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The role of gut microbiota in obesity and its potential therapeutic treatments - A Literature Review

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Abstract

Background. Obesity is a complex disorder driven by genetics, diet, and gut microbiota. The microbiome critically influences metabolic health, energy harvesting, and hunger via the microbiota-gut-brain axis, with gut dysbiosis strongly linked to obesity and cardiometabolic diseases.

Aim. This review summarizes how gut microbiota influences fat accumulation and explores microbiome-targeted therapies for obesity management.

Material and methods. This comprehensive PubMed literature review evaluates five microbiome-targeted obesity interventions (probiotics, prebiotics, symbiotics, postbiotics, and FMT). The analyzed research spans from early germ-free animal models to modern human clinical trials.

Results. Animal studies demonstrate that obesity is transmissible via gut microbiota and that interventions (like probiotics and FMT) successfully improve metabolic profiles, boost satiety

hormones, and reduce inflammation. However, human clinical trials show mixed results: while metabolic markers (e.g., glucose tolerance) often improve, sustained weight loss remains highly variable and depends heavily on specific bacterial strains, dosage, and donor-recipient compatibility.

Conclusions. The gut microbiome is a major factor in obesity and a promising therapeutic target. While treatments like probiotics, prebiotics, and FMT improve overall metabolic health, further research on treatment optimization, patient compatibility, and long-term safety is required before their standard clinical application for weight loss.

Keywords: gut microbiota, obesity, probiotics, prebiotics, symbiotics, dysbiosis, FMT, postbiotics

1. Introduction

1.1. Obesity

Obesity is a disorder in which there is an excessive increase in weight compared to height, caused by the accumulation of excess fat tissue [1,2]. The pathophysiology of obesity is complex, and the etiological triad of the genome, diet, and gut microbiota contributes to the pathophysiology of obesity through immunological response, energy harvesting, and systemic inflammation in the host [1]. In addition to environmental factors such as dietary changes, obesity is influenced by genetics [3]. Obesity has a genetic component, but is influenced by demographics, epigenetics, appetite control, lifestyle, and hormone signaling [4]. From a clinical perspective, obesity is recognized as a global public health risk that is associated with metabolic syndrome, type 2 diabetes mellitus, cardiovascular disease, nonalcoholic fatty liver disease, and certain cancers [5, 6].

Epidemiologists consider obesity to be the disease of the twenty-first century, among both the children and adults population, and one of the most significant public health threats of the modern era [1, 5, 7]. The epidemic has spread rapidly across Western societies over the last four decades, and worldwide prevalence has nearly tripled since 1975 [3, 4]. Recent data from the WHO show that over 39% of adults globally are overweight, and over 13% are obese [6,

8]. In response to this growing prevalence, associated with a global burden of cardiometabolic risk factors, such as insulin resistance and dyslipidemia, novel treatment approaches, such as GLP-1 receptor agonists and microbiome-targeted therapies, have been developed.[5, 6, 9].

1.2. Gut microbiota

The gut microbiota, also known as the gut microbiome, is a dynamic community of microorganisms within the human digestive tract consisting of bacteria, fungi, viruses, phages, protists, nematodes, protozoa, and archaea [5, 6, 10]. Since this ecosystem coevolved with its host, it is now understood to function as an organ with metabolic, immunologic, and endocrine-like functions that play a vital role in maintaining human health [11]. In terms of the physical nature of the microbiota, it is estimated that there are 100 trillion microorganisms comprising 1.5 kg of the total genome, which equates to about 1 kg of body weight [11, 12]. In comparison to the human genome, this population is 100–150 times more genetically diverse than the human genome and ten times more abundant than all human cells in the body [10, 12].

These microorganisms are not distributed evenly; greater than 70% of all body microorganisms reside in the large intestine, and the concentration of bacteria increases from the proximal to the distal regions of the GI tract [13]. The colon contains 10^{12} microbial cells per gram of content, whereas the stomach contains about 10^{1}[13]. Most of these species are anaerobic and belong to two major phyla: Firmicutes, which comprise 60–80%, and Bacteroidetes, which comprise 20–30% [12, 13]. Other phyla present but less common include Actinobacteria, Proteobacteria, Verrucomicrobia, Fusobacteria, and Cyanobacteria [12, 13]. The primary methanogenic archaeon species in these groups is Methanobrevibacter smithii [14].

