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Review article

GUT MICROBIOTA AND OBESITY

CREVNA MIKROBIOTA I GOJAZNOST

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Abstract

Obesity represents a multifactorial, systemic disorder strongly associated with adverse health outcomes, including cardiometabolic syndrome. Beyond caloric imbalance between caloric intake and expenditure, recent evidence highlights the essential role of gut microbiota in the development and progression of obesity and related metabolic dysfunctions. The gut microbiota, composed of diverse bacterial species, archaea, fungi, and viruses, influences host metabolism through the production of low-molecular-weight metabolites and gastrointestinal hormones, significantly modulating energy homeostasis, appetite regulation, and insulin sensitivity. Specific bacterial taxa are implicated in either promoting metabolic health or contributing to obesity through mechanisms involving chronic systemic low-grade inflammation, increased intestinal permeability, and altered energy harvest. Dysbiosis – marked by reduced microbial diversity and compositional imbalance is consistently linked to enhanced adiposity and systemic inflammation. Dietary patterns are key modulators of gut microbial composition and function.

This review underscores the complex interplay between dietary patterns, gut microbiota-derived metabolites and host endocrine responses that contribute to dysregulation of gut–brain axis communication observed in obesity.

Keywords:
gut microbiota,
obesity,
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gut-brain axis

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Sažetak

Gojaznost predstavlja multifaktorski, sistemski poremećaj koji je snažno povezan sa nepovoljnim zdravstvenim ishodima, uključujući kardiometabolički sindrom. Savremena naučna saznanja prevazilaze tradicionalni model energetske neravnoteže između unosa i potrošnje energije, ističući važnu ulogu crevne mikrobiote u razvoju gojaznosti i metaboličkih poremećaja. Crevna mikrobiota, koju čine različite bakterijske vrste, arheje, glivice i virusi, utiče na metabolizam domaćina putem proizvodnje metabolita male molekularne mase i gastrointestinalnih hormona, i time značajno utiče na energetsku homeostazu, regulaciju apetita i osetljivost tkiva na insulin. Različite bakterijske vrste mogu povoljno ili nepovoljno uticati na metabolizam i razvoj gojaznosti i to putem mehanizama kao što su hronična sistemska inflamacija niskog stepena, povećana propustljivost creva i izmenjena energetska efikasnost. Disbioza, koja podrazumeva smanjenu raznovrsnost crevne mikrobiote i/ili neravnotežu u njenom sastavu, povezuje se sa razvojem gojaznosti i sistemskom inflamacijom. Pri tome, raznovrsnost ishrane ima značajan uticaj na sastav i funkciju mikrobiote.

Ovaj rad naglašava uzajamnu povezanost navika u ishrani, metabolita crevne mikrobiote i endokrinih odgovora domaćina, koji zajedno oblikuju poremećaje koji nastaju u gojaznosti u osovini crevo-mozak.

Ključne reči:
crevna mikrobiota,
gojaznost,
metaboliti,
osovina crevo-mozak

Introduction

Obesity is a multifactorial chronic disorder defined by excessive adipose tissue accumulation, which may manifest with aberrant regional distribution and/or compromised adipose tissue functionality (1). Despite substantial advances in biomedical research, the etiological pathways underlying obesity remain incompletely elucidated, involving a complex interplay of genetic, epigenetic, environmental, behavioral, and sociocultural determinants. Clinical obesity refers to a systemic pathological state in which adiposity exceeds physiological thresholds and precipitates dysfunction at the cellular, tissue, and organ levels. Obesity is a chronic, systemic condition marked by dysfunction across tissues, organs, or the individual as a whole, resulting from excessive fat accumulation (1). This maladaptive condition contributes to a cascade of deleterious consequences, including impaired metabolic homeostasis, endocrine disturbances, and heightened susceptibility to life-altering or life-threatening complications such as myocardial infarction, cerebrovascular accidents, and progressive renal insufficiency (1).

