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The Critical Role of Gut Microbiota and its Association with Obesity and Related Diseases

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Abstract

Heredity and the environment contribute to obesity, a major global health problem. Recent studies have demonstrated a connection between obesity and gut microbiota. The treatment of obesity through gut microbiota management is becoming more popular. There is, however, a lack of understanding of the complex interactions between genetics, the environment, and the gut microbiota that contribute to obesity. The study focused on both the relationship between obesity and fecal microorganisms and their metabolites, as well as factors that could stimulate growth and remodeling of microbiota. Several criteria were used to categorize and evaluate the articles, and conclusions were drawn based on those criteria. Studies and articles examined acknowledge that intestinal microbiota may play a significant role in human homeostasis. Metabolically ill patients and people who are obese have altered gut microbiotas. We also tried to provide support for understanding the complex relationship between obesity and microbiota by describing the characteristics of the gut microbiota in obesity, the mechanisms by which obesity is caused by the gut microbiota, and the influence of genetic and environmental factors on the gut microbiota and obesity. There is a possibility that an imbalanced microbiome composition, such as changes in the Bacteroidetes/Firmicutes ratio and the presence of *Lactobacillus* species, may lead to obesity and comorbidities. Despite this, there are also studies that contradict it. To improve our understanding of how microbiota, its metabolites, and probiotics influence obesity, further well-designed studies are needed.

Keywords: Gut microbiota, Obesity, Morbidities, Disease

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Introduction

An overview of the obesity epidemic

A number of genetic and nongenetic factors (such as environmental factors) contribute to obesity. Depending on the country, the World Health Organization defines obesity as having a body mass index (BMI) above 30. An obese person in the USA, for example, has a BMI of 28 or higher. According to a comprehensive analysis, approximately one-third of the world's population is overweight, and approximately 10% is obese. According to few other projections, 81% of Americans will be obese or overweight by 2030, while approximately 39% of children and 46% of adolescents will have abnormally high BMIs [1, 2]. The risk of adult obesity is increased by a meta-analysis of available data showing that half of obese children were still obese as adults; the risk is doubled if both parents are obese. Childhood obesity (defined as a BMI for age (or BMI-for-age) percentile greater than 95%) is a major risk factor for adult obesity. Several factors contribute to obesity's etiology, including genetics, hormones, socioeconomics, and environmental factors [3]. It is also possible that comorbidities and their treatment might play a role in the prevalence and progression of obesity [4]. Obesity is caused by primary and secondary disease-related factors. Globally, there will be 1.12 billion obese people by 2030. There has been widespread concern about obesity's health risks, and it has become a global health concern. It is not only associated with changes in appearance, but also with lipid and glucose metabolism disorders, chronic inflammation, oxidative stress, and an increased risk of several diseases, including cardiovascular disease, diabetes, and cancer [5]. Increasing evidence suggests that obesity may be caused by an imbalance in the gut microbiota.

There are about 100 trillion symbiotic microbes living in the gut, known as the gut microbiota, which is 10 times as many as the body's own cells. To maintain its high population levels, the gut microbiota eats food residues that the human body doesn't digest, secretes mucus, and sheds dead cells. As a result of gut microbiota activity, a wide range of physiologically active substances will be produced, including short-chain fatty acids, vitamins, anti-inflammatory, analgesic, and antioxidant products, as well as potentially harmful substances like neurotoxins, carcinogens, and immunotoxins. In addition to entering the bloodstream, these products directly regulate gene expression and affect the human immune system and metabolism [6, 7]. In order to maintain a healthy metabolism and an even energy balance, the gut microbiota must be in good health. Dysbiosis of the gut microbiota can lead to metabolic disorders as well as an increase in central appetite, resulting in obesity. Among the genetic syndromes associated with obesity are physical characteristics, such as dysmorphic features, developmental delays, and mental retardation. Genetic defects usually involve multiple genes and are often chromosomal abnormalities [8]. A common cause of obesity in children is Prader-Willi syndrome. There are many secondary causes of obesity, including systemic dysfunctions and disorders of regulatory mechanisms that cause metabolic changes in the body, leading to obesity secondary to primary illness. Homeostasis

