The Gut Microbiome and Human Diseases

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Abstract

The gut microbiome is a complex ecosystem of microorganisms that live in the GIT tract, and play a crucial role in metabolism, immune function, vitamin biosynthesis, nutrient absorption, and protection against pathogens. The gut-brain communication is facilitated by a bidirectional communication network known as the microbiota-gut-brain axis. Gut microbiota imbalance is linked to dysbiosis which can lead to autoimmune disorders and diseases like obesity, coronary artery disease, high blood pressure, atherosclerosis, and diabetes. A balanced microbiome (eubiosis) supports gut barrier function, and immune modulation, and supports host nutrition through primary fermentation. Gut health can be restored through various therapies, including next-generation therapies targeting microbiome and dietary modifications. Ongoing research in personalized medicine and microbiome-based therapies is rapidly evolving, focusing on integrating microbiome data with host genetics and health outcomes.

Keywords: Gut microbiome, Microbial diversity, Gut-Brain axis, Chronic diseases, Metabolic disorders, Microbiome therapeutics

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Introduction

1. Definition and Overview of Gut Microbiome

Microbiomes are organisms or the collective genome of a microbial community, at a particular site or habitat called microbiota (Young, 2017). The human gut microbiome comprises the entire collection of genetic material. Bacteria, protozoa, fungi, and viruses live inside the gastrointestinal tract (Liang et al., 2018). The term gut microbiome is the collection of symbiotic microorganisms, trillions of bacteria, viruses, fungi, and eukaryotic organisms in the GIT and their collective interacting genomes (Sidhu & Van Der Poorten, 2017; Anto & Blesso, 2022). The diversity of the human gut microbiota increases from birth until 12 years of age. The mature gut microbiome is established between the ages of one and three years, remains stable throughout adulthood, and declines in later years; however, it changes throughout life (Sidhu & Van Der Poorten, 2017; Mohajeri et al., 2018). The microbiome in the human body is over 50% of the cells found within the body weighing up to 2kg on average. According to researchers, the number of microbes in the gut is ten times greater than that of human somatic cells. A study estimated the total number of bacteria in the human body to be around 3.8×10^{13} (Sidhu & Van Der Poorten, 2017).

Microbes except defined pathogens are important to human health. Microbiome interactions with the human body are abundant (Jovel et al., 2017). To study the “healthy” microbiome a study was done underlining the relationship between the microbiome and multiple external factors. In which the gut microbiome of individuals highlighted diet as a key influencer for variations of gut microbiome composition (Mohajeri et al., 2018). To date, there is no established definition of a healthy gut microbiome, significant disruptions in the gut microbiome stability are produced by lifestyle and dietary changes (Sidhu & Van Der Poorten, 2017).

Microbial diversity expands during the initial months of infancy. The accomplishment of the microbiome in early life during pre and postnatal events is an integral phase of human life. The first exposure of a baby to microbiota happens in the mother's birth canal. Vaginal delivery and breastfeeding contribute to promoting healthy microbiota in newborns, whereas cesarean or premature delivery and exposure to infections affect the diversity and composition of microbiome in neonates. Introducing solid food in the first few years of life causes abrupt changes in the composition of microbiota (Jovel et al., 2017; Mohajeri et al., 2018).

2. Composition of the Gut Microbiome

There is no ideal composition of gut microbiota because it differs for everyone. The unique microbiota of each individual has an important role in regulating nutrient metabolism, preserving the structural stability of the gut mucosal lining, modulating immune responses, and defending against pathogenic organisms (Rinninella et al., 2019a). Gut microbiota changes in the same individual due to environmental factors, use of antibiotics, age and transitions in birth gestational date, type of delivery, methods of milk feeding, and weaning period. It varies functionally and systematically in each part of the GI tract (Muhammad et al., 2024).

The GI tract is an abundant microbial community comprising more than 100 trillion microorganisms including bacteria, yeast, and viruses. Although more than 160 species are identified, only a few phyla are represented. Researchers identified approximately 2,172 species isolated from humans and classified them into 12 distinct phyla. 93.5% of the gut microbial phyla are Bacteroidetes, Firmicutes, Verrucomicrobia, Actinobacteria, Proteobacteria, and, Fusobacteria out of which 90% of gut microbiota are made by Firmicutes and Bacteroidetes. 95% of the Firmicutes phyla are represented by the genera Clostridium. Lactobacillus, Bacillus, Enterococcus, and Ruminicoccus are other genera that make up the Firmicutes phylum. Bacteroidetes consist of genera such as Prevotella and Bacteroides. The phylum Actinobacteria occurs in lower proportions and is mainly represented by the genus Bifidobacterium (Thursby & Juge, 2017; Rinninella et al., 2019b).

