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GUT MICROBIOTA IN HEALTH AND DISEASE

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ABSTRACT

Human body is home to 100 trillion microbes, that constitutes bacteria, fungi, archae, viruses, and eukaryotes which play an essential role in maintenance of health and have been found to be associated with various pathological processes. The human gut microbiome and its role in health and disease has been a subject of extensive research. The gut microbiota has a role to play in the normal biological, physiological, nutritional and immune processes and an imbalance in them has been linked to several diseases such as atopy, irritable bowel syndrome, inflammatory bowel disease, type 1 Diabetes mellitus, infectious diseases, gastrointestinal cancers, liver diseases,respiratory diseases as well as certain neurological, psychological and autoimmune diseases. A lot of research and advances are on going in the field of microbial DNA sequencing, metabonomics and proteomics in order to understand the implications of host-microbiome interaction and thereby pave the way for the possible targeted therapy in diseases where the microbiota has been found to play a pivotal role.

KEYWORDS: *Microbiome, Human Gut, Dysbiosis, Probiotic.*

INTRODUCTION

The human microbiota constitutes around 10^{14} cells which colonizes virtually every surface of the human body that comes in contact with the external environment. Microbes flourish on our skin, in the genitourinary, gastrointestinal, and respiratory tracts.[1,2] The gastrointestinal tract (GIT); is most heavily colonized and the colon alone is estimated to harbour over 70% of all the microbes in the human body. The gastro-intestinal tract is preferred for colonization owing to its large surface area and being an extremely nutrient rich source for the microbes.

The gut microbiome is the collective genetic material of all the microbes, e.g. bacteria, fungi, protozoa and viruses which reside in a particular environment eg. the digestive tracts of humans. The human gut microbiome has co-evolved with its host and, therefore, has been extensively involved with a variety of essential activities in the host such as digestion and nutrition[3,4], detoxification and body defense[5], maturation of the host immune system and disease mediation[6] and thereby are involved in the pathogenesis in various disease conditions.

Role of microbiota in health

The gut microbiota helps in fermentation of nondigestible substrates like dietary fibres and endogenous intestinal mucus to produce short chain fatty acids (SCFAs).[7] The important SCF As produced are acetate, propionate and butyrate. Butyrate has beneficial effects on glucose metabolism and homeostasis. It is the main energy source for human colonocytes. It has also been found to induce apoptosis of colon cancer cells, and activate intestinal gluconeogenesis.[8] Butyrate prevents dysbiosis of the gut by stimulating the epithelial cells to consume large amounts of oxygen through β oxidation thereby creating a state of hypoxia that maintains oxygen balance in the gut.[9]

The other SCFAs also play an important role in maintaining metabolism. Propionate helps to regulate gluconeogenesis and modulates satiety by interacting with fatty acid receptors. The most abundant SCFA, Acetate, besides being an essential metabolite for the growth of other bacteria— also plays a role in central appetite regulation by its action on cholesterol metabolism and lipogenesis. Higher production of certain SCFAs such as acetate, propionate thereby correlates with lowering of diet induced obesity and reduces insulin resistance.[10]

Gut microbial enzymes contribute to metabolism of bile acids generating unconjugated and secondary bile acids that act as signalling molecules and metabolic regulators that influence important host pathways.[11] The gut microbiota is influenced by diet. The inclusion of meat and dairy products in diet causes presence of dietary phosphatidylcholine and carnitine which increases production of trimethylamine which is oxidized in the

liver to trimethylamine N-oxide. This has been found to be positively associated with increased risk of atherosclerosis and cardiovascular events.[12] On the contrary increased dietary fibre increases the level of Indolepropionic acid which has been found to have potent radical scavenging activity in vitro, which seems to reduce the risk of incidence of type2 diabetes.[13,14]

The microbiota also provides a physical barrier protecting the host from foreign pathogens. It helps in development of the intestinal mucosa and immune protection of the host.

Role of microbiota in disease

Various individual and cohort studies have established an association between the human intestinal microbiota and various diseases.