disruptions caused by diseases lead to the body's inability to maintain energy balance, abnormal hormone synthesis, and altered consumption patterns. Maternal gestational weight gain has been linked to obesity in infancy, and maternal gestational weight gain is an independent predictor [9-11]. Genetics is strongly associated with obesity, meaning that multiple genes and their complex interactions can result in monogenic (5% of cases) or polygenic obesity. In addition to medical treatment, bariatric surgery can extend a person's life expectancy. An overview of research into the relationship between obesity and gut microbiota is presented in this article [12].

We can influence our physiology in several ways through the body's microbiome, which includes bacteria, viruses, archaea, and eukaryotic microbes. Researchers have shown that gut microbiome composition increases dietary energy intake, and therefore promotes obesity [13]. There are differences in the composition of microbial populations throughout the gastrointestinal tract. Because of the esophageal motility and the acidic unfavorable environment of the stomach, there are quantitatively few microorganisms, with most bacteria coming from the oral cavity [14]. There are already numerous bacteria in the intestinal microbiota, for example, Streptococcus is the most abundant in the Jejunum, while the ileocecal region is inhabited by bacteria from the phylum Firmicutes, primarily Streptococcaceae), bacteria from the phylum Actinobacteria (especially the subgroups Actinomycinaeae and Corynebacteriaceae), Bacteroidetes, and Lachnospiraceae. Due to the favorable pH for bacteria to colonize, the distal segment of the ileum and colon has the most bacteria and the greatest microbial diversity, as well as the fact that food content is retained longer in the intestinal lumen due to antiperistaltic contractions. Bacteroides and Clostridium are primarily Gram-positive bacteria, followed by Lactobacillus, Enterococcus, and Enterobacteriaceae [15]. Recently, several molecular pathways and some substances produced by the gut microbiota have been linked to obesity, suggesting a relation between gut microbiota imbalance and obesity. It is important to note that the correlations remain complex, so only a few will be discussed in the following sections. Based on the results discussed here, manipulation of the gut microbiota may be a potential treatment or prevention of obesity and its metabolic consequences [16].

A key factor inhibiting DNA damage repair mechanisms is obesity, which increases the risk of other associated diseases. An irreversible cell-cycle arrest can occur as a result of DNA damage, activation of adipocyte differentiation and hypertrophy proteins, disturbances in cell metabolism, impairments in glucose metabolism, and the development of insulin resistance in the system. BMI is correlated with insulin resistance, type 2 diabetes, and cardiovascular disease, which are well-established weight-related comorbidities. Additionally, obesity causes adverse health outcomes including sleep apnea, hypertension, heart disease, stroke, osteoarthritis, and certain types of cancer, as well as psychosocial problems like stigmatization and low self-esteem [17].

It is indisputable that obesity adversely affects cardiometabolic health; abdominal obesity is especially associated with cardiovascular disease, and it has been shown to disrupt adipocyte biology and adipose tissue inflammation, which have direct systemic metabolic consequences such as endothelial dysfunction and atherogenesis. A significant association has also been found between COVID-19 and obesity in multiple studies. There is an enhanced hospitalization rate, a more severe progression, and a worse outcome for COVID-19 patients with obesity. Urbanization is widely credited with contributing to the worldwide increase in BMI because diet and lifestyle in cities contribute to adiposity; however, a persistently higher rural BMI for women was observed in high-income and industrialized countries [18]. Obesity is associated with sedentary behavior and time spent watching television The.re are several factors associated with a lower quality diet, including being male, living outside the university city, having a mother who is low socioeconomic status, and studying a health-related course. BMI and consumption of a high protein/fat Westernized diet were positively correlated. Researchers found that experimental reductions in sleep duration lower leptin levels, increase ghrelin levels, and increase appetite and hunger in adults [19-22].