Functionally, the gut microbiota establishes a mutualistic symbiosis in which the microbes live in harmony with the host by performing essential functions that the human body cannot accomplish itself [11, 12]. These include fermentation of otherwise indigestible food components, production of essential micronutrients and vitamins (such as B and K), metabolism of dietary toxins, and regulation of intestinal angiogenesis and immune system maturation [11, 13]. A microbiota with high diversity and richness is generally considered healthy, whereas dysbiosis, a disruption of this composition, has been associated with immune disorders, obesity, type 2 diabetes, and diseases of the heart, liver, or brain [10, 11]. The microbiota-gut-brain axis theory, which states that metabolites produced from bacteria can

influence metabolic health through modification of the gut-brain axis, supports this connection [10]. Research of the microbiota of older adults is both challenging and advantageous, because the gut microbiota is impacted by many hosts and environmental factors, such as genetics, lifestyle, diet, physical activity, and diseases [15, 16].

2. Research materials and Methodes

A comprehensive literature review was conducted to summarize current knowledge regarding the gut microbiota in the context of obesity and emerging treatment perspectives. A systematic search of databases, including PubMed, was performed to identify relevant publications. The search strategy utilized combinations of the following keywords: "obesity," "gut microbiota," "FMT," "probiotics," "prebiotics," and "symbiotics." The included research spans from early foundational experiments using germ-free animal models to modern preclinical and human clinical trials.

3. Main body

3.1. The microbiota-gut-brain axis

The microbiota-gut-brain axis allows for two-way communication between the brain and the GI tract via three main signaling pathways: immunological, endocrine, and neural [10]. The immunological pathway involves the vagus nerve transmitting information directly from the gut to the hypothalamus to help the host regulate hunger and energy balance[10]. The endocrine pathway depends on the microbiota digesting carbohydrates to produce SCFAs and other metabolites that stimulate the production of key hunger and satiety-related hormones such as GLP-1 and PYY [10]. Since obese individuals often exhibit low levels of these hormones, it is thought that these hormones are necessary for controlling food intake and body weight [10]. Furthermore, the immune pathway involves the relationship between the microbiota and the immune system to maintain the integrity of the intestinal barrier, which if disturbed, may be associated with the onset of cardiometabolic disorders such as type 2 diabetes and obesity and is capable of inducing inflammation [10]. Finally, further research into the axis and its benefits against inflammation and improving intestinal barrier function brings optimistic possibilities for innovative obesity management methods [10].

3.2. Gut microbiota and Obesity - Evidences from germ-free animal models

The exact causative function of gut microbiota in the pathogenesis of obesity remains an open question among different hypotheses in the scientific literature [5]. The first evidence of the influence of the microbiota on the host's body mass came from studies involving germ-free animals maintained in isolators. These mice required 30% more energy to sustain their body mass compared to conventionally reared mice, based on pioneering results published in 1983 [11]. The hypothesis about the essential role of gut microbiota in the acquisition of fat mass and energy was subsequently confirmed by novel research, especially from Jeffrey Gordon's laboratory [5]. These scientists found that conventionally raised mice have substantially higher amounts of both total and gonadal body fat compared to germ-free mice, although germ-free mice consume greater amounts of food [11]. In addition, several other studies point out that germ-free mice exhibit strong resistance to diet-induced obesity, gaining lower amounts of body fat and weight compared to their conventional littermates despite eating identical amounts of calories through a high-fat diet [5, 11, 13].

It's interesting to note that scientists have shown that the obese phenotype is transmissible; transferring the gut microbiota from conventional or obese subjects into germ-free mice can result in a significant increase in body fat mass along with insulin resistance and partially replicates the increased body weight [1, 5, 11]. The observation that the gut microbiota of obese subjects contains more genes encoding enzymes for carbohydrate metabolism, giving them a greater capacity to extract energy and produce short-chain fatty acids, is one of the biological mechanisms that researchers have proposed to explain this phenomenon in various studies [13].

