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THE ROLE OF THE GUT MICROBIOTA IN NUTRITION AND HEALTH

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Abstract:

The microbiome refers to the collective genomes of microorganisms in a particular environment, and the microbiota is the community of microorganisms themselves. Approximately 100 trillion microorganisms (most of them bacteria, but also viruses, fungi, and protozoa) exist in the human gastrointestinal tract-the microbiome is now best viewed as a virtual body organ. The human genome consists of approximately 23,000 genes, while the microbiome encodes more than three million genes, producing thousands of metabolites that replace many host functions and therefore affect host fitness, phenotype and health.

Keywords: Gut microbiota, antibiotics and pesticides

INTRODUCTION:

Twin studies have shown that although the gut microbiota have an heritable component, environmental factors related to diet, medications, and anthropometrics are more important determinants of microbiota composition. Intestinal microbes play a key role in many aspects of human health, including immune, metabolic, and neurobehavioral traits (Figure 1). Evidence at various levels supports the role of the gut microbiota in human health from animal models and human studies. Animal models can help identify gut microbes and mechanisms, although the extent to which the results apply to humans is unknown.In humans, observational studies can show cross-references between microbes and health traits, but they are limited by the inability to measure causal relationships. The strongest level of evidence comes from interventional clinical trials, particularly randomized controlled trials. The composition of the gut microbiota is usually quantified using DNA-based methods, such as next-generation 16S ribosomal RNA gene sequencing or whole genome shotgun sequencing, which also allow inferences about microbiota function. Metabolic products of the microbiota can now be measured in feces and serum using metabolic methods. The gut microbiota provide the necessary opportunities for fermentation of non-digestible substrates such as dietary fiber and endogenous intestinal mucus. This fermentation supports the growth of specialized microbes that produce short chain fatty acids (SCFAs) and gases. The main SCFAs produced are acetate, propionate, and butyrate

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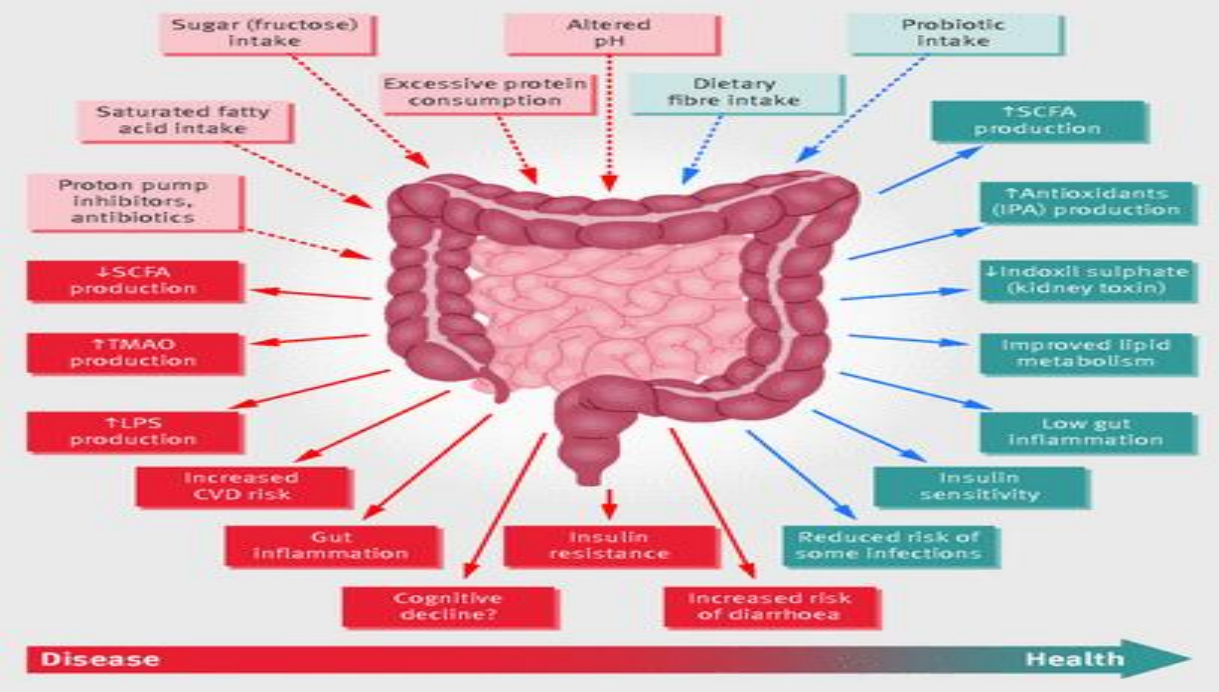

