Microbiome and Chronic Disease

MalekJazzan

Internal medicine specialist, Mediclinic Al Ain - Abu Dhabi –UAE
E-mail: *dr.jazzan@gmail.com*

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ABSTRACT
The origin of "microbiota" can be dated back to early 1900s. It was found that a vast number of microorganisms, including bacteria, yeasts, and viruses, coexist in various sites of the human body (gut, skin, lung, oral cavity). The gut microbiome, in particular, has been closely linked to metabolic conditions such as obesity, type 2 diabetes, and non-alcoholic fatty liver disease (NAFLD). Dysbiosis, or an imbalance in the gut microbiota, can impair the gut's ability to regulate metabolism, insulin sensitivity, and inflammation. Key mechanisms by which the microbiome affects metabolic diseases include: Short-chain fatty acids (SCFAs), inflammation and energy harvest. The gut microbiome is crucial for regulating metabolism, energy balance, and immune function. Disruptions in the gut microbiome have been associated with conditions such as obesity, type 2 Diabetes and non-alcoholic fatty liver disease (NAFLD).Maintaining a healthy microbiome through a balanced diet, regular exercise, and careful use of antibiotics can help reduce the risk of conditions like obesity, type 2 diabetes, cardiovascular disease, autoimmune disorders, and even some cancers. As research in this area continues to evolve, the microbiome may become a key target for the prevention and treatment of chronic diseases.

Introduction

The origin of "microbiota" can be dated back to early 1900s. It was found that a vast number of microorganisms, including bacteria, yeasts, and viruses, coexist in various sites of the human body (gut, skin, lung, oral cavity). In addition, the human microbiota, also known as "the hidden organ," contribute over 150 times more genetic information than that of the entire human genome. Although "microbiota" and "microbiome" are often interchangeable, there are certain differences between the two terms. Microbiota describes the living microorganisms found in a defined environment, such as oral and gut microbiota**(1)**. The normal respiratory tract and gut microbiota protect against pneumonia by preventing pathogenic bacteria colonization and by modulating immune responses. Therefore, it is not surprising that the dysbiosis of respiratory tract microbiota is considered a risk factor of pneumonia.The upper airways are the main source of microbes to the lower airways. Recently, researchers have shown that the reduction of nasal microbiota diversity increased susceptibility to pneumonia. Particularly, three microbiota profiles dominated by *Lactobacilli*, *Rothia*, and *Streptococcus* were significantly associated with pneumonia **(2)**.

This study aimed to describe the associations between microbiome composition and various types of chronic diseases

Microbiota in the development of diseases

Microbiota are complex systems consisting of trillions of microorganisms.When subjected to external changes, the balance of microbiota community can be affected, leading to dysregulation of bodily functions and diseases. To date, mounting evidence has confirmed that microbiota is associated with the development of CVDs, cancer, respiratory diseases, diabetes, IBD, brain disorders, chronic kidney diseases, and liver diseases**(3)**.