Function of Gut Microbiota

The gut microbiota is composed of about 80 trillion bacteria that play an important role in maintaining homeostasis in humans. Among these are metabolism regulation, intestinal barrier function, and immunomodulation. There are over 100 species of bacteria in the intestines, and the gut microbiota contains ten times more bacteria than human cells. It is mainly anaerobic bacteria that make up the gut microbiota, which belongs to four phylotypes: Bacteroidetes, Firmicutes, Proteobacteria, and Actinobacteria. A variety of viruses, protozoa, archaea, and fungi can also be included in intestinal microflora [23, 24].

Gut microbiota development begins at birth, when the fetus is exposed to bacterial populations for the first time during passage through the birth canal. Thus, infants' microbiota can be similar to their mothers' vaginal microbiota [25]. Additionally, caesarean section babies and vaginal delivery babies have different gut microbiota compositions. As we grow older, our intestinal microbiota changes significantly. However, the microbiota of one-year-old children stabilizes and begins to resemble that of adolescents. Due to this, the initial colonization of the gastrointestinal tract might play an important role in determining the composition of the microbiota in adulthood. It has even been shown that the bacterial colonization during birth influenced the microbiota of monozygotic and dizygotic twins more than their genetics [26]. Further studies are necessary to fully establish the parental role in determining the composition of the adult gut microbiota as the process of microbiota development is complex and depends on many different factors (e.g., diet, probiotics, antibiotics). The function of the human gut microbiota has been the subject of numerous studies over the last few years. In addition to maintaining metabolic balance and the proper function of the immune system, microbiota also appears to influence brain development and neurogenesis as well as interact with the central nervous system (CNS) via the "gut-brain axis". As a result, a better understanding of this complex system may lead to new treatment options not only for obesity but also for depression, inflammatory bowel diseases (IBD), and cancer [27].

Microbiota in the gut contributes to immune system function in two ways. In addition, it maintains the structural integrity of the intestinal barrier, providing physical protection against enteropathogens. Immunomodulation is also influenced by intestinal microbiota. In addition to improving the function of macrophages and natural killer cells (NK cells), symbiotic bacteria can influence the immune response of the host. Additionally, they regulate inflammation-related pathways and promote tolerogenic dendritic cells (Figure 1) [28].

As a result of the bacteria present in the intestines, the body creates an extraordinary metabolic "organ" that can extract nutrients and energy from ingested food. During digestion, human enzymes cannot completely hydrolyze dietary fiber, which is catabolized by the gut microbiota. The main product of this process is short chain fatty acids (SCFAs), which consist of fatty acids with less than six carbons [29]. A number of studies have shown that SCFAs can affect appetite regulation as well as lipid metabolism and glucose metabolism. A number of these molecules could also affect the integrity of the intestinal barrier by promoting the function of tight junctions (TJs) between epithelial

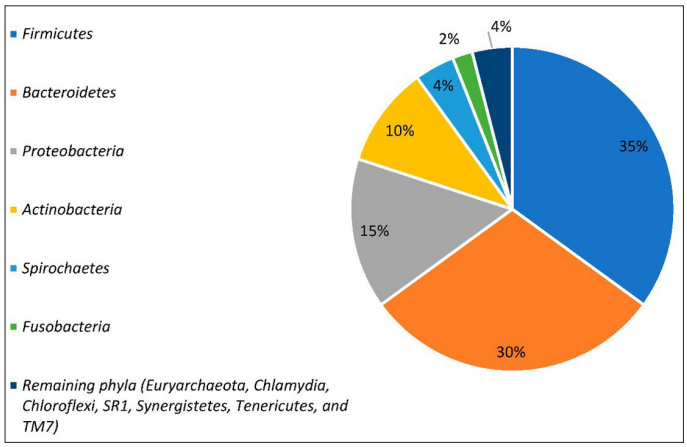

Figure 1: Distribution of microbiomes based on HOMD.

