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Gut Microbiome Dysbiosis During Metabolic Disorders: Diabetes

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Abstract

Understanding the intricate interplay between gut microbiome dysbiosis and diabetes is crucial due to the escalating prevalence and impact of diabetes mellitus globally. This comprehensive review examines the current understanding of this relationship, elucidating how alterations in the gut microbiome composition contribute to diabetes pathogenesis by influencing metabolic homeostasis, immune regulation, and insulin resistance. Dysregulation of gut microbial communities leads to shifts in diversity and abundance, exacerbating chronic low-grade inflammation and gut barrier dysfunction, which further perpetuates metabolic dysfunction. Microbial metabolites, such as short-chain fatty acids and bile acids, play pivotal roles in modulating host metabolism and immune responses, thereby influencing the development and progression of diabetes. Importantly, dietary factors significantly shape the diabetic gut microbiome, offering avenues for dietary interventions to modulate microbial composition and function. Various therapeutic strategies targeting the gut microbiome, including probiotics, prebiotics, and dietary supplements, hold promise for improving metabolic outcomes in diabetes. However, integrating these interventions into clinical practice poses challenges but offers potential benefits for optimizing treatment outcomes and reducing disease complications. Continued research efforts are essential to unravel the complex interactions between the gut microbiome and diabetes, paving the way for innovative therapeutic approaches and personalized interventions in the future. This review underscores the significance of understanding the gut microbiome-diabetes nexus and its implications for disease management and future research directions.

Keywords: Diabetes, dysbiosis, guts microbiome, microbial metabolites, therapeutic strategies

INTRODUCTION

Our intestines harbor a unique community of microorganisms called the microbiota, consisting of bacteria, archaea, and viruses . This microbial world outweighs our human genes by over 100 times (in terms of genetic information) and has a significant biomass exceeding 1.5 kg [1–3]. While past research focused on the microbiota's role in digestion and immunity [1–3], recent evidence suggests it may also play a key part in regulating metabolism in both healthy and diseased states [4–7].

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New sequencing technologies have revolutionized our understanding of the microbiota's complexity and diversity. However, most of the estimated 1000+ bacterial species remain unculturable, hindering our ability to fully characterize their functions [8].

The cause of chronic inflammation in metabolic diseases remains debated [9]. The rising obesity epidemic is a major driver of T2D, with over 80% of T2D patients being overweight. Insulin resistance, primarily caused by obesity, is the main underlying factor in T2D [10]. Since insulin

resistance often coincides with metabolic inflammation, researchers have been exploring the connection between these two phenomena over the past decade. It's widely accepted that insulin resistance has a complex cause involving various pathways [11]. However, there's growing evidence that inflammatory pathways play a crucial role in their development [12]. Diet and overnutrition are potential triggers, potentially altering the gut microbiota, impacting lipid metabolism, and ultimately leading to systemic inflammation [13, 14]. Exactly where this inflammation begins remains unclear, but the GI tract with its altered microbiota could be an early point in this process [14].

The adjustment of gut functions impacting permeability, inflammation, and microbiota appears to be closely linked with controlling inflammation, which can contribute to the destruction of beta cells. While the precise mechanisms involved are not completely clear, recent studies indicate potential avenues for preventing Type 1 Diabetes (T1D) [15–37].

Research suggests that typical diets, minor components in food, and even additives can influence the gut microbiome's makeup and function. This translates to changes in the end products of microbial fermentation and the immune system's response [38]. These alterations may ultimately play a role in the development of type 1 diabetes (T1D). Since diabetes affects multiple systems in the body, maintaining a healthy balance of nutrients through diet is crucial as a preventive or protective measure [27]. Separate research highlights that various factors contribute to the vascular complications of diabetes mellitus. These include high blood pressure (hypertension), abnormal cholesterol levels (dyslipidemia), smoking, age, how well diabetes is controlled metabolically, and the presence of systemic inflammation. The relative importance of each factor likely varies depending on the specific type of diabetes a person has and the unique combination of risk factors they possess [28].