The Gut–Brain Axis. The gut microbiota is related to brain function as it integrates neural, hormonal, and immunological signaling between the gut and the brain, offering the intestinal microbiota and its metabolites a potential route through which to access the brain.[15] This axis is bidirectional, whereby the brain commands functions of the GIT, such as peristalsis and mucin production, and immune functions. Foster and McVey Neufeld[16] found that stress influences the composition of the gut microbiota and inversely bidirectional communication between the gut microbiota and the central nervous system influences a host's stress reactivity. Stress also influence the integrity of the gut epithelium and alter peristalsis, secretions, and mucin production, thereby altering the gut environment that induce changes in microbial composition and/or metabolism.

The Gut- Liver Axis. There is a close interaction of the GIT and the liver, since the liver is chronically exposed to gut-derived microbiota including bacteria and its components-- the "gut-liver axis".[17] Gut microbiota is also responsible for altering the liver metabolism by production of ethanol, ammonia, and acetaldehyde.

This microbial dysbiosis, alteration of gut-brain and gut-liver axis is responsible for various disorders.

The following are a few such studied associations due to the dysbiosis.

a) Infections

Infection is one of the most common cndition associated with dysbiosis. Both the infectious disease and its treatment has an impact on the microbiota which in turn affects the outcome of the infection in the host. The invasion of the intestinal mucosa by the pathogens induces a strong inflammatory response that causes translocation of the gut bacteria. The dysbiosis and altered host gut microbiota has been implicated in clostridium difficile infection, progression of HIV, Hepatitis B infection (HBV) etc.

C difficile infection is associated with antibiotic use. Antibiotics disturb the homeostasis of the intestinal mucosa, thereby decreasing the resistance against toxin-producing *C. difficile* thus promoting its progression. Antibiotic treatment have been found to be associated with decrease in putative butyrate-producing anaerobic gut bacteria and an increase in endotoxin-producing opportunistic pathogens and lactate- producing Phylotypes, irrespective of the presence of *C difficile* infection.

The use of antibiotics in neonates has a positive correlation with increased risk of intestinal intussusception, demonstrating the increased risks of pediatric gut dysbiosis.

Helicobacter pylori (*H pylori*) is associated with peptic ulcer disease. Its association has also been found recently in the progression of periodontitis. The frequencies of Porphyromonas gingivalis, Prevotella intermedia, Fusobacterium nucleatum, and Treponema denticola are significantly higher in patients infected with *H. pylori* than in those without infection, whereas the frequency of Aggregatibacteractinomycetemcomitans is lower. The results indicate that patients with *H. pylori* show significantly higher probing depth and attachment loss, and that *H. pylori* might promote the growth of some periodontal pathogens and aggravate the progress of chronic periodontitis[18]

Bacterial vaginosis has been associated with preterm birth, sexually transmitted diseases and other adverse outcomes. Ling et al. found a definite dysbiosis in healthy and diseased subjects with *H pylori*. These genera may therefore be used for the clinical diagnosis of Bacterial Vaginosis using various molecular methods.[19]

HIV infection significantly affects the microbiomes with a preferential increase in Firmicutes/Bacteroidetes ratio in patients infected with HIV-1. The altered fecal microbiota in HIV patients have been found to persist inspite of treatment. A vaginal bacteria, Prevotellabivia has been identified as causing inflammation. Cohen, recently found a bacterium GArdnerella in the vaginal microbiome in patients suffering from HIV, associated with high infecton rates in South African women. Gardnerella "gobbles up" tenofovir, thus rapidly decreasing the levels of the drug and leading to tenofovir treatment failure[20]

Viral infections of the gut, such as Rota virus infection is a worldwide cause of diarrhea in children. Gut microbiota is altered after infection with Rotavirus, mainly affecting the Bacteroides species. Probiotic treatment was found to be effective in rotavirus diarrhea, demonstrating that a healthy gut microbial community provides the host with protection against rotavirus infections.[21]

b) Irritable bowel syndrome

Irritable bowel syndrome (IBS) mainly compromises of abdominal pain and altered bowel habit, which may either be diarrhea predominant, mixed or constipation predominant.