cells, thus regulating the absorption of xenobiotics. There is still a lack of understanding of the mechanism by which gut microbiota and brain communicate bidirectionally. Researchers have discovered that this pathway can function in many ways, including the neuroanatomical pathway and the immune, metabolic, and endocrine systems. The brain can manipulate the sensory and secretion function of the intestines through this network. Alternatively, gut microorganisms are capable of producing neurotransmitters (e.g., dopamine) and promoting the release of gut hormones. Neurotransmitters are responsible for affecting brain function.

Microbiota and Obesity

Metabolic disorders like obesity, diabetes, and eating disorders, as well as stress-related neuropsychiatric disorders like depression and anxiety alter the composition of the human gut microbiota. A few studies found that microbiota encroaches within the gut wall when using human colonic tissue, and the degree of encroachment was directly related to adults' dysglycemia. There are some mechanisms proposed to explain the role of gut microbiota in obesity development. Indigestible fibers are polysaccharides and oligosaccharides, which are chemically polysaccharides and oligosaccharides, which are metabolized by the gut microbiota. SCFAs such as acetate, propionate, and butyrate are formed when they are converted into SCFAs by the gut [3]. Inducing lipogenesis and increasing triglyceride stores are possible after SCFAs are absorbed. The carbohydrate-responsive element-binding protein and the sterol regulatory element-binding transcription factor 1 are both involved in lipogenesis. The rate of SCFA metabolism determines the direction of host energy balance by increasing the effectiveness of calorie absorption. In addition, SCFAs suppress fasting-induced adipocyte factor, which inhibits lipoprotein lipase, leading to triglyceride accumulation in adipocytes. SCFAs are found primarily in dietary fibers, which are thought to assist in maintaining a healthy weight [30].

Methanobrevibacter smithii is another methanogenic archaea that oxidizes H2 produced by other bacteria using carbon dioxide (CO_2). Based on animal models, this process resulted in higher extraction of polysaccharides from diets, as well as increased production of SCFAs. It removes excess H2 from the intestine, which compromises fermentation, and reduces the amount of H2 used for methane production, allowing a hypocaloric diet to be utilized more effectively [31]. In comparison to conventional mice that fed the same diet, germ-free mice lose twice as many calories in their stool and urine, supporting the notion that gut microbiota facilitate host energy balance and weight maintenance by enabling the host to extract more energy from food source. Despite contradictory evidence, it is unclear whether SCFAs influence host metabolism positively or negatively. There is increasing evidence that SCFA supplementation promotes the production of incretin and other gut hormones, including GIP, PYY, and GLP-1 and GLP-2. Gut motility, satiety, and glucose metabolism are regulated by them [32]. A SCFA supplement improved insulin resistance and obesity in mice with diet-induced obesity. Other animal studies have found that butyrate-producing bacteria, such as *Faecalibacterium prausnitzii,* can alleviate insulin resistance by causing the colonic L cells to secrete glucagon-like peptide-1 (GLP-1) through the fatty acid receptor FFAR2. However, butyrate and propionate may also influence host glucose metabolism by activating intestinal gluconeogenesis. The role of SCFAs in obesity remains controversial, despite their beneficial effects on intestinal homeostasis and energy metabolism. There is an association between higher fecal SCFA levels and gut permeability, metabolic disorder markers, obesity, and hypertension. In spite of their ability to prevent diet-induced obesity, excessive SCFAs can provide the host with additional energy, which can lead to obesity [33].

