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The importance of the gut microbiota in the onset and development of obesity

Ivanna Lazarchuk[1], Wojciech Plizga[1], Mateusz Sydor[1], Greta Stołecka[1], Bartosz Barzak[1], Patrycja Lipska[1], Kornelia Hankus[1], Tomasz Pytrus[2], Sławomir Woźniak[1]

Abstract

Obesity is recognized as a civilization disease constituting a serious global health problem and an increasing number of recent studies emphasize a key role of intestinal flora in maintaining the overall function of the body. In this article we want to present the link between the gut microbiota and obesity. We highlight, that the gut microbiome influences the immune system by affecting GALT maturation, enhancing intestinal barrier function and secreting various proteins and cytokines. In addition, we show that intestinal bacteria produce short-chain fatty acids that impact anti- and pro-inflammatory responses and intestinal epithelial function. Moreover, dysbiosis is closely related to the development and persistence of obesity. It causes impairment of intestinal barrier as well as prompts changes in the immune system leading to an inflammatory response. It is worth noting that probiotics and prebiotics, containing Bifidobacterium and Lactobacillus strains, have great potential in modulating the composition of intestinal microflora and alleviating metabolic disorders associated with obesity.

Running title: The gut microbiota and development of obesity

Keywords: dysbiosis, fecal microbiota transplant, intestinal microflora, obesity, probiotics, short-chain fatty acids

[1]Division of Anatomy, Department of Human Morphology and Embryology, Wroclaw Medical University, Wroclaw, Poland
[2]2nd Department of Paediatrics, Gastroenterology and Nutrition, Wroclaw Medical University, Wroclaw, Poland
***Correspondence:** slawomir.wozniak@umw.edu.pl
Full list of author information is available at the end of article

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Introduction

Overweight and obesity is a chronic complex disease defined as abnormal or excessive fat accumulation that can affect health A body mass index (BMI) above 25 indicates overweight and over 30 implies obesity [1]. In children, centile girds are essential for assessment; overweight is defined as a BMI above the 90th percentile and obesity above the 97th percentile. Currently, obesity is treated as a civilization disease due to the fact that its prevalence has increased dramatically over the past few decades. The World Health Organization estimates that in 2022, 2.5 billion adults worldwide were overweight, and 890 million of those were obese. Among those aged 5 to 19 years, 390 million were overweight and 160 million were living with obesity. Moreover, almost 39 million children under the age of 5 were overweight [1]. According to Wisevoter, a community project aimed at educating voters about their representatives but also focusing on health, the incidence of adult obesity in Poland is 24.3% and ranks 41st among other countries around the world. In contrast, the top-ranking countries for obesity are Kuwait, leading with 39.7%, followed by the USA in second place with 38.5%, and Saudi Arabia in third place with 37.6% [2]. Kelly T. et al., states that if recent trends continue, 57.8% of the world's adult population (3.3 billion people) could be either overweight or obese by the end of the year 2030 [3]. Obesity is not merely an aesthetic concern; it also has significant metabolic, inflammatory, and oxidative consequences. These include disturbances in lipid and glucose metabolism, chronic inflammation, oxidative stress, and an elevated risk of various diseases, particularly cardiovascular diseases, diabetes, and cancer [4]. The purpose of our article is to present the link between the composition of the gut microbiota and the development of obesity in humans through its influence on the immune system, nutrient metabolism and inflammatory response.

Physiology of the gut microbiota

The gut-brain axis (GBA) includes various pathways, such as metabolic, endocrine, nervous, and immune which can simultaneously influence the development of obesity. It should be noted that the intestinal microbiota, characterized by bacterial diversity, play a key role in the operation of this axis. Changes in the composition of the intestinal microflora can affect physiology of the host, consisting of metabolism and appetite regulation. Numerous studies have concluded that dysregulation of GBA may contribute to obesity [5]. However, more research is needed to fully understand these mechanisms and their implications for obesity management. The intestinal microbiota is diverse and heterogeneous. The number of bacteria in the mammalian gastrointestinal tract demonstrates a progressive increase from 10^1 to 10^3 bacteria per gram of content in the stomach and duodenum, progressing to 10^4 to 10^7 bacteria per gram in the jejunum and ileum, and reaching 10^{11} to 10^{12} cells per gram in the large intestine [6]. Bacteria in the large intestine constitute over 70% of all microbes found in the body [7]. The gut microbiota can be divided into two main categories: beneficial and opportunistic bacteria, which can potentially cause infections. The dominant bacterial phyla in the human intestine are Bacteroidetes, Firmicutes and *Actinomycetota* collectively combining around 90% of the adult intestinal flora [8]. Beneficial microorganisms include *Lactobacillus, Bifidobacterium, Enterococcus* and *Propionibacterium*, whereas the opportunistic group encompass *Bacteroides, Bacillus, Clostridium, Enterobacter, Actinomyces, Peptococcus, Staphylococcus* and *Streptococcus* [9].