3. Functions of the Gut Microbiome

The gut microbiome acts as a symbiotic partner for the body, playing an important role in nutrient absorption and digestion (Jansen et al., 2021; Y. Wu et al., 2023). It aids in the breakdown of food and carbohydrates, helps in nutrient uptake, and synthesizes essential vitamins, especially vitamin B, contributing to overall digestive health (Putnam & Goodman, 2020; Y. Zhang et al., 2023).

The gut microbiota synthesizes vitamins B12 and K, which are essential for metabolic functions impacting health at different life stages (Tarracchini et al., 2024). It also produces Short-chain fatty acids (SCFAs) like acetic and butyric acid through carbohydrate fermentation. SCFAs provide defence against pathogens and aid in human nutrition and metabolism by supporting metabolic processes (Ramakrishna, 2013; Ghoniem et al., 2022).

The gut microbiome is essential for the regulation of glucose and lipid intake, it improves insulin sensitivity and supports the development and functions of immune cells (J. Wu et al., 2021). It synthesizes nutrients, supports the immune system, maintains hydration and plays an important part in detoxification (Strand, 2022).

4. Gut Microbiome and the Gut-Brain Axis

The microbiome is linked to the gut-brain axis by a bidirectional communication system that connects the GIT and the brain through the nervous systems (Carabotti et al., 2015). The signals transmitted through this communication pathway between gut microbiota and the central nervous system are facilitated by the vagus nerve (Dinan & Cryan, 2017; Benakis et al., 2020). These immune signalling molecules facilitate the gut CNS, through Endocrine and Nervous pathways that transmit hormones and neurochemicals from the gut to the brain maintaining equilibrium, mood regulation, stress response, and immune function influencing digestive and mental health (Bakshi et al., 2024).

Dysfunction of GBA leads to impaired cognitive functions and neurodegenerative disorders such as Alzheimer's and Parkinson's disease. This highlights the need to preserve healthy gut microbiota for maintaining neurological health and prevention of neurodegenerative conditions (Y. Zheng et al., 2023; Luesma et al., 2024; Mehta, 2024). Prebiotics, probiotics, and FMT improve gut-brain communication for the management of neurological disorders (Bakshi et al., 2024).

5. Gut Microbiome and Chronic Diseases

The gut microbiome plays a crucial role in diseases such as obesity, cancer, and diabetes by affecting the immune system and metabolic functions influencing inflammatory conditions and metabolic disorders (Rumyantsev et al., 2024).

i. Gut Microbiome and Obesity

Gut microbiota composition influenced by diet impacts obesity and weight management (Mcburney & Cho, 2024). Dietary patterns high in processed foods and sugars are linked to a higher abundance of Firmicutes and a lower presence of Bacteroidetes (Figure 1) leading to reduced gut microbiome diversity commonly observed in obese individuals (Hassan et al., 2024; Wulandari, 2024). In obese individuals amino acid metabolism pathways are enriched while SCFAs biosynthesis pathways are diminished. This causes a reduction in key SCFA-producing gut microbes like Alistipes and Odoribacter splanchnicus. This decline is highly impactful on gut health and metabolic functions in obese (Chanda & De, 2024). Probiotics and prebiotics influence gut microbiota and enhance beneficial bacteria playing an important role in metabolic and appetite control, and weight management, particularly in obese individuals. They help reduce inflammation and fat accumulation, improve glucose tolerance, and regulate hormonal balance (Guimarães et al., 2020; Noor et al., 2023).

ii. Gut Microbiome and Cancer

The gut microbiome is crucial for cancer development and treatment through mechanisms like the driver-passenger hypothesis, alpha-bug hypothesis, and bystander hypothesis. Bacteria associated with cancer progression, particularly colorectal cancer, are Fusobacterium nucleatum, while other microbes may be protective against tumor development. Cancer initiation and progression are influenced by regulating immune responses, promoting chronic inflammation, altering metabolism, and causing DNA damage (Figure 1) (Li et al., 2019; Shiotani et al., 2019).

Gastric cancers are caused by pathogens like Fusobacterium and Helicobacter pylori and Bifidobacteria is a beneficial microbe that may inhibit cancer development. The decrease of antimicrobial protein Lcn2 can cause lung cancer by promoting immunosuppression and inflammation (Rahal et al., 2023; Cao et al., 2024).