Conversely, the term preclinical obesity refers to an intermediate pathophysiological stage characterized by increased body fat and preserved organ function, yet accompanied by an elevated–though variable–propensity for progression toward clinically manifest obesity. Individuals in this state face increased risk for the future onset of a spectrum of non-communicable diseases (NCDs), including type 2 diabetes mellitus (T2DM), atherosclerotic cardiovascular disease, hormonally responsive malignancies, and neuropsychiatric disorders such as depression and cognitive decline (1). From a pathogenic perspective, both preclinical and clinical obesity represent critical phases in the continuum leading to cardiometabolic syndrome – a term that, before the 21st century, was conventionally referred to as metabolic syndrome or syndrome X (2).

Cardiometabolic syndrome is characterized by the co-occurrence of interrelated metabolic and hemodynamic abnormalities that collectively confer an elevated risk of chronic disease development. Its diagnostic criteria typically encompass central (visceral) adiposity, prediabetes or T2DM, atherogenic dyslipidemia, and arterial hypertension (3). The syndrome emerges from a nexus of intrinsic and extrinsic factors, including polygenic predisposition, sustained pro-inflammatory signaling, and lifestyle-related components such as nutritional imbalance and sedentarism. Importantly, cardiometabolic syndrome is recognized as a progressive condition with insidious onset, underscoring the need for early identification and the implementation of diverse management strategies aimed at mitigating long-term morbidity and mortality (3).

Over the past two decades, there has been a marked global shift in lifestyle patterns, characterized by a sustained increase in total caloric intake coupled with a significant decline in physical activity levels (4). This imbalance has contributed to the escalating prevalence of cardiometabolic syndrome. However, recent scientific advances have begun to reframe our understanding of obesity and its comorbidities, moving beyond the traditional energy-centric paradigm and shedding light on the intricate role of gut microbiota in modulating host metabolism (5,6). Emerging data underscore a dynamic and bidirectional relationship between gut microbial communities and host metabolic function (5,6). Alterations in microbial diversity, composition, and metabolite production have been shown to influence individual susceptibility to excess adiposity and related metabolic derangements. For instance, specific bacterial taxa have been implicated in promoting energy harvest from indigestible dietary substrates, shaping systemic inflammation, and influencing endocrine pathways that regulate appetite and insulin sensitivity (7). These findings suggest that gut microbiota function as both mediators and modulators of metabolic health, rendering them a potential target for preventive and therapeutic interventions in the context of obesity

and cardiometabolic disorders.

The gut microbiome plays a pivotal role in the metabolism and breakdown of various nutritional compounds, contributing approximately 10% of circulating low-molecular-weight metabolites that actively participate in host metabolic pathways (8). Consequently, it is not surprising that gut microbiota has been identified as having a significant influence on each element of cardiometabolic syndrome, especially obesity. The link between gastrointestinal microbiota and obesity is primarily mediated by gastrointestinal hormones and different metabolites produced both by human cells and gut microbiota. Dysbiosis (disruption in gut microbiota composition) is thought to contribute to metabolic dysfunction by influencing various processes, including energy extraction and expenditure, inflammatory responses, the integrity of the intestinal barrier, appetite regulation, and fat tissue metabolism (9, 10). These effects are driven by microbial metabolites that communicate with the brain, influencing neuroendocrine pathways at multiple levels of appetite and energy balance, ultimately affecting food consumption and body weight regulation (9, 10).

Insights into the physiological mechanisms underlying gut microbiota – metabolic interactions

The mutual relationship between host and gut microbiota is essential for maintaining health and disease prevention. In adults, more than 90% of the gut microbiota is composed predominantly of two major bacterial phyla: Gram-positive Firmicutes and Gram-negative Bacteroidetes, although their relative abundances vary across individuals and populations (11, 12). Other phyla, such as Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia, are present in smaller proportions but contribute to the overall microbial diversity and functional capacity (11, 12). Gut microbiota diversity and composition are influenced by a range of factors, including dietary habits, host genetic background, age, geographic location, and exposure to medications and to different environmental factors (10).