Figure 1: Schematic representation of the role of the gut microbiota in health and disease with some examples of inputs and outputs. CHD = cardiovascular disease; IPA=indolpropionic acid; LPS = lipopolysaccharide;SCFA = short chain fatty acids; TMAO = N-oxide trimethylamine

Butyrate is a major source of energy for human colonocytes and can induce colon cancer cell apoptosis and activate gluconeogenesis in the intestine, having beneficial effects on glucose and energy homeostasis. Butyrate is necessary for epithelial cells to consume large amounts of oxygen through β-oxidation, creating a state of hypoxia that maintains oxygen balance in the intestine, preventing dysbiosis of the intestinal microbiota. Propionate is transported to the liver, where it regulates gluconeogenesis and satiety signaling through interactions with fatty acid receptors in the gut . metabolism and lipogenesis and may play a role in central appetite regulation. Randomized controlled trials have shown that higher production of SCFAs correlates with lower diet-induced obesity and with reduced insulin resistance. Butyrate and propionate, but not acetate, appear to control gut hormones and reduce appetite and food intake in mice. Intestinal microbial enzymes are involved in bile acid metabolism, generating unconjugated and secondary bile acids, which act as signaling molecules and metabolic regulators affecting important host pathways. Other specific products of the gut microbiota directly affect human health. Examples include trimethylamine and indolpropionic acid. Production of trimethylamine from dietary phosphatidylcholine and carnitine (from meat and dairy products) depends on the gut microbiota, and therefore its amount in the blood varies from person to person. Trimethylamine is oxidized in the liver to N-oxide trimethylamine, which is positively associated with an increased risk of atherosclerosis and serious adverse cardiovascular events. Indolpropionic acid is closely related to dietary fiber intake and has potent in vitro radical scavenging activity, which appears to reduce the risk of type 2 diabetes.

GUT MICROBIOTA AND OBESITY

The gut microbiota appears to play a role in the development and progression of obesity. Most studies of overweight and obese people show less diversity in dysbiosis. 31-39 Germ-free mice that receive fecal microbes from obese people gain more weight than mice that receive microbes from healthy weight people. A large study of twins in the United Kingdom showed that the genus Christensenella was rarely found in overweight people and prevented weight gain when injected into sterile mice. This microbe and others, such as Akkermansia, correlate with lower visceral fat deposits. Although much of the supporting evidence comes from mouse models, long-term weight gain (more than 10 years) in humans correlates with

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low microbiota diversity, and this relationship is exacerbated by low dietary fiber intake.
Dysbiosis of the gut microbiota likely contributes to diet-induced obesity and metabolic complications through various mechanisms, including immune dysregulation, altered energy regulation, altered gut hormone regulation, and proinflammatory mechanisms (such as lipopolysaccharide endotoxins that cross the gut barrier and enter the portal circulation