Furthermore, the intestinal expression of angiopoietin-like 4, an inhibitor that causes increased cellular uptake of fatty acids and triglyceride accumulation in adipocytes, is suppressed by the inoculation of a gut microbiota [11]. The bacterial synthesis of short-chain fatty acids, which bind to particular G protein-coupled receptors expressed in the intestinal epithelium and adipose tissue, is another important mechanism that may directly promote the expression of leptin and adipogenesis [13].

On the other hand, the lean phenotype observed in germ-free mice is associated with elevated levels of phosphorylated AMP-activated protein kinase, an enzyme that stimulates fatty acid oxidation in skeletal muscle, enhanced glucose tolerance, and altered cholesterol metabolism

[11]. The effects of microbiota on fat storage are more complex than initially thought; for example, resistance to diet-induced obesity can vary based on the genetic background of the mice and the specific composition of the diet [11].

In humans, less diverse and differently composed gut microbiota has been linked to obesity, first by a shift in the relative abundance of the two major phyla Firmicutes and Bacteroidetes [2, 5]. After this overly simplistic view of the two major phyla was challenged, the focus has turned to identifying specific bacterial strains, including Bifidobacterium and Akkermansia muciniphila, associated with the pathophysiology of obesity [1, 5]. While weight loss interventions such as gastric bypass have repeatedly shown that changes in the composition of the microbiota are directly linked to physical weight reduction, much more research is needed to confirm these metabolic mechanisms in humans [5, 13].

3.3. Potential therapeutic treatments

There are numerous potential therapeutic treatments available that aim to modulate the composition of the gut microbiome to target the relevant metabolic pathways involved in obesity and related metabolic diseases [17]. To explore these interventions, this article focuses primarily on the use of probiotics, prebiotics, symbiotics, postbiotics, and fecal microbiota transplantation.

3.3.1. Probiotics

According to the World Health Organization, probiotics are defined as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host [6, 18]. These helpful microbes primarily act by outcompeting pathogenic bacteria, strengthening the intestinal barrier, and modulating immune responses [6, 18]. Lactobacillus and Bifidobacterium strains are some of the most common and traditional probiotics that help maintain the balance of the human intestinal microecology [6, 19]. Thanks to recent technological developments like multi-omics, next-generation probiotics are being studied for their potential to treat specific metabolic diseases, including obesity [6]. Increasing these beneficial populations in the gut microbiota of obese individuals is now recognized as a promoting strategy to combat obesity and associated disorders [17, 20].

The anti-obesity effects of probiotics occur through a range of mechanisms, affecting both energy homeostasis and lipid metabolism [21]. At the intestinal level, they normalize the Firmicutes to Bacteroidetes ratio, stimulate short-chain fatty acid production, and detoxify bacterial endotoxins (e.g., lipopolysaccharides) [21]. Some strains decrease intestinal permeability and enhance barrier function, lowering endotoxemia and systemic low-grade inflammation, which are central to the pathogenesis of metabolic diseases [6, 10]. In addition, probiotics inhibit adipogenesis by targeting signaling pathways such as the NLRP3 inflammasome and Toll-like receptors, and may also stimulate fatty acid oxidation or inhibit lipoprotein lipase activity, thus decreasing the deposition of fat [17, 21]. Beyond the gut, these microbes affect the microbiota-gut-brain axis through the modulation of hypothalamic inflammation and the increase of key gut peptides such as GLP-1, leptin, cholecystokinin, and peptide YY that suppress appetite and slow gastric emptying [10, 21]. Even some probiotics directly emulate satiety, including Hafnia alvei HA4597, which synthesizes a ClpB protein that is involved in appetite regulation in a manner similar to alpha-MSH [21].