While dietary changes are a cornerstone of managing diabetes, researchers are exploring exciting new frontiers. This section dives into several promising therapeutic interventions that target the gut microbiome to improve diabetes' outcomes [39–131]. These approaches include manipulating gut bacteria through diet and probiotics, introducing healthy bacteria directly through fecal transplantation (FMT), and even leveraging the metabolic benefits of bariatric surgery [132–152].

While the destruction of insulin-producing beta cells is central to type 1 diabetes (T1D), recent research suggests the gut may play a surprising role in its early stages. This section explores this emerging field, examining how the gut's permeability, the composition of its microbiome, and even exposure to enteral viruses might influence T1D development. We'll also delve into the potential impact of early-life dietary factors [33–45].

The gut microbiome isn't just a collection of microbes; it's a complex ecosystem with far-reaching influence on our health. This section delves into the fascinating interplay between the gut microbiota and the immune system, exploring how they work together to regulate metabolism. We'll explore how short-chain fatty acids act as messengers, how the innate immune system is involved, and the role of a gut-derived molecule called endotoxin in metabolic inflammation [90–117].

ALTERED GUT MICROBIOME COMPOSITION IN DIABETES

An altered gut microbiota in metabolic disease might initiate inflammatory processes. This could occur "locally" and then spread systemically due to a compromised mucosal barrier. Supporting this idea, recent studies have shown elevated levels of endotoxins (bacterial toxins) in patients with metabolic syndrome and T2D [15, 16]. This aligns with the concept of "metabolic infection", where certain gut microbes might influence inflammation throughout the body, including in adipose tissue [17, 18]. Distinct microbiota profiles (fingerprints) have been identified in various conditions like inflammatory bowel disease (IBD) and obesity [19, 20].

Researchers were eager to study the gut microbiome in T2D, considering the association between obesity and a potential "microbiotal signature" observed in initial human obesity studies. Notably, 80% of T2D patients are obese.

A landmark study used high-throughput sequencing on stool samples from Chinese T2D patients. Combining this with clinical data, they performed the first ever metagenome-wide association study (MGWA) in T2D [21]. The results showed moderate gut dysbiosis in T2D patients, particularly a decrease in butyrate-producing bacteria like *Roseburia intestinalis* and *Faecalibacterium prausnitzii*. The study also introduced the concept of metagenomic linkage group (MLG) analysis. This analysis revealed an enrichment of various butyrate-producing bacteria (e.g., *Clostridiales sp.* SS3/4, *Eubacterium rectale*) in healthy controls, while T2D patients harbored more opportunistic pathogens like *Bacteroides caccae*, various *Clostridiales* species, and *Escherichia coli* [21]. Additionally, sulfate-reducing *Desulfovibrio* bacteria were more abundant in T2D. Interestingly, unlike some later studies, this study found a slight increase in mucin-degrading *Akkermansia muciniphila* in the Chinese diabetic group.

Functionally, gut dysbiosis in T2D patients showed enrichment in functions like sugar and branched-chain amino acid transport, sulfate reduction, and decreased butyrate biosynthesis. Importantly, there was also an increase in oxidative stress response, potentially linking directly to the pro-inflammatory state observed in T2D patients [21].

While the authors concluded a moderate T2D-related gut dysbiosis (over 3% difference in gut microbial genes), some limitations existed. First, there was a gender imbalance in the study. Second, the groups weren't age matched. Third, and importantly, no data on medications used by the participants were reported [21].

This first T2D study was followed by another large MGWAS from Europe, but this one focused only on postmenopausal women with T2D [22]. This study used shotgun sequencing and observed increase in four Lactobacillus species (including *Lactobacillus gasseri*), *Streptococcus* mutans, and certain Clostridiales like *Clostridium clostridoforme*. They also found decrease in at least five other Clostridium species. Like the Chinese study, *Roseburia intestinalis* and *Faecalibacterium prausnitzii* (butyrate producers) were significantly lower in T2D patients. Interestingly, when compared to women with impaired glucose tolerance, the T2D group showed increased energy/harvest metabolism and fatty acid metabolism [22].

