

<https://doi.org/10.59298/NIJSES/2025/63.109116>

Gut Microbiome Dysbiosis at the Intersection of Obesity, Diabetes, and Colorectal Cancer

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ABSTRACT

The gut microbiome plays a pivotal role in maintaining host metabolic homeostasis, immune function, and intestinal integrity. Dysbiosis being an imbalance in the microbial ecosystem, has been implicated in the pathogenesis of metabolic diseases such as obesity and type 2 diabetes mellitus (T2DM), as well as colorectal cancer (CRC). Emerging evidence reveals intricate crosstalk among these conditions, suggesting that microbiome alterations act as a shared mechanistic link. In obesity and T2DM, gut microbial changes promote chronic inflammation, insulin resistance, and metabolic endotoxemia through increased production of lipopolysaccharide (LPS) and decreased short-chain fatty acids (SCFAs). These same alterations influence colorectal carcinogenesis by disrupting epithelial barrier function, modulating oncogenic signaling, and altering bile acid metabolism. Moreover, gut microbial-derived metabolites can affect epigenetic regulation and immune responses, fostering a tumor-promoting microenvironment. Understanding these interrelationships offers novel insights into disease pathophysiology and highlights the therapeutic potential of microbiota-targeted interventions, including probiotics, prebiotics, dietary modulation, and fecal microbiota transplantation (FMT). This review explores the current evidence linking gut microbiome dysbiosis to the obesity-diabetes-CRC axis and discusses future directions for research and therapy.

Keywords: Gut microbiome, Dysbiosis, Obesity, Type 2 diabetes mellitus, Colorectal cancer

INTRODUCTION

The human gastrointestinal tract is home to a vast and complex community of microorganisms collectively known as the gut microbiota [1-4]. This diverse microbial population includes bacteria, archaea, viruses, fungi, and protozoa, with bacteria forming the dominant component. Far from being mere passengers in the human body, these microorganisms contribute significantly to various physiological processes [5-8]. They play a pivotal role in nutrient metabolism, synthesis of essential vitamins, protection against pathogenic organisms, maintenance of gut barrier function, and regulation of the host immune system. The intricate interactions between these microbes and their human host are essential for maintaining health and homeostasis [5].

In healthy individuals, the gut microbiota displays a relatively stable composition dominated by beneficial microbes such as *Faecalibacterium prausnitzii*, *Bifidobacterium*, and *Lactobacillus*. However, this equilibrium can be disrupted by several factors, including poor dietary habits, sedentary lifestyle, stress, infections, aging, and the use of medications—especially antibiotics [5, 9]. This disruption leads to a state known as gut dysbiosis, characterized by reduced microbial diversity, loss of beneficial bacteria, and overgrowth of potentially harmful microorganisms [10, 11]. Dysbiosis has been implicated in the pathogenesis of various chronic diseases, including metabolic syndrome, autoimmune disorders, and cancer [11].

Obesity and type 2 diabetes mellitus (T2DM) represent two of the most significant public health challenges of the 21st century [12-15]. Both conditions are increasing at alarming rates globally, largely driven by dietary excesses, physical inactivity, and other lifestyle changes associated with urbanization and economic development. These metabolic disorders are marked by insulin resistance, chronic low-grade inflammation, and altered energy homeostasis [16, 17]. Interestingly, growing evidence has highlighted profound changes in the gut microbiota in individuals with obesity and T2DM, suggesting that microbial imbalances may contribute directly to metabolic dysregulation [12].

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Colorectal cancer (CRC) is another major health burden, ranking among the most prevalent malignancies and leading causes of cancer-related deaths worldwide[18–20]. While genetic predisposition and environmental exposures are well-established risk factors, recent studies have increasingly recognized the role of the gut microbiome in CRC development. Certain bacterial species, such as *Fusobacterium nucleatum* and *Bacteroides fragilis*, have been shown to promote colorectal carcinogenesis through various mechanisms, including inflammation, genotoxicity, and modulation of host signaling pathways[21].

Remarkably, obesity, T2DM, and CRC are often interconnected not only epidemiologically but also mechanistically[22, 23]. Individuals with obesity and diabetes have a significantly increased risk of developing CRC, and these associations appear to be mediated, at least in part, by common pathways involving gut microbial dysbiosis. Inflammation, immune dysregulation, altered metabolite production, and impaired gut barrier function are central features that link these three conditions[24, 25].

