REVIEW ARTICLE

Gut Microbiota and Extraintestinal Disorders: Are They Interrelated?

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Abstract

Normally in health, the commensal gut microbiota lives in a perfectly symbiotic relationship with the host. Initial bacterial colonization occurs through the maternal vaginal/fecal flora and oral feeding. When this symbiotic relationship is lost due to several factors, the condition is known as "dysbiosis." Dysbiosis is associated with the pathogenesis of intestinal disorders, such as inflammatory bowel disease, irritable bowel syndrome (IBS), and coeliac disease, but recent studies have shown that it has also been implicated in extraintestinal disorders, such as allergy, asthma, cardiovascular disease, obesity, autoimmune diseases, inflammatory diseases, and some mental disorders and cancers. The proposed mechanism for the development of such disorders is disruption of the pivotal mutual relationship between the gut microbiome, the metabolic products produced by them, and the host immune response. In this review article, we would like to highlight the role of gut microbiota in the development of extraintestinal diseases.

Keywords: Dysbiosis, Extraintestinal diseases, Gut microbiota, Irritable bowel syndrome.

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Introduction

The "*Charaka Samhita*," the ancient Indian book on traditional medicine, described human being as the microplastic replica of the universe and three humors (*Bayu*, *Pitta*, and *Kapha*, i.e., gas, bile, and mucus) responsible for most of the illnesses. Most of the diseases have their origin from the gut—this concept was described by the father of modern medicine, Hippocrates, more than 2000 years back.[1] Though Hippocrates was not fully correct in suggesting the origin of all disease from the gut, recent evidence has shown that alteration in the homeostasis of the gastrointestinal tract is directly or indirectly related to many extraintestinal diseases. The current concepts on the molecular basis of gut microbiota have explored an important association of them with the pathogenesis of many chronic diseases.[2] The gut microbiota plays a pivotal role in human health and disease. Recent researches have revealed that the resident microbiota may influence the physiology, immune system development, and host metabolism, while perturbation of this community can result in chronic gastrointestinal and extraintestinal diseases.[3]

Overview and Composition of Gut Microbiota

Characterization of the composition of gut microbiota in healthy individuals is very important for understanding the role of the microbiome in health and disease.[4] The gut microbiota comprises trillions of microbes (including more than 1000 species of bacteria); through their host interactions and collective metabolic activities, they maintain normal physiology inside the gut. Proper knowledge about the functional and compositional change is necessary to plan therapies that target the microbiome. *Firmicutes* and *Bacteroidetes*, being the dominant phyla, make up around 90% of gut microbiota. There is a large variation in the composition of microbiota during disease and early development, and even in health also, temporal fluctuation and interpersonal variation are consistent.[5]

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Colonization of the gastrointestinal tract in humans begins immediately after birth. Initial bacterial colonization occurs through the maternal vaginal/fecal flora and oral feeding.[6] Breastfed infants have predominant population of *Bifidobacterium*, which makes up more than 90% of the commensal population, while in artificially fed infants, the microbiota composition is more diverse—predominantly composed of *Bacteroides* and clostridial species.[7] There is also a significant variation in the composition between the babies born through normal vaginal delivery and those delivered by cesarean section. With the start of solids, the population starts to shift toward the adult type of intestinal microbiome predominantly composed of *Bacteroides* and *Firmicutes*. Bifidobacteria are the main component of intestinal microbiome in adults. Urbanization and adaptation to Western habits have been seen to be related to the increase in the gram-negative bacteria among the microbiome.[8]

The possible causes responsible for the alteration in the composition of intestinal microbiome in the recent decade are as follows:

- Adherence to good hygiene practices
- More access to safe water supply
- Injudicious use of antibiotics in the newborns
- Increase in birth through cesarean sections

- Increased tendency toward formula feeding instead of breastfeeding
- Frequent uses of antiseptic solutions and antibacterial soap

Gut Microbiota in Health—Symbiosis

In a healthy environment, there exists a mutualistic interplay between the human gut and microbiome. Microorganisms inside the intestine predominantly act via enzymatic pathways, which help in the digestion of proteins and carbohydrates.[9] They also provide branched-chain amino acids (BCAA), such as glycine, valine, isoleucine, and leucine, which are absolutely necessary for the synthesis of glutathione, the main cellular antioxidant absolutely needed for various physiological functions. In anaerobic conditions, the genus *Bacteroides*, *Clostridiaceae*, and *Lactobacillaceae*, especially *Serratia* and *Citrobacter*, generate short-chain fatty acids.[10] These are fatty acids that can penetrate the blood–brain barrier (BBB) with the help of monocarboxylate transporters, and they are responsible for many biological functions in the host.