Immune system and cytokines

The lymphatic system is a complex network of vessels, nodes and organs that plays a pivotal role in fluid regulation, immune system support and lipid absorption. Additionally, it is responsible for the removal of toxins, the transportation of immune cells and the maintenance of homeostasis within the body. The primary lymphoid tissues involving the thymus and bone marrow produce lymphocytes and antigen-presenting cells, that are then activated in the secondary lymphoid tissues comprising the spleen, lymph nodes and mucosa-associated lymphoid tissue (MALT) [10,11].

The gut-associated lymphoid tissue (GALT), part of the MALT, are lymphoid structures and clusters lining the intestines. These include the multi-follicular Peyer's patches (PPs), numerous isolated lymphoid follicles (ILFs) and the appendix in humans [12]. The main role of GALT is to identify and process antigens from food and commensal bacteria, simultaneously eliminating detrimental ones [13]. Studies on germ-free (GF) mice have shown that GALT maturation is intimately related to the gut microbial colonization [14,15]. GF animals have a reduced number and size of PPs and mesenteric lymph nodes (MLNs) [16] as well as impaired development of ILFs when compared to their wild-type counterparts [17]. In addition, modified microvilli formation patterns and a slower cell replacement rate in the intestinal epithelial cells (IECs) have been observed in GF animals [18]. In obese individuals, there can be a disruption in the balance of different types of microbes in the gut, a condition known as intestinal dysbiosis. This can lead to an impairment of the GALT-promoted intestinal barrier as well as trigger alterations in the immune system leading to an inflammatory response [19]. The gut microbiota also protects the intestines against colonization by various bacteria, viruses and parasites. The IECs form a defensive barrier that separates

the content of the gut lumen from the immune system cells. Commensal bacteria enhance this barrier function by modifying the expression and localization of toll-like receptors (TLRs) on epithelial cells [20]. For instance, they induce the production of antimicrobial defensins by Paneth cells by activating their myeloid differentiation primary response 88 (MyD88)-dependent TLRs consequently limiting bacterial penetration of body tissues [21]. Paneth cells are also known to generate the, expressed in the ileum, antimicrobial C-type lectin RegIIIγ, which has been found to be stimulated by the gram-negative bacterium *Bacteroides thetaiotaomicron* [22]. Interestingly, the expression of RegIIIγ triggers inflammation and eradicates gram-positive bacteria. This suggests that the bacteria in the intestines may be directing the gut's innate immune responses to defend their habitat [23]. Another type of TLR, TLR5 expressed on dendritic cells (DCs) is activated by microbial flagellin, a protein present in flagellated bacteria, prompting the production of interleukin-22 (IL-22), thereby initiating protective pathways and preventing low-grade inflammation [24]. In addition, TLR5 stimulation promotes the differentiation of naive B cells into immunoglobulin A-producing plasma cells [25]. IgA provides passive immunity in gastrointestinal tract by inhibiting pathogen adhesion and neutralizing their activity [26,27]. What is more, gut microbiota can affect the development of regulatory T cells (Treg) and T helper cells (Th) by altering their balance, resulting in inflammatory response. For example, colonization of the small intestine by commensal Clostridia-related segmented filamentous bacteria (SFB) induces the development of Th17 cells leading to increased secretion of IL-17 and IL-22 [28]. Additionally, SFB adhesion to epithelial cells promotes the release of serum amyloid A, contributing to the production of IL-1β and IL-23 in phagocytes [29,30]. In contrast, *Bifidobacterium infantis* boosts the levels of Treg and lowers the levels of Th1 and Th17 cells by stimulating the activity of retinaldehyde dehydrogenase [31]. Intriguingly, short-chain fatty acids (SCFAs), the bacterial fermentation products, also happen to regulate the number and function of intestinal Treg, thus preventing the onset of diseases [32]. Furthermore, intestinal dysbiosis can result in a continuous inflammatory reaction in people with obesity. This has been linked to a rise in obesity-related diseases, including cardiovascular disease [33] and type 2 diabetes [34]. This is most likely due to higher concentration of lipoproteins (Lps), particularly low-density lipoprotein cholesterol (LDL-C), in such individuals [35]. Lps, which play a crucial role in the absorption and transport of lipids, can trigger inflammation [36]. This is seen in conditions like atherosclerosis, where inflammation causes the atherosclerotic plaque to become unstable, leading to major adverse cardiac events [37]. Moreover, increased levels of Lps can cause metabolic endotoxemia that has been associated with the development of insulin resistance commonly observed in obesity [38,39].