The gut microbiota affects immune cell functioning within the tumor microenvironment and enhances or diminishes therapeutic responses. Modifying the gut microbiota through strategies like diet, and fecal microbiota transplantation may enhance the response to immunotherapy (C. Liu et al., 2024; J. Zheng & Chen, 2024).

iii. Gut Microbiome and Diabetes

The gut microbiome is significant for the development of diabetes, particularly type 2 diabetes. Its composition and diversity are crucial in influencing the management risk, and prevention of diabetes mellitus. The most important factors for the establishment of gut microbial composition are the maternal microbiome, gestational environment, and the conditions of newborn delivery (Paun & Danska, 2016; Cunningham et al., 2021). Gut bacteria, *Ruminococcus gnavus*, produce metabolites like phenethylamine and tryptamine, they disrupt insulin signaling through the TAAR1-ERK signaling pathway, affecting major metabolic tissues and contributing to insulin resistance (Zhai et al., 2022). A gut microbiota imbalance marked by less beneficial microbes and a high amount of harmful microbiota disrupts intestinal bacterial homeostasis. This triggers chronic inflammation and the development of metabolic disorders (Figure 1), particularly obesity and Type 2 diabetes (Xu et al., 2024). Interventions to restore gut microbial composition by improving microbiological balance, targeting immune responses, amino acid metabolism, oxidative stress, intestinal permeability, and enhancing short-chain fatty acid production aim to alleviate or reverse metabolic dysfunctions associated with Type 2 diabetes (Jeyaraman et al., 2024; Koneru et al., 2024).

iv.Gut Microbiome and Cardiovascular Disease

The gut microbiota plays an important part in the development of cardiovascular diseases by producing metabolites like trimethylamine N-oxide (TMAO) (Figure 1) and SCFAs. SCFAs have protective effects by reducing inflammation and supporting vascular health, while TMAO is linked to increased inflammation, atherosclerosis, and vascular damage (Datta et al., 2024; Yafarova et al., 2024)

Modulating the gut microbial composition through dietary changes may help reduce CVD risk. TMAO production is highly affected by dietary intake specifically Westernized diets, which can lead to atherosclerosis that can cause heart failure. Fiber-rich diet combined with less intake of red meat can influence the diversity of gut microbiota and the production of short-chain fatty acids lowering the risk of CVD. Adopting a Mediterranean diet can improve gut microbiota balance and lower CVD risk (Arvelaez Pascucci et al., 2024; Ronen et al., 2024).

6. Gut Microbiome and Autoimmune Diseases

Dysregulation of the gut microbiome impacts our immune system. It contributes to autoimmune diseases leading to the migration of pro-inflammatory molecules by allowing pathogens to translocate, activating immune responses (D. S. Y. Tan et al., 2024; Wang et al., 2024).

Microbial dysbiosis is a hallmark of conditions such as IBD, Crohn’s disease and ulcerative colitis, marked by a decrease in beneficial bacteria and an increase in pathogenic microbes. This indicates a significant connection between microbial imbalance and bowel diseases. Patients with IBD, particularly those with Crohn's disease, exhibit lower gut microbial alpha diversity with elevated Actinomyces and Escherichia coli. In UC beneficial microbes like Eubacterium rectale lowers, intensifying inflammation. Decreases in commensal bacteria like Faecalibacterium prausnitzii and Akkermansia muciniphila, are linked with anti-inflammatory properties in patients with CD and UC (Gyriki et al., 2024; Kim et al., 2024; Prast-Nielsen et al., 2024; S. Tan, 2024).

Fecal microbiota transplantation, Intestinal microbiota transplant (IMT), and butyrate supplementation aim to restore balanced microbial communities, rebalance gut flora, enhance immune responses, and promote gut barrier integrity (Fanizzi et al., 2024; Montrose et al., 2024; S. Tan, 2024).

Gut microbiota dysbiosis, particularly a reduced ratio of Firmicutes to Bacteroidetes contributes to rheumatoid arthritis (RA). Heightened immune responses through mechanisms like molecular mimicry, leaky gut, and metabolic dysregulation of gut bacteria can affect RA (Balasundaram et al., 2024; Pażyra et al., 2024).

Probiotics like Lactobacillus casei show potential benefits to help restore balance, reduce inflammation, and improve RA symptoms by replacing harmful bacteria and producing anti-inflammatory metabolites (Balasundaram et al., 2024; Juárez-Chairez et al., 2024).

The gut microbiota significantly influences multiple sclerosis, suggesting that microbial composition may influence the disease's pathobiology with specific bacterial species linked to worsening disease. Notably, Akkermansia, Lachnospiraceae, and Oscillospiraceae were depleted, while Alloprevotella, Prevotella-9, and Rhodospirillales expanded in patients with disease progression (Wang, et al., 2024; Ouyang et al., 2024).