Intestinal microbiome also generates important metabolites adequately, such as vitamin B complex, vitamin A, and folic acid, which help in the regulation of various important physiological and biochemical pathways. Finally, they inhibit the growth of their competitors (pathogenic bacteria) by different mechanisms, which may be considered as a biological strategy to maintain the favorable concentration of beneficial bacterial flora.[11]

Dysbiosis and Disease

The term dysbiosis is used to describe a microbiota community in a diseased state which is different from that of a healthy control state. It is not always clear whether dysbiosis and disease have a direct causal relationship, an association, or a mere coexistence; moreover, diseased state itself leads to changes in the microbiota community through various mechanisms. Dysbiosis is seen to be linked to a myriad of gastrointestinal diseases; in addition, they are also seen to be related to many extraintestinal diseases.

The proposed mechanisms of dysbiosis associated with different diseases mainly include different genetic and environmental alterations; immune imbalance leading to an increase in the production of pro-inflammatory cytokines and a reduction in anti-inflammatory cytokines; chronic inflammatory process resulting in translocation of pathogens; and finally, increased permeability of the intestine.

Microbiota and Gut–Brain Axis

The gut–brain axis (GBA) comprises a two-directional relationship between the enteric nervous system (ENS) and the central nervous system (CNS), thereby acting as a link between the peripheral intestinal functions and brain.[12] This interplay between microbiota and GBA is bidirectional, which means signals from the microbiome to brain and vice versa by means of different neuroendocrine, humoral, and immune-mediated mechanisms. There are four main signaling pathways in GBA: neural pathways through the vagus nerve; enteroendocrine signaling through peptide YY, neuropeptide Y, glucagon-like peptides 1 and 2, and substance P; serotonin and tryptophan pathways; and immune signaling through the gut-associated lymphoid tissue (GALT). Both experimental and clinical evidences suggest that gut microbiota has a major influence on GBA; they act on the intestinal cells and ENS as a local circuit, but also in direct connection with the CNS through different biochemical and neurohormonal links.[13]

Major alteration in gut population of *Acinetobacter* and *Bacteroides* is seen in patients with depression. Dysbiosis may result in hypothalamic–pituitary–adrenal (HPA) axis abnormalities causing an increase in corticotropin-releasing hormone, leading to IBS. Altered GBA may cause low-grade inflammation in the gut, causing altered motility and sensation. Increased levels of *Ruminococcus* and *Bacteroides* along with a decrease in *Firmicutes* are seen to be associated with autism. There is definite evidence of dysbiosis of intestinal microbiome in functional gastrointestinal disorders (FGID) that are thought to be associated with a dysfunction of the GBA. Irritable bowel syndrome, the prototype disorder in the spectrum of FGID, is seen in more frequency among the patients of mood disorders.

Recent evidences have revealed that the influence of CNS on microbiota composition is most likely mediated by an alteration of the normal luminal/mucosal habitat which can also be restored by the use of probiotics. In clinical practice, a very important example of this interaction is FGID, particularly IBS, which is now considered to be a microbiome–GBA disorder.[14]

Gut–Liver Axis and Microbiota

Gut–liver axis (GLA) is the two-directional communication between the gastrointestinal tract and liver. Intestinal epithelium only allows entry of some useful substrates, while it protects the host by preventing the entry of harmful pathogenic bacterial products.[15] Intestinal microbiome has a major role in maintaining the homeostasis of the GLA. Dysbiotic pattern has been seen to be associated with increased permeability of the barrier ("leaky gut"), which results in increased percolation of the bacterial products that reach the liver through the enterohepatic circulation.[16]

Nonalcoholic fatty liver disease (NAFLD) can be defined as a spectrum of diseases that range from fatty liver or hepatic steatosis to nonalcoholic steatohepatitis (NASH), which is characterized by inflammatory changes in the hepatocytes with or without fibrosis. If the process continues, it may lead to cirrhosis of the liver. Along with NAFLD, dysbiosis is also seen to be associated with primary biliary cholangitis, primary sclerosing cholangitis, alcoholic liver disease, cirrhosis of the liver, and hepatocellular carcinoma.