Although reported results are variable, a growing body of preclinical and clinical evidence demonstrates the potential weight management and metabolic health benefits of certain probiotic strains [6]. For instance, various Lactobacillus and Bifidobacterium strains have been shown to decrease body fat mass, enhance blood glucose homeostasis, and reduce serum triglycerides in animal models [6, 17]. For instance, Akkermansia muciniphila supplementation has been shown to prevent obesity in mice by normalizing dyslipidemia and insulin resistance, and it is regarded as a critical bacterium for weight loss [18, 19]. A comprehensive systematic review of randomized control trials also suggests that high-dose probiotic supplementation in overweight and obese populations may be a promising intervention, which typically leads to a moderate but statistically significant decrease in body mass index [10]. Clinical trials in adults have demonstrated significant reductions in low-density lipoprotein cholesterol, visceral adipose tissue, and waistline size with oral supplementation with certain strains [6, 17]. Combination supplements such as VSL#3 have also demonstrated potential in human subjects by improving insulin sensitivity and lipid profiles [18].

While these results are encouraging, the evidence for probiotics as an effective treatment of obesity is mixed and studies are highly heterogeneous [6, 10]; in some recent meta-analyses of randomized controlled human studies, the association between probiotic treatment and weight

loss was statistically insignificant [18]. The efficacy of probiotic interventions is variable and depends on several factors, including the strain, the dose, the duration of treatment, and host-related factors, such as sex [10, 21]. Future research will need to concentrate more on human populations in order to identify the optimal supplementation strategies because findings from mouse models cannot be directly extrapolated to important human biological components[10]. To develop probiotics as a dependable treatment for metabolic diseases, it is still necessary to identify the best bacterial species, minimize long-term side effects, and standardize treatment parameters[10, 18].

3.3.2. Prebiotics

Prebiotics are non-digestible food ingredients that are selectively fermented by host-associated microbiota, positively affecting the host through promotion of the growth or activity of certain colon bacteria, such as Lactobacillus and Bifidobacterium[10, 17, 21]. Whereas probiotics introduce new beneficial microorganisms into the gut, prebiotics serve as nourishing substrates that increase the abundance and activity of resident bacteria to prevent gut dysbiosis and promote host health[18, 21]. The most common forms of these dietary fibers are inulin, fructooligosaccharides (FOS), galactooligosaccharides (GOS), resistant starches, and human milk oligosaccharides (HMOs) [21]. These functional components are not hydrolyzable and are not absorbed by the small intestine; they are naturally present in foods such as fruits, vegetables, grains, garlic, onions, bananas, and chicory root [10, 21].

Prebiotics are the main energy source for gut bacteria and the fermentation of prebiotics produces short-chain fatty acids (SCFAs), mostly acetate, propionate, and butyrate [10, 21]. SCFAs bind to specific receptors (GPR41 and GPR43) to modulate host metabolism and release satiety hormones that reduce hunger, such as glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) [18, 21]. The release of these hormones increases satiety, decreases food intake, and enhances insulin sensitivity[21]. Prebiotics also enhance the integrity of the intestinal barrier by thickening the mucosa and expressing tight junction proteins, thus reducing the leakage of pro-inflammatory lipopolysaccharides (LPSs) into the blood circulation, decreasing endotoxemia and lowering the risk of insulin resistance and systemic inflammation that are key in the management of obesity [17, 21].

Prebiotic consumption typically prevents metabolic diseases by promoting favorable changes in the microbiota composition [10]. In various studies, prebiotics have been shown to alter this composition by enhancing the abundance of the Bacteroidetes phylum and Lactobacillus and Bifidobacterium, and reducing the abundance of the Firmicutes phylum [10, 18], which is associated with improvements in microbiota-gut-brain factors such as leptin sensitivity, glucose homeostasis, and entero-endocrine cell activity [10].

Prebiotic administration has shown great promise in treating obesity and related metabolic disorders in a number of different studies using animal models[18]. For example, a study using FOS injections in rats produced comparable reductions in appetite, fat storage, and weight gain[17], while another study examining inulin in obese rats demonstrated dose-dependent reductions in caloric intake, body weight gain, and fat accumulation[21]. Additionally, these prebiotic interventions have been shown to effectively improve insulin resistance and glucose tolerance while reducing inflammatory conditions in genetically obese mice and other rodent models [17, 18].