Dietary nutrient intake plays a pivotal role in shaping the composition and functional dynamics of the gut microbial ecosystem. Nutrients not only serve as substrates for microbial metabolism but also modulate the structural organization and metabolic activity of resident microbial communities (10). The gut microbiota contributes to the maintenance of the intestinal barrier integrity by competing with pathogenic microorganisms and producing bioactive compounds that enhance epithelial resilience (13). In the distal colon, where fermentable carbohydrates are largely depleted, microbial populations shift towards proteolytic fermentation (10). This metabolic shift results in the production of potentially harmful metabolites, such as ammonia, phenolic compounds, and branched-chain fatty acids, which have been associated with local mucosal toxicity and systemic metabolic disturbances. However, unbalanced diets, particularly those low in fiber and high in proteins or fat, can lead to dysbiosis and increased production of gaseous metabolites (10). These gases contribute to mucosal irritation, epithelial damage, and increased intestinal permeability – factors that collectively impair gut barrier integrity and promote inflammatory responses.

The gut microbiota contributes to the biosynthesis of several essential vitamins – including vitamin K, biotin, and select B vitamins – that the human body is unable to produce endogenously. These micronutrients serve critical functions in physiological processes such as blood coagulation, energy metabolism, and nucleic acid synthesis (13).

Gastrointestinal hormones, known as incretins, play a crucial role in regulating energy balance and metabolism by modulating appetite, insulin sensitivity, nutrient absorption and gastrointestinal motility (9, 14-16). Studies indicate a bidirectional relationship between gut microbiota and the enteroendocrine system, wherein microbial signals influence hormone secretion, and conversely, gastrointestinal hormones shape the gut microbial milieu (17). The region-specific composition of the gut microbiota along distinct anatomical regions of the gastrointestinal tract appears to differentially affect the activity of specialized enteroendocrine cell populations, which themselves secrete various incretins with region-specific and systemic metabolic effects. In the stomach's highly acidic environment, the microbial load is relatively low, and dominant taxa include gram-positive anaerobes like *Helicobacter pylori, Lactobacillus,* and *Streptococcus* species (18). The key gastrointestinal hormones produced in the stomach are gastrin, somatostatin, and ghrelin (9). They are crucial regulators of appetite, stomach emptying, gastric acid secretion, and gastrointestinal motility (9). In the duodenum and jejunum, microbial density remains relatively low, resembling that found in the stomach, but shifts significantly in the ileum, where anaerobic bacteria such as *Bacteroides, Bifidobacteria, Enterococcus,* and *Eubacteria* species become more abundant (19). In these sections of the gastrointestinal tract, the primary gastrointestinal hormones include cholecystokinin (CCK), secretin, substance P, serotonin, peptide YY (PYY), vasoactive intestinal peptide (VIP), glucagon-like peptide-1 (GLP-1), glucagon-like peptide-2 (GLP-2), glucose-dependent insulinotropic polypeptide (GIP), among others (9, 10, 20). They play a role in regulating both the exogenous and endogenous functions of the pancreas, bile secretion, gastrointestinal motility, appetite, and overall metabolism (20). The colon, although not a major site of hormone production, hosts the densest and most diverse microbial community, consisting of *Bacteroides, Clostridium, Lactobacillus, Fusobacterium, Ruminococcus, Streptococcus, Enterococcus, Eubacterioum*. These members of the colonic microbiota play a crucial role in affecting overall hormone levels and metabolic activities (9, 10). Gut microbiota modulate the gastrointestinal microenvironment by altering oxygen levels, pH, and nutrient availability, thereby affecting intestinal cell metabolism and hormone secretion (10, 13). In addition, the gut

microbiota generates metabolites that serve as intermediates or final products of microbial metabolism and contribute approximately 5 - 10% of total daily energy requirements of a human (13). These metabolites may originate directly from bacteria or may result from the transformation of dietary or host-derived substrates. These secondary compounds – such as short-chain fatty acids (SCFAs), secondary bile acids (BAs), and gases, which influence both gut-brain axis (GBA) signaling and host metabolism (10). Short-chain fatty acids produced by the gut microbiota are capable of crossing the blood-brain barrier, where they modulate microglial homeostasis (21, 22). This regulation plays a pivotal role in proper brain development and the preservation of tissue equilibrium, ultimately influencing behavioral outcomes (23).