The pathogenesis is multifactorial with genetic factors, motor dysfunction of the GIT, visceral hypersensitivity, infection, inflammation, and immunity as well as psychopathological factors playing a role in its development. Alongwith these factors gut dydbiosis leads to a low-grade intestinal inflammation facilitating adhesion of enteric pathogens to the intestinal mucosa which aggravates the IBS symptoms. There is a significant, 2-fold increase in the ratio of Firmicutes to Bacteroidetes in IBS patients.[22]

c) Hepatic Disorders

Liver disease is usually accompanied by an increase in Enterobacteriaceae and a decrease in Bifidobacterium. Bacterial translocation occurs due to endotoxemia owing to the gut dysbiosis which may further induce immune dysfunction, thus leading to progressive liver cell necrosis and liver failure.

Activation of the Kupffer cells by bacterial endotoxins and alterations in the intestinal microbiota are responsible for inducing liver damage. Gut dysbiosis has been found to be linked with complications associated with cirrhosis of liver such as spontaneous bacterial peritonitis, hepatic encephalopathy, GI bleed and renal failure.[23]

Patients with Acute-on-chronic liver Failure have been found to have a lower Bacteroidetes species and increase in Proteobacteria and Fusobacteria.[24]

Change in the composition of the gut microbiota and hepatic inflammation through increased permeability have been linked to autoimmune liver diseases as well as Hepatocellular carcinoma through a microenvironment of fibrosis.[25]

Nonalcoholic steatohepatitis is a part of metabolic syndrome where factors such as obesity and insulin resistance promote its development. There is an interplay of gut dysbiosis alongwith other fallouts of the metabolic syndrome such as obesity, high triglyceride, insulin resistance etc. Patients with NAFLD with significant fibrosis were found to have large amounts of Bacteroides and Ruminococcus and decreased levels of Prevotella.[26]

d) GI malignancies

Besides the genetic factors, recent microbial research has shown a significant role of human microbiota in oncogenesis.

H. pylori causes chronic gastritis resulting in loss of acid producing parietal cells, leading to gastric atrophy,metaplasia, dysplasia and carcinoma.[27] *H. pylori* eradication at an early stage of chronic atrophic gastritis has been found to be protective against gastric cancer.

Microbial dysbiosis has also been implicated in the etiology of colorectal adenomas and cancers. An imbalance in the microbial species has been observed in subjects with adenomas compared with normal controls.[28] Patients with adenomas were found to have a high proportion of Pseudomonas, Helicobacter, and Acinetobacter, and by a lower richness of beneficial bacteria, such as butyrate-producing bacteria.[28] Butyrate, which is produced by species within the Lachnospiraceae and Ruminococcaceae, has been shown to be protective against colonic neoplasia through a tumor- suppressing effect by inducing apoptosis, modifying gene expression, and modulating inflammatory responses and cytokine levels . A high fiber intake reportedly leads to a reduction in the risk of developing colon malignancy because of the production of butyrate.[29,30] Therefore, modulation of the gut microbiome through dietary control or antibiotic treatment may offer great therapeutic potential.

Esophageal cancer

Chronic inflammation at lower esophagus caused by chronic gastroesophagealreflux, which has been found to be associated with *H.pylori* infection and gut dysbiosis may favour development of adenocarcinoma of the esophagus.

E) Inflammatory Bowel Disease

Inflammatory Bowel Disease (IBD) have also been found to be closely associated with aberration of the gut microbiome. In some studies done in patients with ulcerative colitis, fecal transplant from healthy donors were found to have disease remission within one week and complete recovery after 4 months.[31] Firmicutes are known producers of important short chain fatty acids (SCFAs), such as acetate and butyrate, that are known to have potent anti-inflammatory properties.[32] IBD patients were found to have a diversity and dysbiosis resulting in a reduced population of the Firmicute species.

F) Metabolic disorders

Dysbiosis of the microbiota is a cause of chronic inflammatory state and leads to metabolic dysfunction by producing inflammatory mediators.

Obesity

Change in the gut microbiota was considered to be an important cause in obesity, when researchers found that metabolically obese mice, with leptin gene mutation, had a significantly different microbiota as compared to those of the non-obese mice.[33] The ratio of the species found in the microbiota also varied among the obese and lean mice indicating dysbiosis as a probable cause for obesity. The microbiota evolves along with the individual and changes in diet, host circadian clock, antibiotic use have

an impact of the microbial composition thereby affecting the metabolic state of the individual.