While the Chinese and European cohorts had some differing results, both showed increases in *C. clostridoforme* MGCs and *Lactobacillus* species, with a decrease in the major butyrate producer *Roseburia_272*. It's important to note that the European study had a low sample size (n = 53) and its design couldn't determine if diabetes medications influenced the microbiota composition [22].

Despite these limitations, these initial studies are exciting advancements in the T2D and gut microbiota field. They suggest a potential "gut signature" in T2D and, importantly, functional analysis revealed the possibility of a pro-inflammatory gut environment that could initiate low-grade systemic inflammation commonly observed in T2D. Smaller previous studies also supported these findings, showing differences in gut microbiota between T2D and non-diabetic adults, with potential increases in certain *Lactobacillus* species in T2D [23].

Another study by Zhang et al. investigated the gut microbiota in prediabetes (n = 64) and a small group of newly diagnosed T2D patients (n = 13) using 16S rRNA-based sequencing [24]. They found that even normal subjects differed from prediabetes patients, with higher levels of *F. prausnitzii* and *Haemophilus parainfluenzae* T3T1 in the normal group. Conversely, *A. muciniphila* and *Clostridiales sp.* SS3/4 were less abundant in the normal group compared to prediabetes. These findings differed from the previous study by Qin et al. [21]. Additionally, *Verrucomicrobiaceae* were significantly lower in both prediabetes and T2D groups [24]. Although the cause of type 1 diabetes differs from T2D, some studies suggest an altered gut microbiota in type 1 diabetes as well [25, 26].

Role of Certain Bacterial Strains

The trillions of bacteria residing in our gut, collectively known as the gut microbiome, are increasingly recognized for their influence on overall health. In the context of type 2 diabetes (T2D), researchers are exploring how specific bacterial strains might play a role. This section delves into two such strains, *Akkermansia muciniphila* and *Faecalibacterium prausnitzii*, and examines their potential impact on T2D development [121, 123].

Akkermansia Muciniphila

A mucin-degrading bacterium residing in the gut mucus layer, has emerged as a bacterium of interest in T2D research. While findings are still evolving, some studies suggest a protective role for *A. muciniphila*.

This Gram-negative bacterium is more abundant in lean individuals compared to those with overweight or T2D [112, 119, 120, 121]. Interestingly, dietary fiber supplementation can significantly increase *A. muciniphila* levels in mice [123].

Several lines of evidence suggest *A. muciniphila* might contribute to gut barrier integrity and reduce inflammation, potentially protecting against T2D development. A key study by Everard et al. demonstrated that *A. muciniphila* levels were significantly reduced in obese mice [122]. Prebiotic treatment with oligofructose restored *A. muciniphila* abundance and improved metabolic health, including reduced inflammation and improved blood sugar control. Furthermore, direct administration of *A. muciniphila* in these mice led to weight loss and reversed hyperglycemia. These effects were absent with heat-killed *A. muciniphila*, suggesting a live, functioning bacterium is necessary for its benefits. Additionally, the study showed that *A. muciniphila* restored the depleted mucus layer, potentially improving gut barrier function. Supporting these findings, another study linked metformin, a common T2D medication, with increased *A. muciniphila* levels [123, 124]. Like the Everard study, administration of *A. muciniphila* in this context improved metabolic health. Early treatment with vancomycin (an antibiotic) in a mouse model of diabetes also resulted in increased *A. muciniphila* and improved disease course, further suggesting a protective role for this bacterium [75]. *A. muciniphila* might even exert anti-inflammatory effects beyond T2D, as its administration improved colitis in mice [125].

