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A review on association of Gut microbiome with irritable Bowel syndrome

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Abstract

The human microbiome is associated with several diseases. The most prominent being gastrointestinal diseases and host microbiome interactions. However the microbial mechanisms in GI disorders are not completely established. Irritable Bowel Syndrome (IBS) remains one of the prominent gastrointestinal disorders with significant changes in gut microbiome composition. IBS has a very severe impact on socio economic and patient's lifestyle. This review provides information about the emerging role of gut microbiome in the pathogenesis of IBS.

Key words : Microbiome, Inflammatory Bowel Syndrome (IBS), Gut Bacteria.

Microbiome is a word that is often exchanged with the word "microbiota". Although both terms, Microbiome and microbiota, are used, interchangeably, there is a slight difference between the two. According to the Human Microbiome Project, the microbiome is "the collective genomes of the microbes (composed of bacteria, bacteriophages, fungi, protozoa and viruses) that live inside and on the human body". The microbiome is thus the whole environment comprising the microorganisms and their "theatre of activity" (structural elements, metabolites/signal molecules, and the surrounding environmental conditions)". Whereas the microbiota only "comprises all living members forming the microbiome". This refers to the taxonomy of the microorganisms, which always live in community and comprise very diverse species.[39]

The microbial cells in the human gut is estimated to be comparable in magnitude to the number of human cells.[34] The human gut microbiome, is mainly composed of bacteria, archaea, fungi, and viruses, with bacteria being the largest constituent. These bacterial cells exist in a complex consortium of ecological

and metabolic interactions that ultimately influence the taxonomy and function of the microbial cells, as well host health. The gut microbiome of healthy individuals is believed to be mainly symbiotic and is known to play important roles in host metabolism, immunological modulation and development.[13,14] It is important to note that association of Microbial cells in human gut results in diseases including diabetes, cardiovascular disease, obesity, inflammatory bowel disease, and various cancers. However, it remains unclear whether disease onset is the consequence or cause of the microbiome disruption. Efforts to investigate the functional gene capacity and transcriptional activity of microbiomes have advanced via shotgun sequencing of extracted DNA (metagenomics) or RNA (meta transcriptomics/RNA Sequence), respectively.[31] These advances in technologies have not only facilitated analysis of the composition and function of human-associated microbiomes, but they also revealed a diverse array of microbial-derived products that facilitate interspecies interactions in the human cell/body.

Furthermore, what constitutes a healthy gut microbiome is still under investigation due to the overwhelming number of bacterial species found in the gut, and the large variation in human populations and individuals. These issues are of great importance as one of the ultimate goals of microbiome research is to modulate the community from a 'dysbiotic' state into a healthy 'homeostatic' one.[18] The diverse gut microbiota is basically composed of some strict anaerobes, some organisms can grow both aerobically and anaerobically, of which the aerobes include up to 100 folds. The microbiota is dominated by 2 phyla, the Bacteroidetes and the Firmicutes.[41]

The colonization of microbiota present in the human gut begins during the birth. It is believed that the intestines of the infants are sterile and consist of very low levels of microbes at the time of the birth, but the gut microbiome is quickly colonized during and after delivery. Infants who were delivered through caesarean section show reduced microbial numbers in the gut at 1 month when compared with those who were delivered vaginally, although these differences do not remain detectable at 6 months of age[19]. During the first year of life, the composition of the gut microbiota is relatively simple and shows wide interindividual variations. The initial gut microbiome helps in shaping the colonization of the adult's gut microbiome. The infant's gut microbiota undergoes several changes that can be correlated with a shift in feeding mode from breast- or formula-feeding to weaning and the introduction of solid food. The microbial succession in the Gastrointestinal Tract (GIT) is influenced by various number of external and internal and host related factors, despite of having similarities in the gut microbiota of mother and their offsprings.[19] External factors include the microbial load of the immediate environment, type of food eaten, and feeding habits, in addition to the composition of the maternal microbiota.

The Bacterial cells can be distributed unevenly along the length of the GIT. The numbers of bacteria present can vary, beginning at between 10 to 10^3 bacteria per gram of stomach and duodenal contents, increasing to between 10^4 and 10^7 bacteria per

gram in the small intestine, and rising to between 10^{11} and 10^{12} bacteria per gram in the large intestine.