High-fiber diets promote beneficial microbial metabolites, which may suppress CNS autoimmunity. Fecal Microbiota transplantation (FMT) shows the potential to improve MS symptoms and gut microbiota composition, alongside reducing inflammatory markers like IL-6 and TNF-alpha (Peipert, et al., 2024; Srija Reddy Kesireddy et al., 2024).

7. Gut Microbiome and Neurodegenerative Diseases

The gut microbiota communicates with the CNS via the gut-brain axis, through the vagus nerve and peripheral circulation. It synthesizes pathogenic proteins and metabolites like butyrate and amyloid, which influence neuroinflammation, neurogenesis, and overall brain health which causes neurodegenerative diseases specifically Alzheimer's and Parkinson's (Figure 1) (Park & Gao, 2024; Cavalcante et al., 2025).

Gut microbes influence Parkinson's disease and Alzheimer's disease through distinct but interconnected mechanisms: Parkinson's disease is associated with a rise in opportunistic pathogens and a decline in beneficial species, promoting gut motility issues, and systemic inflammation. In Alzheimer's, gut microbes regulate innate and adaptive immunity through metabolites. Alzheimer's is developed by influencing β-amyloid metabolism, Tau protein phosphorylation, and neuroinflammation through lipids and neurotransmitters (Chandra & Vassar, 2024; Hamilton et al., 2024; S. Zhang et al., 2024; Cavalcante et al., 2025).

Antibacterial therapies, dietary modifications, probiotics, and synbiotics modulate gut microbiota composition enhancing cognitive function by reducing inflammation and improving CNS health. The kynurenine pathway, a key player in tryptophan metabolism, represents another potential target for therapeutic strategies, as its dysregulation results in the synthesis of neurotoxic metabolites (Ashique et al., 2024; Kearns, 2024; Wei et al., 2024).

Disruptions in the gut microbiome influence variations in microbial diversity which causes various chronic diseases, like obesity, diabetes, cancer, CVD, neurodegenerative diseases, and autoimmune disorders, through metabolic and inflammatory pathways.

8. Factors Affecting the Gut Microbiome

A diet with fiber, fermented foods, and probiotics enhances microbial diversity and influences gut microbiome composition (Piccioni et al., 2023). A plant-based diet is rich in dietary fibers and promotes fiber fermentation, which enhances the production of SCFAs. It positively impacts cognitive and emotional health and promotes immune function. Dietary fibers specifically fructooligosaccharides have prebiotic effects and influence the composition of gut microbiota. Fermented foods improve gut microbiota diversity and modulate the microbiota-gut-brain axis (Den Besten et al., 2013; Schneider et al., 2024).