However, some studies have not observed a clear protective role for *A. muciniphila.* For example, a large Chinese study failed to find an association between *A. muciniphila* abundance and T2D risk [33]. Additionally, some studies showed higher *A. muciniphila* levels in healthy controls compared to those with T2D, while others observed the opposite in a high-fat diet model [86, 126, 127]. These conflicting results highlight the need for further research to clarify the complex interactions between *A. muciniphila*, gut health, and T2D development.

Faecalibacterium Prausnitzii

Faecalibacterium prausnitzii (*F. prausnitzii*) has garnered attention for its potential anti-inflammatory properties within the gut microbiota. Several studies have observed lower levels of *F. prausnitzii* in individuals with metabolic syndrome and diabetes [33, 34, 36, 79]. Interestingly, research also suggests a correlation between overall gut microbiota diversity and *F. prausnitzii* abundance, with both being lower in obese and diabetic patients compared to lean individuals [128, 129].

While functional studies exploring the specific benefits of *F. prausnitzii* in metabolic inflammation models are still lacking, these initial findings suggest a potential role for this bacterium in promoting gut health and potentially reducing the risk of metabolic disorders [3].

Immunometabolic Pathways Regulated by the Microbiota

The gut microbiome's influence extends beyond simple digestion. This section delves into the fascinating world of immunometabolic pathways, where gut bacteria communicate with our immune

system through special molecules. We'll explore how short-chain fatty acids and receptors translate gut health into messages that regulate inflammation and metabolism, potentially impacting the development of type 2 diabetes [90–117].

Short-Chain Fatty Acids and G-Protein Coupled Receptors

The gut microbiota plays a crucial role in regulating immunometabolism through short-chain fatty acids (SCFAs) and G-protein coupled receptors (GPCRs) [87–89]. Our bodies lack the necessary enzymes to break down complex plant fibers, but gut microbes come to the rescue. They ferment these fibers into SCFAs like acetate, butyrate, and propionate, which provide 5–10% of our daily energy [90–93]. Interestingly, dietary fibers improve insulin sensitivity, and SCFAs seem to be the key players.

SCFAs can act in multiple ways. They are absorbed directly by the body as an energy source. Additionally, they bind to specific GPCRs like GPR41 and GPR43, which are expressed in gut epithelial cells, fat cells, and immune cells [94, 95]. Studies have shown that mice lacking GPR43 become obese despite a normal diet, while those overexpressing it stay lean regardless of calorie intake [96]. This effect is entirely dependent on gut microbiota, as germ-free mice or those treated with antibiotics lose the GPR43-mediated benefits. GPR43 activation by SCFAs in fat tissue suppresses insulin signaling, preventing fat storage. Furthermore, GPR43 promotes glucagon-like peptide-1 secretion in the gut, enhancing insulin sensitivity [97]. Notably, GPR43 is absent in the liver and muscle, suggesting that fat tissue-derived GPR43 is the key player in regulating metabolic effects triggered by microbial SCFAs. In conclusion, SCFAs are a vital energy source and signaling molecule, particularly in fat tissue, maintaining energy balance. The data strongly suggests that gut microbiota is the primary source of GPR43 agonists, and its functions rely entirely on the presence of these microbes.

GPR41 appears to play a more complex role in gut microbiota-SCFA interactions compared to GPR43. One study found that mice lacking GPR41 were leaner than their wild-type counterparts, even when colonized by specific gut bacteria [98]. This effect was absent in germ-free mice, suggesting gut microbiota is necessary for GPR41's function.

Further research from France has shed light on how SCFAs might work beyond GPR43 signaling. They observed that butyrate directly stimulates intestinal gluconeogenesis (sugar production in the intestine) through a mechanism independent of GPR43, while propionate affects this process via a gut-brain neural circuit involving GPR41 [99]. Importantly, mice lacking the ability for intestinal gluconeogenesis did not experience the metabolic benefits of SCFAs or dietary fiber, highlighting its crucial role. Overall, accumulating evidence suggests that the microbiota of lean animals produces more SCFAs, particularly propionate and butyrate, which promote leanness by suppressing fat storage and increasing energy expenditure, likely through a combination of GPR41 and GPR43 signaling as well as direct intestinal gluconeogenesis regulation (Figure 1).