Microbiota and Immune-mediated Diseases

A healthy immune system requires the maintenance of homeostasis between the pro- and anti-inflammatory mechanisms. This equilibrium is very crucial at intestinal mucosal surfaces, where the immunological balance is primarily determined by the microbiota. Immunological imbalance due to altered composition of microbiota may arise when the immune system interacts inappropriately with the microbiota.[17] The commensal microbiota influence the innate immune system by producing pathogen-associated molecular patterns (PAMPs) and metabolic by-products, thereby regulating immune homeostasis inside the gut. Gut microbiota also leads to stimulation of the adaptive immune system in addition to the innate one, resulting in the production of secretory IgA, induction of regulatory T cells (Tregs), and more differentiation toward Th17 population. The composition of gut

microbiota can influence the systemic inflammatory responses (both innate and adaptive) that mediate different diseases, such as inflammatory bowel disease, asthma, allergy, diseases related to obesity, and neurodevelopmental or neurodegenerative medical conditions.[18]

Experimental researches in mouse models and emerging clinical studies have shown that therapeutic manipulation of the microbiome, by using probiotics, engineered probiotics, or fecal microbiota transplantation (FMT), may be a promising preventive or therapeutic approach for allergy and autoimmune diseases, and this may also enhance the efficacy of a few cancer immunotherapeutics.

Dysbiosis—Metabolic Syndrome and Diabetes

There is a significant difference in the composition of intestinal microbiome of lean and obese persons. They have a major role in the process of storage and expenditure of energy, which, in turn, determines nutrition and metabolic balance of the body.[19]

There is definite evidence for the effects of gut microbiota on the glucose metabolism in animal models. *Bifidobacterium* is seen to be potentially protective against type 2 diabetes in most of the literature. There are multiple proposed molecular mechanisms of gut microbiota contribution to type 2 diabetes mellitus (T2DM) and metabolic diseases, such as modulation of inflammation by inhibition of pro-inflammatory cytokines and chemokines along with activation of anti-inflammatory cytokines; favorable effects on glucose and lipid metabolism and insulin sensitivity; interaction with dietary constituents; modulation of gut permeability; and control of overall energy homeostasis in the host.[20]

Dysbiosis: Gut–Lung Axis and Atopic Diseases

In recent years, there is a significant increase in allergic disorders, such as eczema, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, and bronchial asthma. Impaired immune system with Th1/Th2 switch has been seen to be associated with dysbiosis. Reduced proportions of bifidobacteria and lactobacilli along with increased proportions of *Staphylococcus aureus* and coliforms are seen in atopic individuals. Several meta-analyses have shown that the use of probiotics has been seen to improve the symptoms of atopic dermatitis.[21]

The two-directional relationship between the gastrointestinal system and the lung is known as Gut–Lung Axis.[22] A decrease in the population of bifidobacteria and a disproportionate increase in clostridia in the gut are seen to be directly related to asthma in childhood and early adolescence.

Conclusion

Though the association between dysbiosis and extraintestinal diseases has been proven in many animal studies, the definite evidence of such association is lacking in humans. Probiotics and FMT are two definite measures that have been proven to cure *Clostridium difficile* infection and also have a promising result in different immune-mediated disorders of the gastrointestinal system, such as inflammatory bowel disease. A randomized controlled trial (RCT) conducted on the benefits of FMT in patients with metabolic syndrome by inoculating organisms from healthy lean individuals revealed that the arm that received FMT from the lean donor group had more insulin sensitivity and more population of butyrate-producing commensals. There are also a few reports showing beneficial effects of FMT on chronic diseases, such as idiopathic thrombocytopenic purpura (ITP), multiple sclerosis, dystonic disorders, myoclonus, chronic fatigue syndrome, and idiopathic Parkinson's disease. However, large studies are needed to explore this aspect.

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