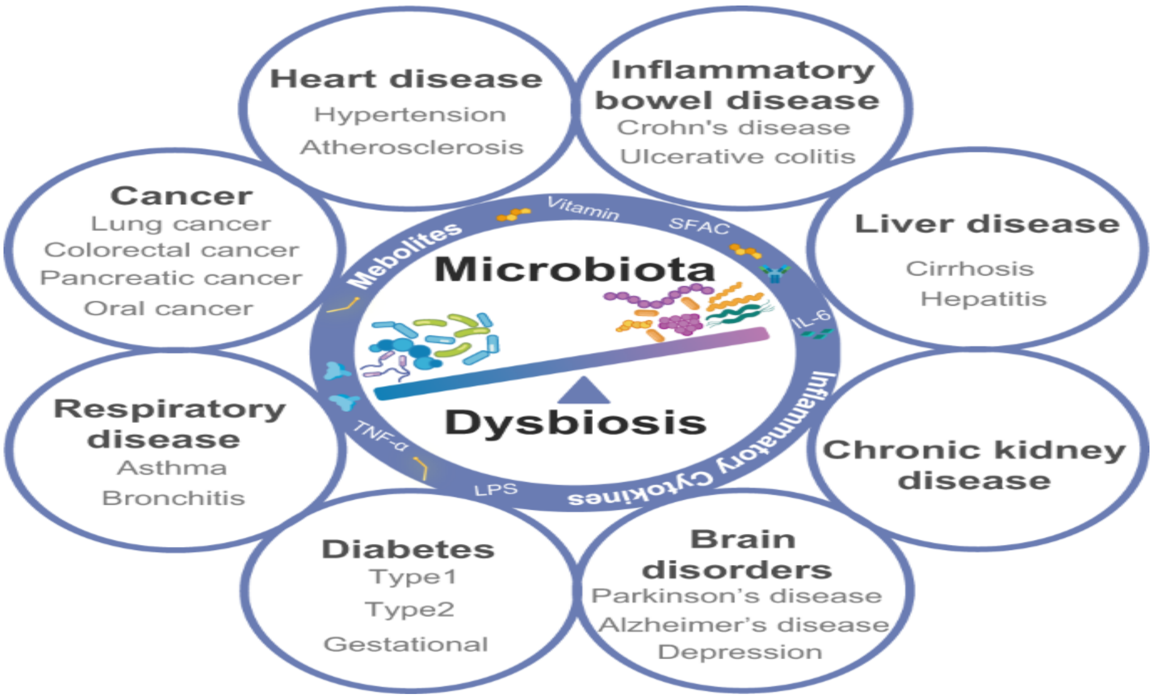

Figure (1): Human microbiota dysbiosis contributes to various diseases(4)

Respiratory diseases

Respiratory diseases are a group of diseases that affect the lungs and other parts of the respiratory system and include chronic diseases (asthma and chronic obstructive pulmonary disease (COPD), pulmonary fibrosis) and pneumonia. Extensive studies have suggested that oral, lung, and gut microbiota are associated with the development of respiratory diseases **(5)**.

Chronic respiratory diseases

COPD and asthma are the two most frequently diagnosed chronic respiratory diseases. COPD is defined as a disease state characterized by the presence of airflow limitation associated with chronic bronchitis or emphysema. Asthma is a heterogeneous syndrome of chronic airway inflammation characterized by bronchial hyper-responsiveness to environmental triggers and by symptoms including wheezing, shortness of breath, and chest tightness. lung microbiota is actively involved in the development of chronic respiratory diseases **(6)**.

Pneumonia

The normal respiratory tract and gut microbiota protect against pneumonia by preventing pathogenic bacteria colonization and by modulating immune responses. Therefore, it is not surprising that the dysbiosis of respiratory tract microbiota is considered a risk factor of pneumonia. Recently, researchers have shown that the reduction of nasal microbiota diversity increased susceptibility to pneumonia. Particularly, three microbiota profiles dominated by *Lactobacilli*, *Rothia*, and *Streptococcus* were significantly associated with pneumonia **(2)**. The microbiome—the complex community of trillions of microbes (bacteria, viruses, fungi, and other microorganisms) living in and on our bodies—plays a significant role in maintaining our health**(7)**.

Gut Microbiome and Metabolic Diseases

The gut microbiome, in particular, has been closely linked to metabolic conditions such as obesity, type 2 diabetes, and non-alcoholic fatty liver disease (NAFLD). Dysbiosis, or an imbalance in the gut microbiota, can impair the gut's ability to regulate metabolism, insulin sensitivity, and inflammation. Key mechanisms by which the microbiome affects metabolic diseases include:**(8)**

Short-chain fatty acids (SCFAs): These are produced by gut bacteria during the fermentation of dietary fibers and are crucial for maintaining gut health, modulating inflammation, and improving insulin sensitivity.