Adenosine monophosphate kinase (AMPK) and fasting-induced adipose factor (Fiaf), circulating lipoprotein lipase inhibitors, are inhibited by gut microbiota, resulting in decreased liver fatty acid oxidation. Fiaf and AMPK are suppressed in the liver and skeletal muscle by bacteria, resulting in weight gain. Fiaf is produced by the intestine, the liver, and adipose tissue. When Fiaf is inhibited, LPL is activated, which causes adipocytes to accumulate triglycerides. Microbiota populated germ-free mice throughout the experiment suppressed Fiaf expression in intestinal epithelial cells. Fiaf-/- germ-free mice had 57% more body fat after conventionalization than their wild-type counterparts and were not protected against diet-induced obesity. Based on 16S rDNA enumeration studies, Bacteroides and Clostridium were the most predominant bacteria in conventionalized mice's digestive tracts. Bacteroides thetaiotaomicron has been shown to play an important function in modulating lipid metabolism by colonization with saccharolytic bacteria. The colonization of germ-free mice by B. thetaiotaomicron altered host genes affecting lipid degradation and absorption and polysaccharide metabolism [34-36].

Despite the magnitude of the increase, colonization with one bacterial species showed a statistically significant increase in total body fat. The results of another study showed that mice fed high-fat diets supplemented with *Lactobacillus paracasei* had reduced body fat and increased Fiaf activity. AMPK phosphorylation has also been shown to be increased in muscle and liver of germ-free mice, which protects them from diet-induced obesity. Acetate-CoA carboxylase and carnitine-palmitoyl transferase I am mitochondrial enzymes that stimulate fatty acid oxidation in peripheral tissues [3, 37]. It was observed that AMPK and adiponectin activity decreased in normal and obese mice, along with fatty acid oxidation and fatty acid influx into the liver being decreased.

As bile acid species change in composition and relative abundance in the gut microbiota, this may explain the effect of the gut microbiota on glucose and insulin homeostasis. Bacterial overgrowth and inflammation are associated with reduced bile acid levels in the gut. FXR signaling has been identified as an important pathway for bile acids' interaction with gut microbiota in recent studies. A decrease in Bacteroides and an increase in Roseburia was observed in studies of human and murine models post-RYGB (Roux-en-Y gastric bypass). In FXR signaling, bile acids and gut microbiota contribute to host metabolism by metabolizing bile acids into primary and secondary bile acids, which then bind to the FXR receptor and stimulate gut hormone secretion, including FGF-19, the growth factor for fibroblasts [38]. In turn, FGF-19 regulates bile acid synthesis, lipid metabolism, and glucose metabolism. Through the stimulation of brown adipose tissue and

skeletal muscle by TGR5, a membrane-bound G protein-coupled bile acid receptor, increased bile acid synthesis leads to an increase in energy expenditure in the host. In addition, type 2 deiodinase activates thyroid hormones. Through binding to cellular receptors, including TGR5, secondary bile acids reduce macrophage inflammation and lipoprotein uptake, reducing the development of atherosclerosis plaques [39].

Obesity, Genetics, and Environment

Despite genes playing an important role in gut microbiota, environmental factors have a greater impact. Among 1000 Israelis with similar eating habits and lifestyles from all over the world, their ancestry was not related to their microbiome [40]. Microbiomes may be less than 2% heritable, and more than 20% of their variation is determined by diet, drugs, and anthropometrics. Obesity is often caused by poor diet. Consumption of fats and sugars has gradually increased in developed countries and regions, contributing to the gradual increase in obesity. A host's diet is essential for gut microbes to survive and harvest energy, and dietary changes impact gut microbes greatly. High-fat-fed mice, for example, had a decrease in Bacteroidetes, whereas Firmicutes and Proteobacteria had an increase. The changes in the microbiome were observed in mice that did not gain weight, suggesting that dietary fat affects the microbiome directly. Obesity also results from sleep disturbances. As a result of lack of sleep, circadian rhythms are disrupted, which may alter the gut microbiome and lead to obesity. With chronic sleep fragmentation, there was an increase in food intake and a reversible change in gut microbiota, as Lactobacillaceae and *Ruminococcus abundance* levels increased, and *Lactobacillaceae abundance* decreased. Insulin sensitivity is altered as a result of these factors, which cause systemic and visceral inflammation in white adipose tissue. By activating metabolism-affecting genes, stress increases appetite and increases fat consumption, contributing to obesity and weight gain. Every stage of life is affected by stress, which influences the microbiota-gut-brain axis. It was found that stress increased the actual diversity of gut microbiota, changed 50% of identified genes, decreased the abundance of Bacteroides, and increased the abundance of less dominant taxa unaffected by diet [41]. Furthermore, obesity can also be caused by unhealthy lifestyle choices (sedentary, no exercise), emotional disorders, and drugs. Because gut microbiota is acquired from the environment, environmental factors can have a greater influence on the occurrence and development of obesity as a "migrant". In humans and mice, two phyla dominate 90% of the bacterial population, out of more than 50 known. Over 200 genera make up the Firmicutes (Gram-positive) microbiota, which comprises 60 - 80% of it. Second are Bacteroidetes (Gram-negative) which comprise around 20 - 30% of the microbiota. Actinobacteria (Gram-positive bacteria), with a predominance of Bifidobacterium, comprise about 10% of the microbiota (Figure 2).