Nutrient metabolism

The composition of the gut microbiota is largely dependent on the quantity of undigested polysaccharides present in the diet. Bacteria ferment microbiota-accessible carbohydrates to generate SCFAs such as acetate, butyrate and propionate [40]. SCFAs play a crucial role in balancing the anti- and pro-inflammatory response, and promoting the integrity of the intestinal epithelium by maintaining symbiosis [41]. Rich microbiota diversity caused by a high-carbohydrate diet correlates with elevated SCFA production [42]. The concentration of SCFAs also differs based on location within the colon: it is lower in the distal segment and higher in the proximal segment, which can be attributed to the greater availability of carbohydrates. Additionally, the variety of metabolites produced by the gut microbiota evolves with age: in adults, propionate and butyrate are more prevalent, whereas in newborns, acetate is more dominant [41]. Breastfeeding promotes colonization by acetate-producing intestinal flora due to the oligosaccharides present in mother's milk. Acetate is mainly produced by *Bifidobacterium*, *Prevotella*, *Bacteroides* and *Akkermansia muciniphila* [43]. The predominant propionate-producing bacteria are *Bacteroides*, *Propionibacterium*, *Veillonella* and *Ruminococcus* [44,45]. Whereas butyrate is generated by many bacteria such as *Roseburia*, *Clostridium*, *Eubacterium*, *Fusobacterium*, *Faecalibacterium* and *Coprococcus* [46]. The effects of butyrate are strongly dependent on the food consumption, age or chronic diseases. For example, butyrate increases glucose uptake by stimulating adipogenesis and lipid accumulation in people with diabetes [47]. However, many studies have shown that butyrate supplementation in high-fat diets reduces weight gain and fat buildup preventing diet-induced obesity [48–53]. Furthermore, research by Sa'ad H Al-Lahham et al., has shown that propionate decreases the levels of fatty acids in the liver and blood, curbs food intake, and enhances insulin sensitivity in tissues, thereby preventing obesity [54].

Individual SCFAs exhibit varying binding affinities with G-protein-coupled receptors (GPRs) such as GPR43 and GPR41. GPR43 is mainly expressed on endocrine L-cells that are responsible for the release of incretin hormones such as peptide YY (PYY) and glucagon-like peptide-1 (GLP-1). They control the secretion of insulin, consequently limiting food intake and reducing body mass. However, a high-fat diet can cause elevated expression of GPR43 on subcutaneous adipose tissue leading to increased fat storage in adipocytes [55]. GPR41 is expressed in the colonic mucosa in PYY-secreting cells, in the co-

lonic smooth muscle, and in the peripheral nervous system [55]. A study conducted by Kimura et al., suggests that activation of GPR41 by SCFAs triggers the sympathetic nervous system thereby regulating body weight [56]. Moreover, it has been reported by some researchers that the stimulation of GPR41 leads to the production of leptin, a hormone produced by adipose tissue, triggering feelings of satiety [57].

Lipid metabolism

The gut microbiota affects cholesterol metabolism through different mechanisms. Some intestinal bacteria produce bile salt hydrolase (BSH), which deconjugates bile acids in the intestine. This process increases the amount of free bile acids, leading to increased excretion of bile acids and their decreased reabsorption into the liver. Since bile acids come from cholesterol, this reduces the amount of cholesterol available to be converted into bile acids, resulting in lower blood cholesterol levels [58]. In addition, some bacterial species, such as *Clostridium*, are involved in biochemical modifications of bile acids in the large intestine, such as dehydroxylation and epimerization. These processes can change the composition of bile acids, therefore affecting cholesterol metabolism [59].

Intestinal bacteria ferment unabsorbable polysaccharides to produce SCFAs, inhibiting the activity of HMG-CoA reductase, a key enzyme in cholesterol synthesis. In addition, SCFAs can increase the expression of LDL receptors (LDLR) on the cell surface, increasing the removal of LDL-C from the bloodstream, further lowering serum cholesterol levels [59]. The gut microbiota, including probiotics such as *Bifidobacterium*, *Lactobacillus* and *Clostridium* can also convert cholesterol into coprostanol, a form less digestible by the body. This process limits the absorption of cholesterol into the bloodstream, consequently promoting its elimination from the body through the feces [59].

