinary approach from project inception. Even overlooked details, such as collection and storage of fecal specimens, may have effects on the

quality of the data down the line. Newly established protocols in this area are improving sample quality while reducing participant burden. Research studying the impact of diet on the microbiome and vice versa has been conducted in the field of microbiology, which is generally unknown to dietitians. Much of this work is highly relevant. For example, many mechanistic studies on the effect of adding dietary components to in vitro models of the colon and how this changes the abundance of different bacteria at this location.[53] Stable isotopes also have been used to show how different dietary components can be used by different bacteria in the gut, which may be of great benefit in dietary research.[54] Including laboratory-based studies that complement clinical studies will maximize the knowledge gained from each individual study because this may explain the clinical findings.

The RDN's role in collaborations investigating the microbiome will be to design dietary interventions, provide the dietary education to patients, ensure food composition data are available for the nutrient of interest, and measure dietary intake and adherence to the interventions. This reinforces the need for continued technological development in dietary assessment methods to improve accuracy while reducing participant burden.[55] RDNs will be required to select and develop appropriate tools for nutrition assessment to calculate the nutrient(s) of greatest interest.

Advances in the understanding of the microbiome offer the opportunity for enhancing our clinical dietetic intervention by incorporating data from the microbiome. RDNs need to gain some understanding of the metabolic potential of the microbiome so they can incorporate this into their clinical practice.

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STATEMENT OF POTENTIAL CONFLICT OF INTEREST

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