The gut microbiota encodes for a substantively huge number of genes than its human host; it implies that they are responsible for undertaking a variety of metabolic functions which are usually performed by humans in only limited capacity. The gut bacteria are able to produce a variety of vitamins, synthesize all essential and nonessential amino acids, and carry out biotransformation of bile.[17] In addition, the microbiome provides the required biochemical pathways which are applied for the metabolism of nondigestible carbohydrates, which include large polysaccharides, such as resistant starches, cellulose, hemicellulose, pectin, and gums; some oligosaccharides that escape digestion; unabsorbed sugars and alcohols from the diet, and host-derived mucins. This functionality results in the recovery of energy and absorbable substrates which are used by the host and a supply of energy and nutrients for bacterial growth and proliferation. Metabolism of carbohydrates is a major source of energy in the colon.[36]

Impact of human microbiome in causing diseases :

The Gut Microbiome has a deep impact on human health. Studies on the function of microbial communities and their respective host suggest that these organisms carry out biochemical activities influencing carcinogenesis, tumour development, and response to immune therapy[20]. According to a well-studied model on factors that may contribute to dysbiosis in the gut, continuous intra-abdominal infections, antimicrobial drugs, or both may lead to an increased risk of colorectal cancer[27]. Aside from colorectal cancer, the microbiome of the intestinal tract may be associated with extraintestinal cancer such as hepatocellular carcinoma[29] through systematic dissemination of these organisms to other parts of the body.

Gut microbiome may also cause an autoimmune disease, bowel inflammatory disease, which can be a life threating condition. The metabolites by the gut microbiota does not only affect the gut but also act systemically all over the body. The production of trimethylamine N-oxide (TMAO)[21] metabolites by certain gastrointestinal organisms may be implicated in heart diseases. Damage in the epithelium of the gut and the abuse of antibiotics disrupts the microbiome, leading to an increase in facultative anaerobes and a defect in the host immune responses.

Irritable bowel syndrome :

Irritable bowel syndrome (IBS) is a functional bowel disorder which is known to occur due to the presence of recurrent episodes of abdominal pain associated with altered bowel habits. IBS is one of the most experienced gastrointestinal problems in clinical practice; the prevalence is 12% in the general population[11]. IBS has a negative impact on an affected patient's quality of life. IBS is a disorder which includes heterogeneous pathogenesis and clinical phenotype. Classically, the pathophysiology for IBS was thought to stem from abnormal brain–gut interactions, visceral hypersensitivity, altered gut motility, and psychological stressors. However, recent research evidence implicates a range of other factors

as potentially important to IBS, including alterations in gut immune activation, intestinal permeability, and gut microbiome.[11]

It is hypothesised that an imbalance in gut microbial communities, or Dysbiosis, activates the gut immune system and potential low-grade inflammation. Dramatically increased risk of developing IBS after acute gastroenteritis is also observed[38]. Study with RNA-targeted pyrosequencing and machine learning has found the role of gut microbiome with severe IBS.

Effects of sex and age on the gut microbiome:

Several studies revealed that there is not much difference in gut microbiome between the sexes however there is significant difference observed between between post and pre menopausal women. The following table summarises the communication between gender and gut microbiota.

Table-1. Effects of sex and age on the gut microbiome:

Author, year	Human/ animal	Sex/age	Specific microorganism	Result in sex difference/ effect of microbiota
Sinha *et al.*,[38]	Human	Both	*Akkermansia*, Bacteroides caccae, *Coprobacillus, Rothia mucilaginosa, Clostridium bolteae,* etc.	Females had higher a ntibiotic resistance genes
Santos-Marcos *et al.*,[33]	Human	Pre-/post-menopausal female	*Lachnospira, Roseburia, Prevotella, Parabacteroides, Bilophila*	Significant difference between pre-and post-menopausal women
Koren *et al.*,[15]	Human	Pregnant women	*Proteobacteria*, Actinobacteria	Microbiota change
Sha *et al.*,[37]	Human	Both	*Bacteroides*, Bifidobacterium, *Helicobacter, Lactobacillus, Enterococcus,* etc.	No sex difference was reported in IBD
Frank *et al.*,[10]	Human	Both	*Bacteroides*, *Proteobacteria, Fusobacteria, Actinobacteria,* Firmicutes, etc.	No sex difference was reported in IBD
Feng *et al.*,[9]	Human	Both	*Faecalibacterium prausnitzii*	Difference between male and female
Aguirre *et al.*,[1]	Human	Both	*Faecalibacterium prausnitzii*	Difference between male and female
Mueller *et al.*,[23]	Human	Both	*Eubacterium rectale, Clostridium coccoides, Bacteroides, Prevotella,* Bifidobacterium	Difference between male and female
Mahnic *et al.*,[22]	Human	Both	Fungal community	No sex difference between male and female

b. Age :