Recent scientific advances suggest that dysbiosis acts as a key driver in this interconnected disease network[10, 11]. The gut microbiota may serve as a common etiological factor that simultaneously affects metabolic and oncogenic pathways. This realization opens up new avenues for understanding the pathogenesis of these conditions from a microbial perspective and also suggests that microbiome-targeted strategies such as dietary interventions, probiotics, prebiotics, and fecal microbiota transplantation could serve as novel preventive and therapeutic approaches. In this review, we aim to unravel the complex relationship between gut microbiome dysbiosis, metabolic disorders (obesity and T2DM), and colorectal cancer. We will explore the compositional and functional changes in the gut microbiota associated with these conditions, elucidate the mechanisms through which these microbial shifts contribute to disease development and progression, and discuss the clinical implications of these findings. By understanding the shared microbial underpinnings of these diseases, we can pave the way for more integrated and personalized medical approaches that target the microbiome to enhance health and prevent chronic disease.

2. Gut Microbiome in Health and Dysbiosis in Disease

In its healthy state, the human gut microbiome performs a multitude of vital functions. It facilitates digestion by fermenting indigestible carbohydrates and synthesizing essential nutrients and bioactive metabolites, such as short-chain fatty acids (SCFAs), namely butyrate, propionate, and acetate[26, 27]. These SCFAs are crucial for maintaining intestinal homeostasis. Butyrate, for example, serves as the primary energy source for colonocytes and has potent anti-inflammatory and anti-carcinogenic properties. Propionate and acetate, on the other hand, influence lipid metabolism, glucose homeostasis, and satiety signaling by acting on peripheral tissues and the central nervous system[28, 29].

Beyond its metabolic roles, the microbiome also supports the structural integrity of the intestinal barrier[30]. A robust epithelial barrier ensures that gut contents remain confined within the lumen, preventing the translocation of harmful substances into the systemic circulation. Moreover, the gut microbiota educates and modulates the immune system, fostering tolerance to non-pathogenic microbes and food antigens while mounting effective responses against pathogens[30]. When this balanced microbial community is disrupted, a condition referred to as dysbiosis, the consequences can be far-reaching. Dysbiosis often manifests as a reduction in microbial diversity and the depletion of beneficial bacteria such as *Faecalibacterium prausnitzii*[10]. Concurrently, there is an overgrowth of opportunistic pathogens, including *Escherichia coli* and *Fusobacterium nucleatum*. This shift in microbial composition results in a significant decline in SCFA production, especially butyrate, which weakens the epithelial barrier and diminishes its anti-inflammatory defense mechanisms[11]. As the intestinal barrier becomes compromised, it becomes more permeable, a condition often referred to as “leaky gut.” This allows microbial-derived toxins and components such as lipopolysaccharide (LPS) to enter the bloodstream[31]. LPS is a potent endotoxin found in the outer membrane of Gram-negative bacteria and a known activator of the immune system. Its presence in systemic circulation leads to the activation of Toll-like receptor 4 (TLR4) on immune cells, initiating a cascade of inflammatory responses. This low-grade chronic inflammation is a central feature in the pathophysiology of obesity and T2DM, contributing to insulin resistance and further metabolic dysfunction[32].

Dysbiosis also alters bile acid metabolism and impairs the production of incretins like glucagon-like peptide-1 (GLP-1), which regulate insulin secretion and appetite. These disruptions exacerbate weight gain, glucose intolerance, and lipid abnormalities[33]. The increased energy harvest capacity observed in dysbiotic microbiota further compounds obesity risk by extracting more calories from the diet than a healthy microbiome would. In the case of colorectal cancer, gut dysbiosis contributes to carcinogenesis through multiple overlapping mechanisms[18, 22]. Certain bacterial strains, such as *Fusobacterium nucleatum*, have been found to infiltrate colorectal tumors and directly interact with host cells, promoting proliferation and resistance to immune clearance. Others, like enterotoxigenic *Bacteroides fragilis* and *Escherichia coli* strains harboring the pks island, produce genotoxins such as colibactin that induce DNA damage in epithelial cells. Chronic inflammation partly fueled by microbial products further accelerates tumor initiation and progression by creating a microenvironment that favors neoplastic transformation[34, 35].

Additionally, dysbiosis disrupts immune regulation within the tumor microenvironment. It skews the balance between regulatory T cells and pro-inflammatory Th17 cells, enhances tumor angiogenesis, and affects the This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited

recruitment and function of immune surveillance cells such as cytotoxic T lymphocytes and natural killer cells[11, 36]. This immunological imbalance supports tumor growth and evasion from immune destruction. Overall, the transition from a balanced to a dysbiotic gut microbiome sets off a cascade of detrimental effects that span metabolic and oncogenic pathways. By compromising intestinal integrity, promoting systemic inflammation, altering host metabolism, and fostering carcinogenesis, dysbiosis becomes a shared underlying factor in obesity, T2DM, and colorectal cancer. Understanding these processes offers valuable insights for developing microbiome-targeted interventions to restore gut health and prevent chronic disease.