MICROBIOTA DIVERSITY AND HEALTH

People with inflammatory bowel disease psoriatic arthritis, type 1 diabetes, atopic eczema, gluten disease, obesity, type 2 diabetes, and arterial stiffness had lower bacterial diversity than healthy individuals. Smokers with Crohn's disease had even lower gut microbiome diversity. The association between reduced diversity and disease indicates that a species-rich gut ecosystem is more resilient to environmental influences, since functionally related microbes in an intact ecosystem can compensate for the functions of other missing species. Hence, diversity in general is a good indicator of a "healthy gut." But recent intervention studies show that a significant increase in dietary fiber can temporarily reduce diversity as microbes that digest fiber become enriched, resulting in altered composition and, as a result of competitive interactions, decreased diversity. The functional role of the intestinal microbiome in humans has been demonstrated with fecal microbiota transplantation. This procedure is effective in cases of severe drug-resistant Clostridium difficile infection and is now routinely used for this purpose worldwide. For other pathologies, fecal transplants are not yet a clinical practice but have been investigated. For example, transplantation of feces from a lean healthy donor (allogeneic) to recipients with metabolic syndrome resulted in better insulin sensitivity, which was accompanied by a change in microbiota composition than with autologous feces.

EFFECTS OF FOOD AND MEDICATIONS ON THE GUT MICROBIOTA

Specific foods and diets can affect the abundance of different types of bacteria in the gut, which, in turn, can affect health .High-intensity sweeteners are commonly used as sugar substitutes because they are many times sweeter than sugar with minimal calories. Although regulators have "generally recognized them as safe," some animal studies have shown that these sugar substitutes can have negative effects on the gut microbiota. Sucralose, aspartame and saccharin have been shown to disrupt the balance and diversity of the gut microbiota. Rats that received sucralose for 12 weeks had significantly higher proportions of Bacteroides , Clostridia and total aerobic bacteria in the gut and significantly higher fecal pH than rats that did not receive sucralose. 47 Mice treated with sucralose for six months showed increased gut expression of bacterial proinflammatory genes and impaired fecal metabolites.

Food additives such as emulsifiers, which are ubiquitous in processed foods, have also been shown to affect the gut microbiota of animals. Mice fed relatively low concentrations of two commonly used emulsifiers, carboxymethylcellulose and polysorbate-80, showed reduced microbial diversity compared with mice not fed emulsifiers. Bacteroidales and Verrucomicrobia were reduced, and mucus-associated proteobacteria contributed to inflammation. Other areas of concern include the side effects of popular restrictive diets on gut health. These include some strict vegan diets, raw or "clean eating" diets, gluten-free diets and low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) diets used to treat irritable bowel syndrome. Some consider vegans to be healthier than omnivores. A study of 15 vegans and 16 omnivores found striking differences in serum metabolites produced by gut microbes, but very modest differences in gut bacteria communities. A controlled experiment of feeding 10 omnivores randomized to receive either a high-fat, low-fiber diet or a low-fat, high-fiber diet for 10 days found very modest effects on gut microbiome composition and no differences in short-chain fatty acid production. Together, these data support a greater role for dietary effects on bacterial derived metabolome than just the short-term bacterial community. Animal and in vitro studies show that gluten-free bread reduces the microbiota dysbiosis seen in people with gluten sensitivity or gluten disease. But most people who avoid gluten do not have gluten disease or a proven intolerance, and a recent large observational study showed an increased risk of heart disease in gluten avoiders, possibly due to reduced consumption of whole grains. One study showed that 21 healthy people had significantly different gut microbiota profiles after four weeks of a gluten-free diet. Most people showed lower numbers of several key beneficial microbial species. In six randomized controlled trials, a diet low in FODMAP was shown to reduce symptoms of irritable bowel syndrome. This is associated with a reduced proportion of Bifidobacterium in patients with irritable bowel syndrome, and the response to this diet can be predicted by bacterial profiles in the feces. Diets low in