In infancy and in adulthood, gut bacteria are associated with obesity. In addition to the environment, the microbiome is a fingerprint of human genetics. According to Ley and colleagues, 16S rRNA gene sequencing was used to analyze the gut microbiota of mice with leptin deficiency on a major phyla level. Mice homozygous for the aberrant leptin gene ob/ob carried different proportions of bacteria in the ceca compared with lean wild-type (+/+) and heterozygous (ob/+) mice. Bacteroidetes populations decreased by 50% in ob/ob mice, but Firmicutes populations increased proportionally [2, 3]. In a similar study, that analyzed cecal microbial DNA using the newer shotgun metagenomic sequencing technique. According to this study, obese mice have a higher ratio of Firmicutes than Bacteroidetes. Additionally, ob/ob mice had a higher proportion of Archaea within their cecal gut microbiota. An obesity-associated decrease in Bacteroidetes abundance

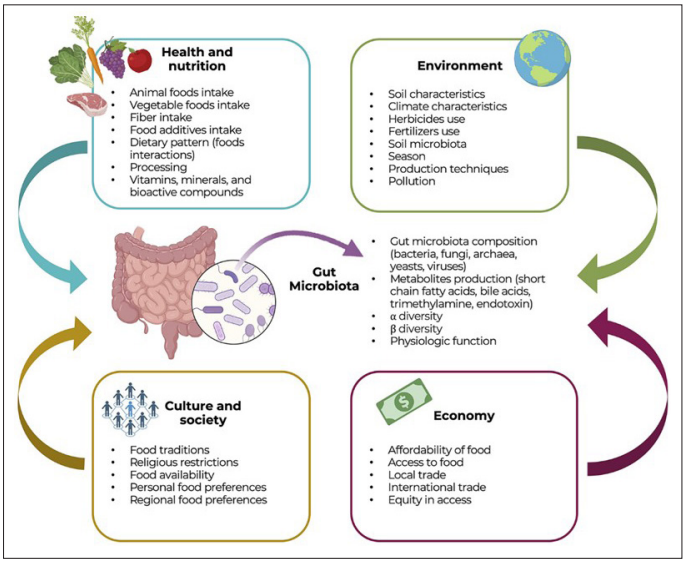

Figure 2: Dietary elements and gut microbiota [42].