Type 2 Diabetes mellitus

Growing numbers of studies indicate that an altered gut microbiome characterized by lower diversity and resilience may lead to translocation from the gut to the tissues inducing inflammation and thereby causing diabetes.[34] Pedersen et al. demonstrated the prevalence of certain species such as Prevotellacopri and Bacteroides vulgates in patients having insulin resistance.[35]

The use of high fibrediet, drugs such as metformin have all found to have an impact on the gut microbiome, and have been found to be associated with reduction in the states of insulin resistance.

G) Allergy and Atopy

Several factors In early life such as mode of delivery, place of delivery, infant breast feeding, use of antibiotics early in life, have been found to affect the gut microbiota and thereby linked to the development of states of atopy, allergy as well as asthma.

H) Psychiatric disorders

The role of the gut-brain axis has already been established and as it involves the endocrine system, neural system, metabolic system, and immune system, dysbiosis in the gut affects their interaction greatly. The release of inflammatory cytokines due to the gut dysbiosis may lead to activation of the vagus nerve and spinal afferent neurons[36] Autism and Major Depressive Disorder has been found to be associated with an imbalance in microbial species. Relatively low abundance of the mucolytic bacteria, Akkermansiamuciniphila and Bifidobacterium spp. have been found in the feces of children with autism[37] and increased levels of Enterobacteriaceae and Alistipes, but reduced levels of Faecalibacteriumin patients with MDD[38]

Effect of Food and Drugs On Gut Microbiota

The gut microbiome evolves with the individual and is largely affected by the change in dietary patterns, the use of high fibre diet, the use of antibiotics etc. The use of sweeteners such as aspartame, saccharin, though low in calories, have been found to have negative effects on the gut microbiota but disrupting its diversity and may have pro-inflammatory effect.[39]

The areas of concern are the use of food additives, such as emulsifiers, restrictive diets such as vegan diet, gluten free diet, low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diets used to treat irritable bowel syndrome, all of which have been found to have an impact on the healthy gut microbiome and have been found to be associated with some levels of dysbiosis, the relevance of which is still a major aspect of research.

Over the counter use of certain drugs such as proton pump inhibitors have also found to have a substantial effect on the microbial community which could be related to much higher rates of gastrointestinal infection and hence commands restriction.[40]

Potential of the human microbiota and future possibilities

Researches have attributed many disease states to imbalances in the gut microbiota. This has paved the way for the use of healthy micriobiota transplant as a potential treatment in certain disease conditions. Khoruts et al. showed how fecal transplant from a healthy donor to a patient suffering from *C Difficile*, significantly modified the bacterial composition in the patient. After 2 weeks the microbiota of the recipient had changed dramatically from a Firmicutes&Bacteriodetes deficient configuration to a community highly similar to that of the donor, dominated by Bacteriodes spp. This dramatic shift in the composition of the microbiota was also associated with disappearance of symptoms of the patient.

The human microbiome is an essential component of immunity, providing a source of genetic diversity, which acts as a functional entity that modifies metabolism and is constantly interacting with the environment. There are various probiotics or beneficial bacteria such as Lactobacillus and Bifidobacterium that may help in preventing or treating certain diseases. Bacteria such as Faecalibacteriumprausnitzii are found beneficially in treating IBD and IBS, and Akkermansiamuciniphila for improving metabolic health.[41] Probiotics have been used in therapy, such as in treatment of *C.difficile* infection, and in liver diseases[42], in IBS, IBD, necrotizing enterocolitis, allergies and modifying metabolic diseases. They may also play a role in modifying the gut microbiota in patients undergoing cancer chemotherapy.

CONCLUSION

The gut microbiota in humans plays a pivotal role in both health and disease. It helps in providing nutrition, maintaining an ecological balance, maintains a physical barrier, generating metabolites that are essential in modulation of the immune system and metabolic health in humans. Gur dysbiosis has been linked with several infective, metabolic, immune-mediated and malignant diseases. The study and advancement in the extradition techniques have helped the use of the healthy microbiota in various conditions. Newer interventions have been used to modulate and stabilize the gut microbiota and to restore to its healthy state from dysbiotic conditions. Most of the studies on the gut microbiota has been done on the western population and dietary modifications of the western diet have been studied. However we need a more extensive study on the Asian population and the role of dietary patterns so as to understand its role in various diseases affecting our population.

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