Inflammation: An imbalanced microbiome can lead to a leaky gut, where the intestinal barrier becomes permeable. This allows endotoxins like lipopolysaccharides (LPS) to enter the bloodstream, triggering systemic inflammation, which is a hallmark of metabolic diseases.

Energy harvest: Some gut microbes are more efficient at extracting energy from food than others, which may influence body weight. For example, certain bacteria can ferment fiber into SCFAs that provide additional calories, contributing to obesity **(9)**.

The **gut microbiome** is crucial for regulating metabolism, energy balance, and immune function. Disruptions in the gut microbiome have been associated with conditions such as:**(1)**

Obesity: Dysbiosis in the gut microbiome can lead to increased energy harvest from food, contributing to weight gain. Some bacteria are better at extracting calories from food, which can promote obesity.

Type 2 Diabetes: Gut bacteria influence insulin sensitivity and glucose metabolism. An imbalanced microbiome can lead to inflammation and insulin resistance, both of which contribute to the development of type 2 diabetes.

Non-alcoholic Fatty Liver Disease (NAFLD): An altered gut microbiome can increase intestinal permeability, allowing harmful bacteria or endotoxins to enter the bloodstream, promoting liver inflammation, and contributing to the development of fatty liver disease **(10)**.

Gut Microbiome and Cardiovascular Diseases

The gut microbiome also plays a role in **cardiovascular health**. Dysbiosis has been associated with atherosclerosis (plaque buildup in arteries) and hypertension, with several mechanisms at play:**(10)**

TMAO production: Gut bacteria convert choline and L-carnitine into trimethylamine (TMA), which is converted by the liver into trimethylamine N-oxide (TMAO), increasing the risk of cardiovascular diseases like atherosclerosis**.**

Blood pressure regulation: The microbiome influences blood pressure by affecting the production of metabolites that regulate vascular tone and fluid balance. Disruptions in this process can contribute to hypertension **(11)**.

The gut microbiome is also connected to **cardiovascular health:(12)**

Atherosclerosis and Heart Disease: Some gut bacteria metabolize certain foods into molecules like **trimethylamine-N-oxide (TMAO)**, which can contribute to the buildup of plaque in the arteries. A higher TMAO level has been linked to an increased risk of heart disease and stroke.

Hypertension (High Blood Pressure): Certain microbes in the gut are thought to influence blood pressure regulation by producing compounds that affect vascular tone. An imbalanced microbiome can contribute to hypertension**(I3)**.

Gut Microbiome and Autoimmune Diseases

Autoimmune diseases occur when the immune system mistakenly attacks the body’s own tissues, and the microbiome is believed to play a crucial role in the development of conditions like rheumatoid arthritis, multiple sclerosis (MS), and inflammatory bowel disease (IBD). Key factors include:**(14)**

Immune modulation: A healthy microbiome helps train the immune system to distinguish between harmful invaders and the body's own cells.

Inflammatory pathways

Gut bacteria can influence systemic inflammation and the balance between pro-inflammatory and anti-inflammatory signals.

Molecular mimicry: Some microbes share molecular structures similar to the body's own tissues, leading the immune system to mistakenly attack both the microbes and the body's cells. This is thought to be a mechanism in diseases like **rheumatic fever** and **MS(15)**.

The immune system is heavily influenced by the gut microbiome, and dysbiosis is thought to contribute to several **autoimmune diseases:(16)**

Rheumatoid Arthritis (RA): Gut bacteria have been implicated in RA, where an imbalance can promote systemic inflammation, leading to joint damage and autoimmune responses.

Multiple Sclerosis (MS): In MS, the immune system attacks the protective covering of nerve fibers.

There is emerging evidence that an altered gut microbiome can influence the development of MS by affecting immune cell function and promoting inflammation.

Inflammatory Bowel Disease (IBD): IBD, including Crohn's disease and ulcerative colitis, is directly linked to an imbalance in the gut microbiome. The gut's immune system responds abnormally to its microbial community, resulting in chronic inflammation in the intestines **(10)**.