Prebiotics show promise as a novel treatment for obesity, as they have also been linked to weight loss and enhanced metabolic parameters in human trials [17, 18]. A study of overweight and obese children showed that oligofructose-enriched inulin supplementation significantly reduced body weight and the inflammatory marker IL-6[18]. Other clinical studies have found that prebiotic consumption, such as FOS in obese women or GOS supplementation in general participants, can increase beneficial gut bacteria, improve lipid profiles, and lower systemic inflammation markers[10, 21]. Natural prebiotics, such as HMOs through breastfeeding, have also been shown to prevent childhood obesity[21].

While these findings are encouraging, however, the evidence of the role of fiber supplementation and SCFAs in human metabolic health is mixed and limited, with some research suggesting that acetate produced by microbes may even be obesogenic and hyperglycemic, depending on the delivery mode[10]. In addition, high doses of prebiotics can lead to gastrointestinal side effects, such as bloating and diarrhea, and the optimal dose and long-term safety for specific clinical applications have not yet been firmly established[21]. Therefore, more research is needed to fully characterize specific microbial pathways to support

standardized prebiotic recommendations in future diet and weight-reduction interventions [10, 18, 21].

3.3.3. Symbiotics and Postbiotics

Probiotics can be combined with prebiotics to create a product called synbiotics (or symbiotics) to create a synergistic effect to increase the viability of the probiotic in the gut [10, 21]. Postbiotics are non-living microorganisms or their products, such as microbial metabolites or cell wall components, that confer health benefits through the use of dead bacteria[21]. Postbiotics are safer than symbiotics because the risk of infection and antibiotic resistance gene transfer is low and because they are easier to transport and store [21].

In animal models, such as mice fed a high-fat diet, symbiotic supplementation results in greater anti-obesity effects than probiotic or prebiotic treatments alone, and can result in decreased weight gain, reduced accumulation of adipose tissue, and improved glucose tolerance[21]. Since the prebiotics are promoting the growth of the probiotics, the symbiotic combination can correct gut dysbiosis by altering the composition from obesity-associated bacteria to non-obesity-associated bacteria[21], which makes these treatments particularly effective.

Clinical trials have also demonstrated the potential of symbiotics in the treatment of human obesity, with a study lasting eight weeks, in which a specific symbiotic combination reduced BMI, total and LDL cholesterol, and serum triglyceride levels in children and adolescents with high BMI when compared with a placebo group[21]. A systematic review and meta-analysis also found that supplementing with symbiotics leads to statistically significant reductions in body weight and waist circumference, most likely mediated through alterations in gut microbiota[21].

These promising findings are not to say that the effects of symbiotics on specific metabolic markers associated with obesity are the same, however, as a 24-week randomized control trial of participants with type 2 diabetes and obesity found that symbiotic supplementation increased beneficial bacterial counts and altered butyric and acetic acid concentrations in the gut microbiome, but it did not significantly alter inflammatory markers relative to the control group [10]. In contrast, a different clinical trial with patients with type 2 diabetes found that symbiotic therapy significantly reduced bacterial translocation across the intestinal barrier, suggesting

that it could be considered as a treatment strategy for low-grade inflammation [10]. Ultimately, although altering the gut microbiome represents a promising new therapeutic avenue for the treatment of obesity, there are limited studies on symbiotics, and evidence suggests that other factors, such as when they are administered, may also be important.

The anti-obesity properties of these postbiotic components have been examined in a number of studies [21]. In one study using Caenorhabditis elegans as an animal model, researchers found that Bifidobacterium animalis subsp. lactis CECT produced lipoteichoic acid that shows anti-obesity effects by actively reducing lipid storage[21]. The beneficial effects of some microbial metabolites, particularly SCFAs, in obesity and liver metabolic function have also been well studied[21]. For example, scientists found that rats fed a high-fat diet with 5% SCFAs added to the diet had lower body weights and blood glucose levels after four weeks compared to control groups, even though total food intake was the same in all groups[21]. Moreover, SCFA-fed rats also had reduced liver total lipid levels and reduced expression of genes involved in fatty acid synthesis, suggesting that dietary SCFAs regulate lipid metabolism and fat deposition through direct host signaling[21]. Another study demonstrated that these metabolic benefits also hold true in humans in an eight-week randomized clinical trial [21]. Obese adults supplemented with the SCFA sodium butyrate on a hypocaloric diet experienced a greater reduction in visceral fat and total fat mass compared to those on a hypocaloric diet alone, and the supplement increased the expression of genes involved in lipid metabolism, such as ADIPOR1 and UCP3, demonstrating its role in energy and lipid homeostasis[21].