Dysbiosis concept

Dysbiosis can be defined as an imbalance between microbial species, changes in their functional structure and metabolic activity. It can be divided into three types: loss of beneficial organisms, overgrowth of potentially harmful organisms and loss of overall microbial diversity [60]. Significant number of preclinical studies in mouse models provide the basis for understanding the composition of the intestinal microflora and its potential role in the host's energy metabolism and the development of obesity. A study conducted by Ley RE et al., revealed that gut microbiota contribute to fat storage in mouse models, finding that wild-type mice contained 42% more body fat than their GF counterparts [61]. Notably, obesity, leptin levels, insulin resistance and metabolic rate were all increased in GF mice colonized with commensal microorganisms. A comparative analysis of obese and lean mice revealed a 50% reduction in Gram-negative *Bacteroidetes* and an accompanying increase in Gram-positive Firmicutes among the obese mice [62].

The predisposition to increased body fat or obesity is determined by the Firmicutes:*Bacteroidetes* (F:B) ratio. Obese individuals had up to 90% fewer *Bacteroidetes* and more Firmicutes than lean individuals. This ratio may change as a result of adequate weight loss by reducing the intake of a high-fat or high-carbohydrate diet [63]. The influence of intestinal microbiota on host energy acquisition is associated with the role of Firmicutes and *Bacteroidetes* in obesity. Factors that can disrupt the normal composition of our gut microbiota can be divided into modifiable variables such as diet, antibiotics, physical activity, and non-modifiable variables such as age, habitat, genetics, and clinical factors. For example, overweight and obese people sometimes show an increase in *Bacteroidetes* over Firmicutes, while in other cases, differences occur at the genus and family level but not at the phylum level. Studies conducted on a Korean adolescent population found higher levels of *Bacteroides* in the normal weight group while obese participants showed markedly higher amounts of *Prevotella*. Additionally, the risk of obesity was also associated with lower abundances of *Bifidobacterium* or *Akkermansia muciniphila* and not just the F:B ratio. Therefore, changes in gut microbiota, in response to diet, must be interpreted in the context of specific study populations [63]. In addition to *Bacteroidetes* and Firmicutes, other species of gut microbiota are associated with aspects of energy metabolism and obesity. Increased levels of *Bifidobacterium* have been shown to correlate with increased SCFA levels, decreased luminal lipopolysaccharide levels and improved intestinal barrier function. Not surprisingly, obese people have lower abundances of *Bifidobacterium* and *Bacteroides thetaiotaomicron*. Moreover, a bacteria called *Enterobacter cloacae* isolated from the feces of the obese human and inoculated into GF mice caused obesity and insulin resistance in those animals [62]. Similarly, mice fed with a high-fat diet and colonized with *Clostridium ramosum* experienced a more potent increase in body weight and fat accumulation. This was accompanied by an upregulation of glucose transporter 2 (GLUT2) and fatty acid translocase [64].

In addition, other species of gut microbiota such as *Akkermansia muciniphila*, *Clostridium histolyticum* and *Faecalibacterium prausnitzii* also showed a correlation between energy metabolism and obesity. The study by Dao MC et al., revealed that people with increased amounts of *Akkermansia muciniphila* had a lower BMI and exhibited a strong metabolism. Moreover, individuals with elevated baseline counts of *Akkermansia muciniphila* showed better improvement in insulin sensitivity after a calorie-restrictive diet compared to those with low baseline counts of this

bacterium [65]. Furthermore, metformin intake by diabetic patients contributed to greater abundance of *Akkermansia muciniphila* and SCFA-producing bacteria [66]. Weight loss has also been linked to a reduction in *Clostridium histolyticum*, a highly proteolytic group that produces acetate as its main metabolic end product, therefore stimulating lipid synthesis. *Clostridium histolyticum* also produces proteases that have cytotoxic effects on cells and tissues, potentially serving as pathogenic elements in the intestinal environment [67]. What is more, the microbiota of healthy adults is dominated by *Faecalibacterium prausnitzii*, identified as a butyrate-producing bacterium that shows an inverse correlation with various proinflammatory markers. In obese people, the number of *Faecalibacterium prausnitzii* is reduced compared to people of normal weight, therefore causing chronic inflammation [68,69].