Gut Microbiome and Neurological Diseases

Emerging research suggests that the microbiome may also affect neurological and mental health disorders like depression, anxiety, Parkinson's disease, and Alzheimer's disease:**(11)**

Gut-brain axis: The gut and the brain communicate through the vagus nerve, hormones, and immune molecules. The gut microbiome can influence this axis, impacting mood, behavior, and cognitive function.

Inflammation and neurodegeneration: Chronic low-grade inflammation, influenced by an imbalanced microbiome, has been implicated in neurodegenerative diseases like Alzheimer's and Parkinson's (**2)**.

The **gut-brain axis** refers to the bidirectional communication between the gut and the brain, and it's increasingly recognized as being involved in several **neurological and psychiatric** conditions:**(15)**

Dysbiosis has been linked to symptoms of depression, anxiety, and other mood disorders.

Parkinson's Disease: Research suggests that the microbiome may play a role in Parkinson's disease. Changes in the gut microbiome are associated with the progression of Parkinson's, possibly by influencing neuroinflammation or gut motility.

Alzheimer's Disease: Chronic inflammation linked to an imbalanced microbiome is thought to contribute to neurodegenerative diseases like Alzheimer's. The gut microbiome's impact on brain health may involve immune activation and the production of harmful compounds that affect brain function **(1)**.

Gut Microbiome and Cancer

Recent studies also suggest a connection between the microbiome and the development of certain types of cancer. For example**:(4)**

Colorectal cancer:Dysbiosis in the gut microbiome can lead to colorectal cancer by promoting inflammation, altering immune responses, and producing carcinogenic metabolites.

Cancer therapy response: The microbiome may affect the effectiveness of cancer treatments, including chemotherapy and immunotherapy**(10)**.

Diet, Lifestyle, and Microbiome Modulation

Diet and lifestyle have a profound impact on the microbiome. Diets rich in fiber, prebiotics (foods that feed beneficial bacteria), and fermented foods (which contain probiotics) promote a diverse and healthy microbiome. Conversely, a diet high in processed foods, sugar, and fat can encourage the growth of harmful microbes and contribute to dysbiosis**(13)**.

Probiotics and prebiotics: Probiotics (live beneficial bacteria) and prebiotics (non-digestible food components that promote the growth of beneficial bacteria) are being studied for their potential to restore a healthy microbiome and mitigate chronic disease.

Antibiotics: While antibiotics can treat infections, they can also disrupt the microbiome, leading to long-term changes that may contribute to chronic diseases, including obesity, IBD, and allergies.

Exercise: Physical activity is associated with greater microbial diversity, which is thought to be beneficial for overall health. Regular exercise may help reduce the risk of chronic diseases by promoting a balanced microbiome**(14)**.

The Role of the Microbiome in Chronic Disease Prevention and Treatment

As research progresses, the microbiome is increasingly seen as both a **cause** and a **potential therapeutic target** for chronic diseases. Strategies to restore a healthy microbiome could involve:**(10)**

Fecal Microbiota Transplantation (FMT): FMT is an emerging treatment for certain conditions, particularly **Clostridioides difficile infection**, and there is growing interest in using FMT to treat other diseases related to microbiome imbalances, including IBD and even metabolic disorders.

Personalized Nutrition: Understanding an individual's microbiome may lead to personalized dietary recommendations that promote a healthier gut microbiome and reduce the risk of disease **(11)**.

Conclusion

The microbiome is a critical factor in the development and progression of many chronic diseases. Maintaining a healthy microbiome through a balanced diet, regular exercise, and careful use of antibiotics can help reduce the risk of conditions like obesity, type 2 diabetes, cardiovascular disease, autoimmune disorders, and even some cancers. As research in this area continues to evolve, the microbiome may become a key target for the prevention and treatment of chronic diseases

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