Moreover, certain gut bacteria are capable of synthesizing host-active neurotransmitters (e.g., GABA, dopamine, serotonin), further shaping intestinal neuronal activity and systemic metabolic responses via the GBA (10, 24). Gastrointestinal hormones, in turn, modulate gut microbiota composition and function by modulating intestinal milieu, nutrient absorption, metabolic dynamics, microbial diversity, and bacterial behavior (10).

Gut microbial dysregulation in obesity: composition, function, and host interactions

Alterations in the gut microbiome associated with obesity occur at both the microbial taxonomic and functional (enzymatic and metabolic) levels, with host genetics and dietary habits playing crucial and interconnected roles in shaping these changes. Numerous studies have reported that obesity is frequently accompanied by a significant reduction in gut microbial diversity, as well as shifts in the relative abundance of specific bacterial taxa. Despite some inconsistencies in the findings, the gut microbiota associated with obesity is characterized by a decrease in members of the phylum Bacteroidetes and a compensatory increase in the members of the phylum Firmicutes, and a general decline in microbial diversity and richness (21, 25-27). The Firmicutes phylum has been linked to enhanced energy extraction from the diet through fermentation of the complex carbohydrates into SCFAs and other absorbable metabolites utilized by the host (28). Le Chatelier et al. have expanded our understanding of microbial diversity by assessing bacterial variety through gene count analysis. Profiles with a low gene count, which are frequently linked to conditions such as obesity, and chronic inflammation, are predominantly composed of microbial species such as *Bacteroides, Campylobacter, Staphylococcus* and *Ruminococcus* (26). In contrast, profiles with a high gene count are associated with beneficial species such as *Bifidobacterium, Faecalibacterium, Methanobrevibacter* and *Akkermansia* (26). David et al. have shown that dietary habits significantly impact the composition of gut microbiota, in a way that animal-based diets are associated with the presence of bile-resistant bacterial taxa such as *Alistipes, Bilophila,* and *Bacteroides*, while plant-based, fiber-rich diets support the growth of polysaccharide-degrading genera like *Prevotella* (27).

The one's diet and gut microbiota composition influence the production of different gut microbiota metabolites, which in turn affect host metabolism and energy expenditure by altering insulin sensitivity and glucose metabolism (21). Some of the most significant and extensively studied gut microbiota-derived metabolites associated with obesity and cardiometabolic syndrome include: BAs, SCFAs, trimethylamine N-oxide (TMAO), tryptophan-derived metabolites and imidazole propionate (IMP) (29-32).

These metabolites act via diverse mechanisms, including G-protein coupled receptors, nuclear receptors (e.g., FXR, PPARs), and inflammatory signaling pathways in order to influence host energy metabolism and systemic inflammation (33).

a) Bile acids

Bile acids are small molecules produced from cholesterol in the liver and stored in the gallbladder before their secretion into the duodenum. The primary bile acids, chenodeoxycholic acid (CDCA) and cholic acid (CA), are linked to glycine or taurine and play crucial roles in the digestion and absorption of lipids and vitamins. Approximately 95% of these acids are actively reabsorbed from the terminal ileum and recycled in the liver via enterohepatic circulation. Additionally, 5% of primary bile acids are converted into more than 50 secondary bile acids by gut microbiota (29). These can either be passively reabsorbed to rejoin the circulating bile acid pool or be excreted in feces (29). Secondary bile acids modulate physiological and metabolic functions via different receptors highly expressed in the liver and intestines and thus regulate transcriptional pathways involved in glucose, lipid, and cholesterol metabolism (34, 35).

In individuals with obesity, the metabolism of BAs is disrupted, which is linked to liver fat accumulation and imbalances in glucose and lipid metabolism. It is confirmed that in individuals with obesity, increased levels of total circulating bile acids are positively correlated with body mass index and serum triglycerides (36). Consumption of dietary animal fat promotes the production of taurocholic acid (TCA), which supports the expansion of the sulfite-reducing bacterium *Bilophila wadsworthia* (21). This expansion has been associated with increased intestinal permeability and inflammation. Alterations in the gut microbiota impair the ileal absorption of BAs, reduce the transformation of primary conjugated BAs to secondary BAs in the colon, and diminish bile salt hydrolase (BSH) activity, leading to the accumulation of primary conjugated BAs in the colon (21). Conjugated primary BAs induce pro-inflammatory effects on intestinal epithelial cells, whereas secondary BAs possess anti-inflammatory properties (37).