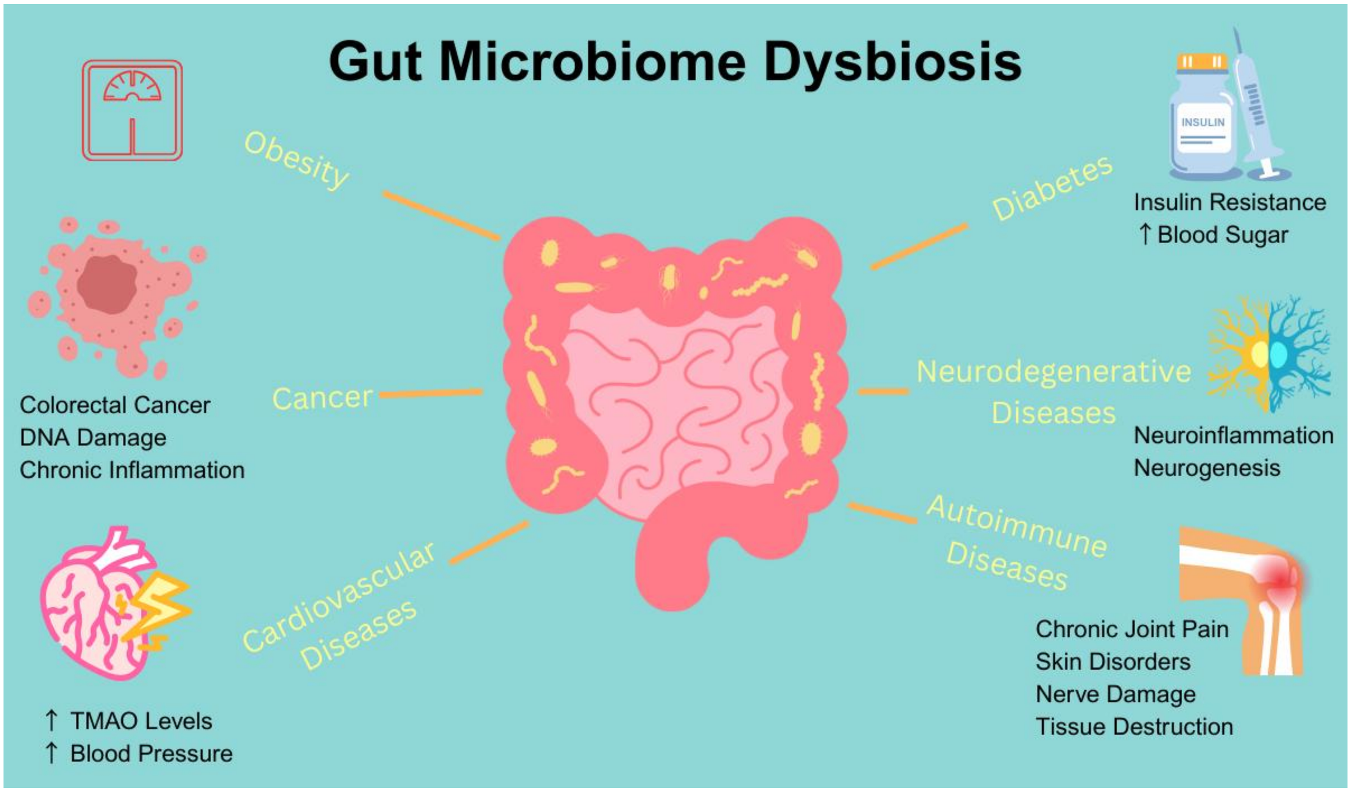

Fig. 1: Gut microbiome dysbiosis and its role in chronic illness

The composition and diversity of the gut microbiome are also affected by prolonged use of antibiotics. It decreases beneficial bacteria and increases harmful pathogens leading to dysbiosis (Aasmets et al., 2024; Gao et al., 2024).

Stress management and regular exercise are important for preserving a healthy gut microbiota because it is highly affected by an individual's lifestyle, physical activity, psychological health, and sleep schedule. Individual variabilities also influence overall gut health, highlighting the need for an understanding of their interactions (Seredyński et al., 2024; Van Hul et al., 2024).

9. Restoring and Maintaining a Healthy Gut Microbiome

For maintaining a healthy gut microbiome an important approach considered is fecal microbiota transplantation. In this method by addressing microbial imbalance and dysbiosis the fecal material from a healthy donor is transferred to a recipient. It helps in restoring beneficial bacteria like Lactobacillaceae and Lachnospiraceae and promotes overall gut microbiome health (Kumari et al., 2024; Yoo et al., 2024).

Probiotics and prebiotics are also important in restoring and maintaining a healthy gut microbiome. Probiotics are live microorganisms; they enhance the composition of gut microbiota and improve the intestinal barrier. Prebiotics are non-digestible fibers that act as food for probiotics and stimulate their growth and the function of probiotics. They enhance their effectiveness by working synergistically known as Synbiotics; a combination of both probiotics and prebiotics to improve gut health (Pathak & Soni, 2024).

Maintaining a healthy diet and lifestyle with some modifications helps in managing and preserving a healthy gut microbiome. The introduction of dietary fiber in solid food consumption, and fermented foods aid in microbial balance. These modifications can improve gut microbiota imbalance, enhance its composition and effectively extend a healthy life promoting overall health (Tulasi & Rashmi, 2024; Xiao et al., 2024).

10. Future Perspectives in Gut Microbiome Research

Some future perspectives in gut microbiome research include microbial modulation strategies as therapeutic approaches. A formula, "Xuanfei Baidu" can effectively modify gut microbiota by reducing inflammation and mortality. Artificial therapies for gut microbiota, like artificial probiotics, microbiota consortia, and bacteriophages are also emerging therapies in gut microbiome modulation (Bu et al., 2024; L. Liu et al., 2024; Porcari et al., 2024).

Conclusion

The gut microbiome is crucial as it impacts overall digestive health and protects against pathogens. A diverse gut microbiome is crucial for the proper function and development of the immune system. The imbalance in gut microbiota affects metabolism and immune regulation influencing disease progression. This highlights its role in various body systems like the gut-brain axis. Therapeutic strategies including probiotics, prebiotics, dietary modifications, and fermented foods aid in restoring overall microbial balance and enhancing gastrointestinal well-being. Continued research to shape future microbiome research modification and technological advancements are important for disease prevention and treatment.

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