Short-chain fatty acids (SCFAs) emerge as a fascinating connection between gut microbiota and inflammatory diseases. Recent studies have shown that butyrate, a specific SCFA, directly promotes the development of anti-inflammatory regulatory T cells outside the thymus [100]. Additionally, SCFAs regulate the generation of regulatory T cells in the colon and protect against inflammatory bowel disease in a GPR43-dependent manner (Figure 2) [101]. Further research by Marsland et al. demonstrated that a high-fiber diet alters the gut microbiota in mice, protecting them from allergic airway inflammation [102]. Propionic acid, another SCFA, was identified as the key regulator, influencing allergic inflammation, bone marrow cell production, and the function of dendritic immune cells. Interestingly, propionate's effects relied on GPR41 but not GPR43. Microbiota-derived propionate has also been shown to limit cancer cell growth in the liver, suggesting potential anti-tumor properties. Collectively, these findings suggest that gut microbial metabolites can influence immune responses and blood cell production in the lungs [103].

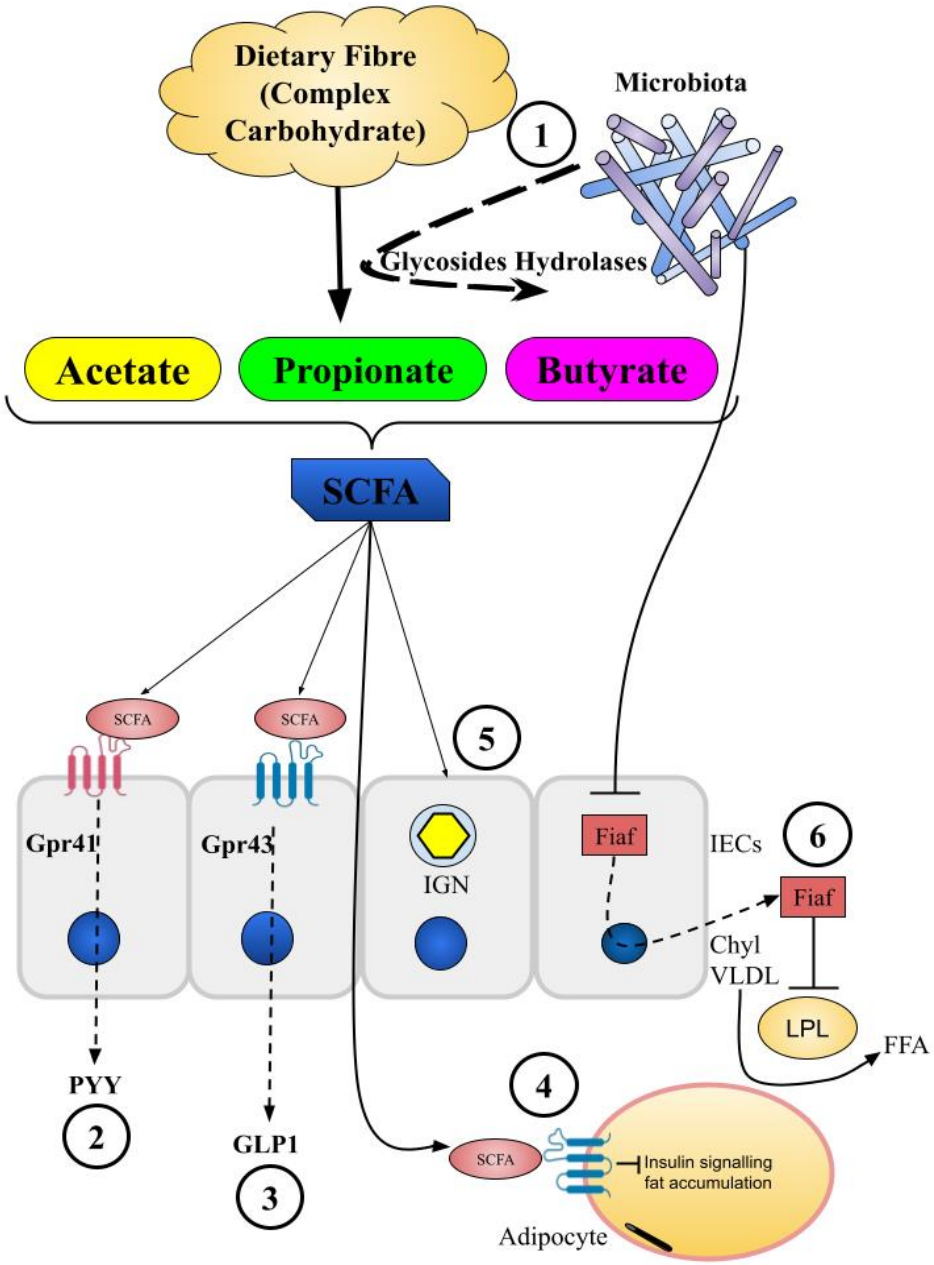

Figure 1. Illustrate the metabolic pathways involving short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate, which are produced by microbiota during the fermentation of dietary fiber.

This strengthens the idea that products from the gut microbiota significantly impact the development of local and systemic immunity and inflammation. Notably, studies in type 2 diabetes consistently report a decrease in SCFA production, particularly butyrate. It is reasonable to hypothesize that these mechanisms might contribute to the low-grade inflammation observed in such disorders.

While SCFA research has provided significant insights into diet, gut microbiota, and host interaction, other mechanisms are emerging. The gut microbiome can influence the type and amount of bile acids present, with lower levels observed in obesity [104]. In obese mice, bile acid-regulated genes like farnesoid X receptor and fibroblast growth factor 15 are more active, directly impacting metabolism.