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FODMAP lead to profound changes in the microbiota and metabolome, the duration and clinical significance of which are still unknown. In addition to diet, medications are a key modulator of gut microbiota composition. A large Dutch-Belgian population-based study showed that medications (including osmotic laxatives, progesterone, TNF-α inhibitors and rupatadine) have the greatest explanatory power with respect to microbiota composition (10% variation in the community). Other studies have shown serious effects of commonly prescribed proton pump inhibitors on the microbial community, which may explain the higher rates of gastrointestinal infections in people taking these drugs. Antibiotics clearly affect gut microbes, and cattle are usually given low doses to increase their growth and weight. Most antibiotics in many countries are used in agriculture, especially in intensive poultry and beef production. Several observational studies in humans, as well as many studies in rodents, have indicated obesity in humans even in the tiny doses found in foods. But people have very different reactions to antibiotics, and interventional studies have not shown consistent metabolic effects. Pesticides and other chemicals are commonly sprayed on food, but while levels may be high, there is currently no conclusive evidence of their harm to gut health and exposure to organic foods. There is insufficient clinical data to draw clear conclusions or recommendations for particular food preferences based on gut microbiota. But future research on dietary supplements, medications, and the safety and efficacy of dietary modifications should take these advances and their effects on the gut microbiota into account. This is becoming evident in cancer patients receiving immunochemotherapy, bone marrow recipients and autoimmune disease patients taking biologic drugs, in whom small changes in their microbiota can cause major changes in their response. Furthermore, animal experiments have shown that the protective effect of phytoestrogens on breast cancer depends on the presence of gut microbes (such as Clostridium saccharogumia, Eggerthella lenta, Blautia producta, and Lactonifactor longoviformis) that can convert isoflavones into bioactive compounds.

MANAGING THE GUT MICROBIOTA THROUGH DIET

Changes in the gut microbiota can occur within days of a dietary change; notable differences were found after African Americans and rural Africans changed their diets for just two weeks. An increase in known butyrate-producing bacteria in African Americans consuming a rural African diet resulted in a 2.5-fold increase in butyrate production and a decrease in secondary bile acid synthesis. Another study comparing extreme shifts between plant-based and animal-based diets showed these changes after just five days. But healthy microbiota are resistant to temporary changes in dietary interventions, meaning that homeostatic responses restore the original community composition, as recently shown in the case of bread.

PREBIOTIC FOODS AND DIETARY FIBER

Most national authorities define dietary fiber as edible carbohydrate polymers with three or more monomeric units that are resistant to endogenous digestive enzymes and thus are not hydrolyzed or absorbed in the small intestine. Some sources of dietary fiber are fermentable, which means that they serve as a substrate for microbial growth in the distal intestine. Some non-digestible carbohydrates are called "prebiotics," which are defined as food components or ingredients that are not digested by the human body but specifically or selectively feed beneficial colon microorganisms. The prebiotic concept has been criticized for being poorly defined and overly narrow, and some scientists prefer the term "microbiota accessible carbohydrates," which are essentially equivalent to fermentable dietary fiber in the sense that they become available as substrates for growth of gut microbes that have the necessary enzymatic capacity to use them. Consumption of resistant starches has been shown to enrich certain groups of bacteria (Bifidobacterium teenis, Ruminococcus bromii and Eubacterium rectale) in some people. Enriched taxa vary in the type of resistant starches and other dietary fiber, indicating that shifts depend on the chemical structure of carbohydrates and the enzymatic ability of microbes to access them. Microbes must also "stick" to the substrate and withstand conditions resulting from fermentation (e.g., low pH). The effect of carbohydrates available to the microbiota on the composition of the gastrointestinal tract microbiome can be significant, with certain species being enriched and making up more than 30% of the fecal microbiota. Thus, carbohydrates available to the microbiota provide a potential strategy for improving beneficial members of the minority microbiome. These changes last only as long as carbohydrates are consumed and are highly individualized, providing the basis for personalized approaches. Many short-term trials of feeding purified dietary fiber or even whole plant-based diets either do not affect or reduce microbiota diversity, but may still have clinical benefits, possibly due to metabolites such as small-chain fatty acids.