Age-related changes in the microbiota have been observed, as evidenced by a study showing that the core microbiota of elderly individuals differs from that of younger adults. Sex differences in childhood gut microbiota have not been extensively explored due to the absence of significant gonadal hormone activity during this period. However, as puberty approaches, there is a notable surge in sex steroid levels in plasma, marking a distinct difference between the sexes.[12] Elderly subjects exhibit a higher proportion of Bacteroides species and distinct abundance patterns of Clostridium groups.[5] Centenarians show a rearrangement in the Firmicutes population and an enrichment in facultative anaerobes.[30] In individuals over 70 years old, changes in gut physiological function can influence the composition of the gut microbiome.[3] Lactobacillus and Bifidobacterium remain stable throughout life.[4]

Microbiome-based treatments for IBS:

Prebiotics: Prebiotics are non-digestible food like oligosaccharides and polysaccharides that promote the growth or activity of bacteria that provide a health benefit to the host. It was observed that certain prebiotics promoted the growth of potentially beneficial bifidobacteria while inhibiting the growth of potentially harmful Bacteroides and Coliforms[7]. The benefits of prebiotics to gut health are multi-pronged. One of the synthetic prebiotics developed is lactulose, which shows an increase in gut bacteria, which in turn enhances the water retention in stools and is associated with laxative effects. Few Other prebiotics include fructo-oligosaccharides (FOS), soybean oligosaccharides, galacto-oligosaccharides (GOS), isomalto-oligosaccharides, xylo-oligosaccharides, and transgalacto-oligosaccharides (TGOS). There are many other sources of prebiotics that exist in nature including cereals, fruits and vegetables. Commensal bacteria in the colon can ferment prebiotics to produce short chain fatty acids (SCFAs) such as acetate, butyrate and propionate. The cholesterol biosynthesis and lipid production in the host can be regulated through prebiotics[8].

Probiotics: Probiotics are living microorganisms that impact gut microbial communities in a way that imparts a health benefit to the host. In the case of IBS, probiotics have been suggested to reduce visceral hypersensitivity or exert anti-inflammatory effects[40]. Probiotics have been studied in IBS patients with many effects on gut symptoms. Patients with IBS often have psychological distress like depression or anxiety.[25] Recent studies show that patients with IBS and depression share dysbiosis, altered intestinal permeability, and gut immune activation[26]. Several studies have reported beneficial effects of probiotics on psychological symptoms in healthy people around the world.[21] A recent study by Meenes *et al*.,(2018) found that a "psychobiotic" containing *Bifidobacterium longum* for 6 weeks improved depression but not anxiety or GI symptoms in patients with IBS to a greater degree than placebo[24]. Improvements in depression were associated with changes in brain activation pattern by functional magnetic resonance imaging in the "psychobiotic" group.

Antibiotics: The broad-spectrum of antibiotics were shown to negatively impact the gut microbiota by reducing diversity and potentially beneficial bacteria. On the other hand, there is evidence suggesting that non-absorbable antibiotics lead to significant improvement of symptoms in subset of patients with IBS.

Diet : It is important to understand that diet significantly impacts the composition of the gut microbiome[12,28]. For example, reduction in the intake of foods that are high in fermentable oligosaccharides, disaccharides, and monosaccharides and polyols (FODMAP) reduces GI symptoms and improves disease-specific quality of life in patients with IBS.[6,16]

Socio-economic impact and burden of IBS:

IBS has its remarkable negative impact on a patient's personal life, and subsequently on their family and the society. IBS has also made its negative effect on work life including less reliability for travelling, reduced socializing and loss of earning. Individuals with IBS report unpredictability of their symptoms and emphasize that they can feel stigmatized by family and friends, who might struggle to understand the impact of IBS on their quality of life [35]. IBS brings substantial costs directly and indirectly to the patients and society[2].

Gut microbiome plays an important role in the human gastrointestinal tract. In the present review, we have listed specific bacteria that are associated with microbiomes of patients with IBS. The pathogenesis of IBS is multifactorial although consensus opinion within the medical profession holds that the gut microbiota plays a central role in disease development. Increase in the cases with IBS has emphasised the need to evaluate the role of prebiotics, probiotics, antibiotics, and diet. Apart from other pharmacologic therapies, treatments targeting the microbiome have shown significant benefits for the IBS symptoms over time. Further studies which involve large scale, controlled trials of existing and new treatments will merge for enhancing our understanding in this field.

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