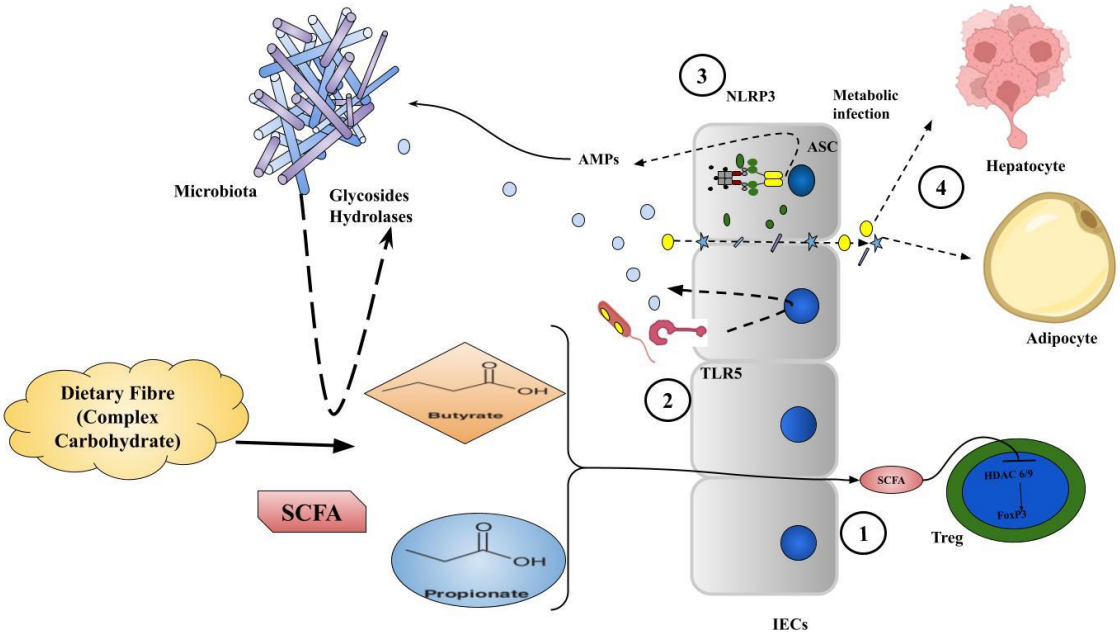

Figure 2. The role of short-chain fatty acids (SCFAs), particularly butyrate and propionate, derived from dietary fiber, in regulating immune responses and metabolic pathways through interactions with the gut microbiota and various immune and metabolic cells.

Studies comparing germ-free and conventionally raised mice highlight the microbiota's influence on fat storage. Conventionally raised mice accumulate more body fat, and when germ-free mice are populated with gut bacteria, they show a decrease in intestinal expression of fasting-induced adipose factor (Fiaf), a protein that inhibits fat storage [83, 105]. Interestingly, germ-free mice lacking Fiaf have similar fat levels to conventional mice, suggesting Fiaf as a key player in microbe-controlled fat storage.

Another pathway involves AMP-activated protein kinase (AMPK), which protects against diet-induced obesity. Germ-free mice stay lean even on a high-fat, high-sugar diet. This leanness is associated with increased activity of AMPK in the liver and muscle, along with improved insulin sensitivity in the liver [106, 107]. These findings suggest additional mechanisms by which the gut microbiota influences metabolism beyond SCFAs.

Innate Immune System

The interplay between the gut microbiota and the innate immune system is gaining attention in understanding metabolic syndrome, a complex disorder characterized by obesity, insulin resistance, and other factors.

Toll-like receptor 5 (TLR5) appears to be a critical player. Mice lacking TLR5 displayed increased food intake, high blood lipids, hypertension, insulin resistance, and obesity, along with a disrupted gut microbiota [108, 109]. Notably, transferring gut bacteria from TLR5-deficient mice to germ-free mice induced metabolic syndrome in the recipients. This suggests that innate immune signaling through TLR5 and alterations in the gut microbiota are instrumental in the development of metabolic syndrome (Figure 2).