3.4. Fecal microbiota transplantation (FMT)

FMT, or the transfer of an entire microbial community with its metabolites from a healthy donor into the gut of a recipient, has been used to re-establish a healthy microbiome and is termed a donor-like microbiome[10, 17, 18, 21]. For example, FMT from obese mice generated a distinct metabolic phenotype in aseptic mice, which are normally refractory to diet-induced obesity[17], while in another study FMT from healthy donors dramatically improved the metabolic profiles of high-fat diet-induced obese mice [18].

Specific studies demonstrated that despite having no effect on body weight, FMT from resveratrol-treated mice to obese recipients improved glucose tolerance and decreased intestinal pro-inflammatory cytokines [21]. Another model, found that FMT from healthy

donors to mice with induced abdominal obesity was able to prevent weight gain and decreases in abdominal fat, as well as decreased systemic inflammation and restoration of the intestinal mucosal barrier [21].

The potential of FMT for obesity has shown promising preliminary results from human studies, but larger clinical trials have yielded conflicting results[18, 21]. Early pilot studies have shown that transfer of intestinal microflora from lean or emaciated donors to obese recipients with metabolic syndrome improved peripheral insulin sensitivity within six weeks[17, 18]. Moreover, FMT from Roux-en-Y gastric bypass donors to obese humans also mediated the microbiota-gut-brain axis through changes in serotonin and dopamine transporters [10]. However, recent randomized clinical trials, including the placebo-controlled trial found no significant differences between obese patients receiving FMT from lean donors and those receiving an autologous placebo in terms of mean weight loss, body composition, or metabolic markers [21]. Another subsequent meta-analysis clarified these findings, showing that while FMT led to a significantly increased caloric intake, insulin and glucose metabolism, lipid profiles, and inflammatory markers, its impact on actual weight loss was insignificant [21]. To resolve these contradictory clinical outcomes scientists investigated the relationship between human donors and recipients and concluded that enterotype compatibility is a significant factor in determining the treatment success, with lower beta diversity increasing the likelihood of successful colonization [21]. Ultimately, human trials provide insight into the treatment of metabolic disorders, but they also require additional safety research, as adverse events such as constipation, vomiting, diarrhea, and abdominal pain have been reported [17, 18].

4. Conclusions

The gut microbiome is a core component of obesity as it functions as an internal organ that regulates fat storage, metabolism, and hunger, and the link between obesity and the microbiome is supported by animal studies that show that the obese phenotype can be transferred to healthy subjects by transferring gut bacteria. Promising new therapies including probiotics, prebiotics, symbiotics, postbiotics, and fecal microbiota transplantation (FMT) to modulate the microbiome have been developed, with many showing success in improving metabolic health, insulin sensitivity, and fat reduction in animal models, but mixed results in human clinical trials, especially with regards to sustained weight loss. Finally, although microbiome-targeted therapies may be an effective treatment, more research is required to determine which therapies

are most effective, how to ensure compatibility with patients, and long-term safety before they are implemented as standard medical therapies.

Disclosure

Author's Contribution

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Declaration of the use of generative AI and AI-assisted technologies in the writing process:

AI was utilized for two specific purposes in this research. Text analysis of clinical reasoning narratives to identify linguistic patterns associated with specific logical fallacies. Assistance in refining the academic English language of the manuscript, ensuring clarity, consistency, and adherence to scientific writing standards. AI were used for additional linguistic refinement of the research manuscript, ensuring proper English grammar, style, and clarity in the presentation of results. It is important to emphasize that all AI tools were used strictly as assistive instruments under human supervision. The final interpretation of results, classification of errors, and conclusions were determined by human experts in clinical medicine and formal logic. The AI tools served primarily to enhance efficiency in data processing, pattern recognition, and linguistic refinement, rather than replacing human judgment in the analytical process.

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