was observed in another mammalian model. It has been shown that obesity is associated with changes in the Bacteroidetes/Firmicutes ratio, with obese individuals having a predominance of Firmicutes and a smaller proportion of Bacteroidetes. In contrast, some studies have found the Firmicutes-to-Bacteroidetes ratio does not influence human obesity. Numerous studies have examined how diet modulates Firmicutes-to-Bacteroidetes ratios. African children consuming high-fiber diets showed a significant increase in Bacteroidetes and a depletion of Firmicutes in the fecal microbiota, with high levels of Bacteroidetes compared to European children eating a Western diet. Gram-negative bacteria, such as Shigella and Escherichia, were underrepresented in African children, and their detection was confounded by large interperson variations and insufficient sample sizes. Vaginally delivered neonates are initially colonized by the vaginal and distal gut bacteria of their mothers, whereas babies delivered by caesarean section (C-section) are mostly colonized by their mothers' skin bacteria. Bacteroides and Bifidobacteria species are more abundant in vaginally delivered neonates than in those born by C-section. Increased Bacteroidetes populations in obese children and those delivered via C-section may contribute to the subsequent 40% increased obesity risk in children and young adults [43]. It has been shown that *Staphylococcus* and *Clostridium* are positively associated with obesity. Following LSG (laparoscopic sleeve gastrectomy), a decrease in the genus *Faecalibacterium* was reported, while this genus increased following RYGB (Roux-en-Y gastric bypass). This phylum is made up of all Firmicutes genera. The microbiota composition is related to body weight and obesity at the species level within the Lactobacillus genus, including Lactobacillus reuteri and *Lactobacillus gasseri* and *Lactobacillus plantarum* [44]. Researchers found that *Akkermansia muciniphila* abundance in obese mice was lower than that in non-obese mice. Further, increasing its intestinal abundance either with oligofructose or live culture gavage resulted in decreased endotoxemia, body fat, increased insulin sensitivity, and improved gut barrier integrity. There may be a lack of consensus regarding the relationship between specific bacteria and obesity due to different methods used for metagenomics sequencing, differences in the microbial load of samples, and the inability to determine the key bacteria contributing to obesity at the phylum level [45]. Obese people have an unbalanced gut microbial community with a low diversity; therefore, increasing the diversity of gut bacteria may be more effective for preventing obesity than feeding them or removing them.

Conclusions

Obesity has been linked to many gut microorganisms. As a result, they increase energy absorption, increase central appetite, enhance fat storage, contribute to chronic inflammation, and regulate circadian rhythms. As the gut microbiota is complex and diverse, further research is needed to understand how the gut microbiota induces obesity. Several factors contribute to obesity, including genetics and environment. Scientists around the world continue to struggle with finding solutions to reduce the magnitude of the problem due to the wide range of comorbidities that are associated with excess body weight. The etiology of obesity is influenced by a wide range of factors. A study has been conducted on changes in gut microbiota composition as one of them. Intestinal bacteria can play a vital role in maintaining metabolic balance through their complex, multifunctional system. Those with metabolic diseases (e.g., obesity with associated conditions) have altered gut microbiotas. There has not yet been a complete explanation of the mechanism underlying this relationship. Even so, the studies reveal that a few molecular pathways are involved. Dietary fiber is converted into SCFAs by the gut microbiota, which could be absorbed or excreted. According to studies, SCFAs may help maintain a healthy body weight. Incretin, GIP, PYY, and GLP-1, and GLP-2 are gut hormones that influence lipid metabolism on a molecular level. The hormones in question contribute to the regulation of satiety and glucose metabolism, which may alleviate insulin resistance and limit the development of obesity. In contrast, consuming an excessive amount of SCFAs could reduce this beneficial metabolic effect due to an increase in energy supply. The role of SCFAs in obesity remains controversial for this reason. There is no scientific evidence to support the link between the composition of gut microbiota and obesity, but patients with unbalanced and undifferentiated microbial communities are likely to develop obesity and associated comorbidities. Therefore, the gut microbiota plays a vital role in obesity prevalence, considering all the environmental and lifestyle factors that have an impact on alterations in the composition of this complex system. Potential new treatments for metabolic diseases might be derived from these conclusions. A fecal transplant as well as the use of probiotics could prevent obesity by changing the composition of gut microbiota. Efficacy and practical application of these types of treatment will require further research.

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Conflict of Interest

None..

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