b) Short-chain fatty acids

Short-chain fatty acids, including butyrate, propionate, and acetate are the major end products of microbial

fermentation of dietary carbohydrates (38). They are the primary mediators of the interactions between the host and the gut microbiome, and play roles in numerous physiological processes such are: maintaining the integrity of the intestinal mucosa, enhancing glucose and lipid metabolism, regulation of energy expenditure, and modulation of the immune system and inflammatory responses (22, 30, 38-40). Different bacterial species have varying capacities to break down and use specific carbohydrates, resulting in a broad range of SCFAs and individual variability in SCFA profiles (41). Intestinal transit time, alongside dietary fiber intake, plays a critical role in shaping bacterial carbohydrate utilization and SCFAs biogenesis, as accelerated transit may hinder complete carbohydrate breakdown, thereby altering microbial fermentation dynamics (42). SCFAs mediate host-microbiome interactions through two major mechanisms signaling: (1) inhibition of histone deacetylase (HDAC) and (2) activation of G protein-coupled free fatty acid receptors 2 and 3 (FFAR2/3). These signaling pathways induce region-specific physiological effects along the gastrointestinal tract (43, 44). Functionally, SCFAs increase satiety, slow stomach emptying, and reduce body weight by stimulating the intestinal secretion of gut hormones such as 5-hydroxytryptamine (5-HT) and GIP (45). Propionate and butyrate mainly have anti-obesity effects by promoting the release of gut hormones that suppress appetite (GLP-1 and PYY) and by boosting leptin production and supporting insulin sensitivity (46). Butyrate suppresses triglyceride synthesis, while propionate enhances insulin secretion and modulates fat storage by promoting lipogenesis (47). Butyrate also reduces inflammation and triggers the activation of the peroxisome proliferator-activated receptor-γ (PPARγ), which helps maintain anaerobic conditions in the gut lumen (48). In contrast to butyrate and propionate, acetate is likely to have properties that contribute to obesity. This is because it serves as a substrate for *de novo* lipogenesis in the liver and adipose tissue, encourages overeating by boosting ghrelin secretion, and enhance insulin secretion, collectively contributing to increased energy storage and fat accumulation (49).

In individuals with obesity and T2DM, there is a noted reduction in the quantity of SCFAs-producing bacteria and SCFAs in fecal samples (50). However, targeted supplementation, such as inulin-propionate ester or propionate, has been shown to stimulate the GLP-1 and PYY secretion, contributing to reduced weight gain and improved metabolic parameters (22).

c) Trimethylamine N-oxide (TMAO)

The gut microbiota plays a key role in the metabolism of dietary nutrients such as choline and L-carnitine from dietary sources such as red meat, eggs, and certain types of fish. These microbial transformations result in the production of trimethylamine (TMA), which is subsequently converted to trimethylamine N-oxide (TMAO) in the liver (31). Elevated levels of TMAO are observed in individuals with obesity, T2DM, dyslipidemia and cardiovascular disease, particularly through mechanisms involving endothelial dysfunction, cholesterol metabolism impairment, enhanced platelet reactivity, and promotion of vascular inflammation (31).

d) Tryptophan metabolites

Tryptophan is an essential aromatic amino acid present in various common foods such as milk, cheese, oats, fish, and poultry. It acts as a precursor for several important metabolites, including 5-HT, kynurenine, indole, and their derivatives (51). It has been observed that over 80% of the body's total 5-HT synthesis is influenced by gut microbiota (52). Notably, 5-HT plays a crucial role in GBA signaling by influencing eating behavior and satiety, making it significant in the context of obesity development (53). Patients with metabolic disorders often exhibit elevated plasma levels of 5-HT metabolites (54). Impaired metabolism of kynurenine and indole results in reduced production of certain incretins and interleukins, contributing to increased intestinal permeability, which leads to inflammation, insulin resistance, and liver steatosis (55).

e) Imidazole propionate (IMP)

The gut microbiota converts histidine, another essential aromatic amino acid obtained from dietary sources, into a bioactive microbial metabolite, imidazole propionate (IMP). Elevated levels of IMP have been observed in individuals consuming an unhealthy, high-fat or Western-type diet and are primarily produced by specific gut bacteria, including *Streptococcus mutans* and *Eggerthella lenta*. IMP has been shown to impair insulin signaling and promote low-grade inflammation, thereby contributing to insulin resistance and development of T2DM (32).