3. Gut Microbiome and Obesity

Obesity is increasingly recognized as a condition intricately linked to gut microbiota dysbiosis, characterized by significant alterations in microbial composition and function. One of the most consistent findings in obese individuals is an increased Firmicutes-to-Bacteroidetes ratio, which is believed to enhance the capacity for energy harvest from the diet[37]. This microbial shift facilitates the breakdown of otherwise indigestible polysaccharides into short-chain fatty acids (SCFAs), which can be absorbed and stored by the host, contributing to increased caloric availability and fat deposition. Additionally, obese individuals tend to have reduced microbial diversity, a feature associated with metabolic dysfunction and chronic disease risk[37, 38].

Another critical component of obesity-related dysbiosis involves increased intestinal permeability, commonly referred to as a "leaky gut." This phenomenon allows gut-derived endotoxins such as lipopolysaccharide (LPS) to translocate from the intestinal lumen into the systemic circulation[39]. The result is a condition known as metabolic endotoxemia, characterized by chronic low-grade inflammation that contributes to the development of insulin resistance and adipose tissue dysfunction[39]. Adipocytes exposed to this inflammatory milieu become hypertrophic and dysfunctional, secreting pro-inflammatory cytokines such as TNF- α and IL-6, which further impair insulin signaling pathways.

Furthermore, the gut microbiota influences bile acid metabolism, which is markedly altered in obesity. Bile acids are not only important for lipid emulsification and absorption but also act as signaling molecules that regulate glucose and lipid homeostasis via nuclear receptors like FXR and TGR5[40]. In obesity, the shift in microbial composition disrupts bile acid deconjugation and transformation, leading to impaired signaling and metabolic regulation. This disruption contributes to systemic metabolic imbalances that exacerbate weight gain and insulin resistance[40].

Collectively, these alterations microbial composition shifts, enhanced energy harvest, increased gut permeability, inflammation, and disrupted bile acid metabolism—create a complex interplay between the gut microbiome and host metabolism. This complex relationship makes the gut microbiota a potential target for therapeutic intervention in obesity. Modulation of the gut microbiota through prebiotics, probiotics, dietary interventions, and even fecal microbiota transplantation (FMT) holds promise in reshaping the microbial landscape to restore metabolic balance and aid in the prevention or treatment of obesity and its associated complications.

4. Gut Microbiome and Type 2 Diabetes Mellitus

Type 2 diabetes mellitus (T2DM) is a multifactorial metabolic disorder characterized by insulin resistance and hyperglycemia, both of which have been increasingly linked to alterations in the gut microbiome[41]. Dysbiosis in T2DM involves a shift in microbial composition that contributes to systemic inflammation, impaired glucose homeostasis, and altered lipid metabolism[41]. One key feature observed in diabetic individuals is the reduced production of short-chain fatty acids (SCFAs), particularly butyrate, which plays an essential role in maintaining intestinal barrier integrity and regulating glucose and insulin sensitivity. Lower levels of SCFA-producing bacteria such as *Roseburia* and *Faecalibacterium prausnitzii* have been consistently reported in individuals with T2DM, leading to impaired gut function and metabolic control[42].

In addition, T2DM-associated dysbiosis is characterized by an increased abundance of bacteria that produce branched-chain amino acids (BCAAs), such as *Prevotella* and *Bacteroides* species. Elevated BCAA levels are strongly correlated with insulin resistance and have been implicated in the disruption of insulin signaling pathways[43]. These metabolites, alongside microbial-derived endotoxins like LPS, contribute to systemic low-grade inflammation, a major driver of insulin resistance and pancreatic β -cell dysfunction. The gut microbiome also affects bile acid metabolism in T2DM. Dysregulated microbial conversion of primary to secondary bile acids interferes with receptor-mediated signaling pathways such as FXR and TGR5, which are vital in regulating glucose and lipid metabolism[43]. Impaired bile acid signaling further contributes to metabolic disturbances and insulin resistance. Moreover, microbial imbalance affects gut-derived hormones like GLP-1 and PYY, both of which influence insulin secretion, satiety, and energy expenditure.