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Low fiber intake reduces the production of low-chain fatty acids and shifts gastrointestinal tract microbiota metabolism toward the use of less beneficial nutrients, resulting in the production of potentially harmful metabolites. Convincing evidence shows that a Western diet low in fiber destroys the mucosal barrier of the colon, causing microbiota to invade, leading to pathogen susceptibility and inflammation providing a potential mechanism to link Western diets to chronic disease. Two recent studies have shown that the deleterious effects of a high-fat diet on mucosal permeability and metabolic function can be prevented by dietary administration of inulin. Overall, these results, along with the role of butyrate in preventing oxygen-induced dysbiosis of the intestinal microbiota, make a strong case for enriching dietary fiber intake to maintain intact mucosal barrier function in the gut. Significant observational data show that fiber intake is beneficial for human health. Two recent meta-analyses found a clear association between dietary fiber and health benefits in a wide range of pathologies, and a recent interventional study showed that dietary fiber significantly reduced insulin resistance in patients with type 2 diabetes with a clear association with shifts in microbiota and beneficial metabolites (such as butyrate).

PROBIOTIC PRODUCTS

Probiotics are living microorganisms that, when administered in adequate amounts, benefit the health of the host). Probiotics (mainly Bifidobacterium and Lactobacillus species) can be included in a variety of products, including foods, supplements or drugs. There are concerns that most microbial supplements cannot take root in the gut and have no effect on the local population. But probiotics can affect health independently of the gut microbiota through direct effects on the host; for example, through immunomodulation or production of bioactive compounds. The therapeutic effects of probiotic supplements have been studied in a wide range of diseases.

We searched the Cochrane Library of Systematic Reviews for "probiotic*," obtaining 39 studies, and we searched Medline for "systematic review" or "meta-analysis" and "probiotic*," obtaining 31 studies. We included information on systematic reviews of randomized controlled trials published in the past five years in which probiotics (rather than supplements in general) were the primary treatment. Only studies that focused on comparing probiotics to a control group that contained at least a few randomized controlled trials of moderate or high quality as assessed by the authors of the systematic review, resulting in a total of 22 systematic reviews. An analysis of 313 trials and 46,826 participants showed substantial evidence of positive effects of probiotic supplements on the prevention of diarrhea, necrotizing enterocolitis, acute upper respiratory tract infections, pulmonary exacerbations in children with cystic fibrosis, and eczema in children. Probiotics also improve cardiometabolic parameters and reduce serum C-reactive protein concentrations in type 2 diabetic patients. It is important to note that the studies were not homogeneous and did not necessarily match the type or dose of probiotic supplements or the duration of the intervention, which limits accurate recommendations. Emerging areas of probiotic treatment include the use of novel microbes and their combinations, combining probiotics and prebiotics (synbiotics), and personalized approaches based on candidate microbial profiles for inflammation, cancer, lipid metabolism or obesity. For example, stable engraftment of the probiotic Bifidobacterium longum has been shown to depend on individual characteristics of the gut microbiota, providing a rationale for personalizing probiotic use. Personalized nutrition and future directions

Given the differences in gut microbiota from person to person, a person's optimal diet may need to be adapted to their gut microbiota. Zeevi et al. obtained a multivariate microbiota profile of 900 people and tracked food intake, continuous blood glucose levels, and physical activity for one week. Researchers developed a machine-learning algorithm to predict personalized glucose response after meals based on clinical and gut microbiome data and showed that it provided significantly better predictions than approaches such as carbohydrate counting or glycemic index assessment. In a follow-up double-blind, randomized crossover study involving 26 participants, personalized dietary interventions based on the algorithm successfully normalized blood glucose levels. A bread response study using a randomized crossover study of one-week dietary interventions showed significant interindividual variability in glycemic response to different types of bread. The type of bread that caused a lower glycemic response in each individual could be predicted solely from microbiome data collected before the intervention. Much more research is needed to establish whether such personalized approaches are feasible, sustainable, and have a positive impact on clinical outcomes.

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CONCLUSIONS:

We are entering an era where we can increasingly modify health with food and measure effects with our microbes or metabolites. Fiber is a key nutrient for a healthy microbiome, and it has been overlooked while the sugar and fat debate rages on. The adverse effects on the microbiome of drugs and processed food ingredients can no longer be ignored. Given the current gaps in knowledge, we need clinical data that can be translated into clinical practice, ideally through randomized controlled trials using matrices of prebiotics or probiotics or fecal microbiota transplantation to assess changes in gut microbiota composition and health outcomes.

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