Treatment

Probiotics and prebiotics

Probiotics are live, non-digestible microorganisms that, when administered in appropriate amounts, provide health benefits by selectively stimulating the growth or activity of beneficial bacteria [70,71]. Probiotics offer their benefits through four main mechanisms: competing with nutrients and adhesion sites to hinder pathogenic bacteria, enhancing the intestinal barrier function, immunomodulation, and influence on other organs of the body via the immune system and neurotransmitter production. Probiotics are mainly gram-positive bacteria such as *Lactobacillus*, *Bifidobacterium* and *Enterococcus* being the most commonly utilized strains in human nutrition [72]. It is noteworthy that numerous studies have shown the effectiveness of probiotics in ameliorating obesity [73,74]. Probiotics containing *Bifidobacterium* have been found to have positive impacts in mice and rats fed with a high-fat diet, primarily by enhancing gut barrier function, reducing bacterial translocation and improving inflammation, insulin sensitivity, fat accumulation, as well as cholesterol and triglyceride levels in the blood [75]. Supplementation of *Lactobacillus* in glucose-tolerant humans increase secretion of insulin, C-peptide, and proglucagon-derived gut peptides while parameters affecting insulin sensitivity, such as body mass and ectopic fat content, alongside systemic inflammation or oxidative stress, show no alteration [76].

The most commonly examined prebiotics include both inulin and various forms of fructo-oligosaccharides. These prebiotics mainly affect gut microbial composition, enhancing the growth of *Bifidobacterium* and *Lactobacillus* [75]. Supplementation with fructooligosaccharides and isomaltose in children with simple obesity and Prader-Willi syndrome led to improved glucose tolerance and reduced body weight, cholesterol, triglyceride and LDL levels.

Fecal microbiota transplant

Fecal microbiota transplant (FMT) involves the infusion of a liquid filtrate containing fecal bacteria and other microorganisms from a healthy donor into the recipient's intestine to cure a specific disease. Conclusion of Aron-Wisnewsky J et al., research indicates that the gut microbiome in obese people increase energy storage compared to lean people with the same caloric intake. Furthermore, FMT from obese donors to germ-free recipients partially transfers weight gain [77]. This has led to speculation that FMT from lean donors may help to reduce weight in overweight or obese people [77,78]. However, recent studies have shown mixed results. In mice, FMT from lean donors sometimes led to increased weight gain, and in humans, FMT has shown the potential to induce weight gain in malnourished patients by restoring healthy gut microbiota and energy storage [79]. Notably, in human studies, FMT from lean donors did not result in weight loss in overweight or obese patients [80]. There are also concerns about the careful selection of donors to avoid the transmission of infectious diseases and unintended weight gain. Interestingly, FMT from bariatric surgery donors in obese, insulin-resistant men, did not improve insulin sensitivity or body weight, whereas FMT from donors with metabolic syndrome worsened insulin responsiveness [77]. Overall, further research is needed to understand the specific effects of FMT and to identify appropriate donors to achieve desired therapeutic outcomes.

Conclusions

In this article, we presented a complex and multifaceted link between gut microbiota and obesity, covering different physiological, metabolic and immune pathways. We showed that the balance between Firmicutes and *Bacteroidetes* plays a key role in energy metabolism and fat storage. Dysbiosis is closely related to the development and persistence of obesity. It causes impairment of intestinal barrier as well as prompts changes in the immune system leading to an inflammatory response. It is worth noting that probiotics and prebiotics, containing *Bifidobacterium* and *Lactobacillus* strains, have great potential in modulating the composition of intestinal microflora and alleviating metabolic disorders associated with obesity. These strains, along with inulin, have shown positive effects on intestinal barrier function, inflammation, and metabolic health. In addition, there are other methods such as the fecal microbiota transplantation, that is accomplished by transferring beneficial microbial communities from healthy donors to obese people. Unfortunately, the efficacy of this procedure is highly debatable and, as a consequence, it is not widely used in the treatment of obesity. Many researchers emphasize the relationship of intestinal microflora

in the development of obesity but the exact mechanisms of its influence have not yet been discovered. Future research should focus on identifying specific species associated with obesity, explaining causal relationships between microbiological changes and metabolic outcomes, and developing targeted microbiota-based therapies.

Ethical approval
The study was a descriptive one. No humans or animals were a subject of examinations.

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Corresponding author
Sławomir Wozniak MD, PhD, Division of Anatomy, Department of Human Morphology and Embryology, Wroclaw Medical University, Chalubinskiego 6a, 50-367 Wroclaw, Poland; phone: +48717841331; email: slawomir.wozniak@umw.edu.pl.

Conflict of interest
The authors declare they have no conflict of interest.

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