Metagenomic and metabolomic studies have revealed unique microbial signatures in T2DM patients. For example, an increase in opportunistic pathogens such as *Ruminococcus* species and a decrease in beneficial microbes like *Akkermansia muciniphila* have been observed. These findings suggest that specific microbial profiles may serve as diagnostic markers or therapeutic targets in diabetes management[44]. The cumulative effect of these microbial disruptions is a hostile metabolic environment that exacerbates insulin resistance and hyperglycemia[44]. As such, therapeutic strategies aimed at restoring microbial balance, including dietary modification, prebiotics, probiotics, synbiotics, and FMT, are being explored as adjuncts in the prevention and treatment of T2DM. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited

treatment of T2DM. Understanding and manipulating the gut microbiome represents a promising avenue for controlling the progression of this global epidemic.

5. Gut Microbiome and Colorectal Cancer

Colorectal cancer (CRC) is a complex disease influenced by genetic, dietary, environmental, and increasingly, microbial factors[45]. The gut microbiome plays a crucial role in colorectal carcinogenesis through its impact on inflammation, immune regulation, and genotoxicity. Dysbiosis, or imbalance in the gut microbial community, is frequently observed in CRC patients and is believed to contribute to tumor initiation, promotion, and progression. One of the key mechanisms through which the microbiota influences CRC is inflammation[45]. Certain pathobionts, such as *Fusobacterium nucleatum*, have been shown to activate oncogenic pathways like NF- κ B and β -catenin signaling, leading to a pro-inflammatory and proliferative environment conducive to tumor growth[46]. Moreover, specific microbial species such as genotoxic strains of *Escherichia coli* produce toxins like colibactin that directly damage host DNA, initiating mutations that drive tumorigenesis[46]. These bacterial genotoxins impair DNA repair mechanisms and enhance genomic instability, key features of cancer development. In addition to promoting DNA damage, dysbiotic microbiota contribute to immune evasion. Microbiota-derived metabolites such as secondary bile acids and polyamines can suppress antitumor immune responses by modulating regulatory T cells, dendritic cells, and tumor-associated macrophages, creating an immune-suppressive microenvironment that facilitates tumor survival and growth[46, 47].

The influence of microbial metabolites extends to epigenetic regulation. SCFAs like butyrate and propionate can affect histone acetylation and methylation, thereby altering gene expression in epithelial cells. While butyrate is generally considered protective due to its anti-inflammatory and apoptotic properties in colonocytes, its effects may be context-dependent and influenced by local microbial ecology and host metabolism[48]. Furthermore, CRC development is often accelerated in the presence of metabolic disorders such as obesity and T2DM, which are themselves associated with microbial dysbiosis. Chronic inflammation, insulin resistance, and altered bile acid metabolism in these conditions create a tumor-promoting milieu. The convergence of these factors illustrates how the gut microbiome serves not just as a passive player but as an active modulator of colorectal cancer risk [48].

Targeting the gut microbiota is an emerging strategy in CRC prevention and therapy. Interventions such as dietary modulation, probiotics, and microbiome-based diagnostics are being developed to identify and mitigate CRC risk by restoring microbial balance and enhancing antitumor immunity.

6. Shared Mechanistic Links Across Obesity, T2DM, and CRC

The gut microbiome serves as a central hub connecting obesity, type 2 diabetes mellitus (T2DM), and colorectal cancer (CRC), orchestrating a series of overlapping pathophysiological processes that contribute to the development and progression of these conditions. One of the most significant shared mechanisms is chronic low-grade inflammation[49, 50]. Gut dysbiosis, characterized by an increased presence of endotoxin-producing gram-negative bacteria, results in elevated systemic levels of lipopolysaccharide (LPS). This triggers toll-like receptor 4 (TLR4)-mediated activation of pro-inflammatory signaling pathways, leading to increased production of cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α). These inflammatory mediators are key contributors to insulin resistance, adipose tissue dysfunction, and tumor-promoting microenvironments[50].

In parallel, dysbiosis compromises the integrity of the intestinal epithelial barrier. Reduced expression of tight junction proteins such as occludin and claudin facilitates increased intestinal permeability or "leaky gut," allowing microbial antigens and toxins to enter circulation. This further exacerbates systemic inflammation and immune dysregulation, hallmarks of metabolic diseases and cancer[50, 51]. The altered gut microbiome also influences immune homeostasis by impairing regulatory T-cell function and shifting macrophage populations toward pro-inflammatory phenotypes, thereby reducing effective immune surveillance and promoting oncogenesis[51].