An imbalance in the gut microbiota (dysbiosis) or inflammation resulting from such an imbalance, additionally, can weaken intestinal barrier integrity, leading to altered intestinal immunity, increased epithelial permeability and translocation of microbial-derived molecules into the systemic circulation. This process triggers the release of gastrointestinal hormones and inflammatory mediators that further perturb metabolic homeostasis (56). One such molecule is Lipopolysaccharide (LPS), a structural component of Gram-negative bacterial membranes. Under healthy conditions, an intact intestinal epithelium prevents LPS from entering the circulation, even during intestinal microbial lysis (7). However, disease states and high-fat diets disrupt this barrier, leading to an increase in the plasma LPS level, resulting in metabolic endotoxemia. This, in turn, activates Toll-like receptor 4 (TLR4)-mediated inflammatory signaling, promoting systemic inflammation, impairing insulin and lipid metabolism, and contributing to obesity and insulin resistance (7, 57).

Taken together, these insights underscore that dysbiosis of the gut microbiota has emerged as a significant contributor to the development and progression of obesity, acting through multiple intertwined physiological and biochemical mechanisms. Disruptions in the balance and diversity of intestinal microbes can lead to impaired energy

harvest and metabolism, favoring increased caloric extraction from dietary substrates. This metabolic imbalance often enhances lipogenesis and adipose tissue accumulation, exacerbating fat storage. In parallel, gut microbiota dysregulation has been linked to dysregulated neuroendocrine signaling, particularly pathways involved in appetite and satiety control, including modulation of key hormones such as leptin, ghrelin, GLP-1, and PYY. Additionally, dysbiotic microbial profiles promote a pro-inflammatory state characterized by chronic low-grade systemic inflammation, which further impairs insulin signaling and exacerbates metabolic dysfunction. Collectively, these multifaceted mechanisms underscore a direct and causative association between gut microbial alterations and the pathogenesis of obesity.

Conclusion

The human gut microbiota represents a highly diverse and interconnected microbial ecosystem that plays a crucial role in maintaining host physiological homeostasis. Through the production of a wide range of metabolites – including SCFAs, BAs, and tryptophan derivatives – these microbial communities engage in complex bidirectional communication with the host, influencing numerous processes such as immune function, endocrine signaling, and metabolic regulation. Depending on their composition and metabolic activity, these microbial communities can exert either protective or pathogenic effects, thereby shaping overall health outcomes. Accumulating evidence indicates that diminished microbial diversity is negatively associated with metabolic health, with reductions in species richness linked to increased risk of metabolic syndrome, enhanced energy harvest, chronic low-grade inflammation, and insulin resistance. Beneficial strains such as *Akkermansia muciniphila* and *Faecalibacterium prausnitzii* support intestinal barrier integrity, modulate inflammatory responses, and improve glucose and lipid metabolism, while opportunistic or pathogenic taxa may compromise gut permeability and promote adiposity. Dietary patterns have emerged as pivotal determinants of microbial structure and function. Diets rich in dietary fiber, plant-derived polyphenols, and fermented foods have been shown to foster microbial diversity and enhance metabolic resilience, whereas Western-style diets, high in saturated fats and refined carbohydrates, are consistently associated with dysbiosis and obesogenic microbial profiles. Although recent advances in multi-omics technologies and microbiome research have expanded our understanding of host–microbiota interactions, the intricate nature of microbial networks – along with their dynamic responses to environmental and lifestyle factors – continues to present substantial scientific challenges. Further research is essential to elucidate the functional relationships among microbial species, their metabolites, and host metabolic outcomes, with the ultimate goal of developing targeted microbiome-based strategies for preventing and managing metabolic disorders, including obesity.

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