Metabolic alterations represent another critical shared mechanism. SCFAs, especially butyrate, play key roles in maintaining colonic health, regulating appetite, and improving insulin sensitivity. However, dysbiosis leads to diminished SCFA production, undermining these protective effects[52]. Concurrently, disrupted bile acid metabolism, driven by microbial imbalance, impairs FXR and TGR5 receptor signaling, thereby promoting dyslipidemia, insulin resistance, and carcinogenic pathways. At the molecular level, microbial metabolites and toxins can activate oncogenic signaling cascades such as STAT3, PI3K/Akt, and MAPK pathways. These pathways contribute to increased cell proliferation, angiogenesis, and inhibition of apoptosis in epithelial tissues, particularly in the colon. Moreover, epigenetic modifications mediated by microbial-derived compounds influence gene expression patterns that are common in both metabolic syndrome and cancer[52].

Collectively, the interplay between microbial dysbiosis, immune dysfunction, metabolic imbalance, and epigenetic regulation underscores the gut microbiome's pivotal role in linking obesity, T2DM, and CRC. Understanding these shared mechanisms opens avenues for microbiota-targeted interventions that may prevent or attenuate the burden of these interrelated diseases.

7. Therapeutic Implications and Microbiome-Targeted Strategies

Targeting the gut microbiota has emerged as a promising therapeutic avenue to disrupt the interconnected axis of obesity, type 2 diabetes (T2DM), and colorectal cancer (CRC). A growing body of evidence supports that restoring microbial balance also known as eubiosis can improve metabolic health and reduce cancer risk[53]. Among the most widely studied interventions are probiotics, which involve the administration of beneficial bacterial strains such as *Lactobacillus* and *Bifidobacterium*. These probiotics have been shown to restore microbial diversity, enhance gut barrier integrity, modulate immune responses, and reduce systemic inflammation, all of which are crucial in countering the chronic low-grade inflammation associated with obesity and T2DM and implicated in CRC development[32, 53].

In addition to probiotics, prebiotics a non-digestible dietary fibers that selectively promote the growth of short-chain fatty acid (SCFA)-producing microbes, play a crucial role in maintaining gut health. SCFAs like butyrate not only serve as an energy source for colonocytes but also exert anti-inflammatory and anti-tumorigenic effects. High-fiber diets, particularly those rich in whole grains, fruits, and vegetables, are known to enhance the abundance of these beneficial microbes, leading to improved glucose metabolism, reduced adiposity, and lowered CRC risk[54]. Dietary modulation through the reduction of saturated fats and processed foods further complements microbiota-friendly interventions, as such diets reduce the proliferation of pro-inflammatory and carcinogenic microbial species[54]. Another innovative approach is fecal microbiota transplantation (FMT), which involves transferring stool from healthy donors into patients with dysbiosis[55]. FMT has shown promising results in restoring microbial balance and improving metabolic parameters, with emerging data suggesting its potential benefits in cancer prevention and therapy. While still in early stages of application for obesity and CRC, FMT represents a compelling strategy to reset the gut ecosystem and improve host-microbe interactions[55].

Furthermore, advancements in precision microbiome therapeutics are paving the way for more targeted interventions. These include engineered probiotics designed to deliver specific metabolic or immunological functions and postbiotics, which are microbial-derived metabolites or components that confer health benefits without requiring live organisms. As the field progresses, future clinical trials will be essential to validate the efficacy of these microbiome-targeted therapies, refine administration protocols, and identify specific microbial biomarkers that predict therapeutic response. Ultimately, integrating microbiome modulation into clinical practice could revolutionize the prevention and management of obesity, diabetes, and colorectal cancer.

CONCLUSION

Gut microbiome dysbiosis is a central mediator at the crossroads of obesity, T2DM, and colorectal cancer. By promoting inflammation, metabolic dysfunction, and tumorigenesis, an altered gut microbial ecosystem contributes to the initiation and progression of these interrelated conditions. Targeting the microbiome through diet, probiotics, or microbiota-based therapies represents a promising avenue for integrated prevention and treatment strategies. A deeper understanding of host-microbiome interactions, coupled with personalized medicine approaches, will be critical to translating these insights into clinical practice.

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CITE AS: Ernest Nsubuga (2025). Gut Microbiome Dysbiosis at the Intersection of Obesity, Diabetes, and Colorectal Cancer NEWPORT INTERNATIONAL JOURNAL OF SCIENTIFIC AND EXPERIMENTAL SCIENCES 6(3):109-116 <https://doi.org/10.59298/NJSES/2025/63.109116>