Inflammasomes, protein complexes involved in the immune response, are emerging as another potential factor in metabolic inflammation. Studies suggest that certain inflammasomes might influence the gut microbiota, metabolic syndrome, and fatty liver disease [59, 60]. For instance, research by Henao-Mejia et al. observed that mice lacking inflammasomes developed fatty liver, liver

inflammation, and type 2 diabetes when fed a specific diet. This diseased state could be transmitted between mice living together, indicating that the microbiota from inflammasome-deficient mice has the potential to induce inflammatory liver disease. However, the relevance of these findings to human disease remains to be investigated.

Endotoxin – A Major Gut-Derived Player in Metabolic Inflammation

Gut-derived endotoxin, specifically lipopolysaccharide (LPS), is increasingly recognized as a key player in the chronic inflammation observed in type 2 diabetes (T2D). Cani et al. showed that a high-fat diet (HFD) elevated LPS levels in the gut microbiota, leading to metabolic endotoxemia – the presence of LPS in the bloodstream [130]. Interestingly, they found that directly injecting LPS into mice mimicked the insulin resistance and obesity caused by the HFD. Further supporting this link, studies using antibiotics and prebiotics to alter gut microbiota composition observed improvements in metabolic inflammation markers in mice feed a high-fat diet or genetically predisposed to obesity [110, 111, 112]. Animal models investigating metabolic adaptation also highlight the connection. Mice fed with HFD either developed diabetes or remained resistant. The diabetic mice displayed increased gut permeability, endotoxemia, and a distinct gut microbial profile compared to the resistant mice [113]. These preclinical findings are bolstered by clinical studies showing elevated endotoxin levels in patients with metabolic syndrome and T2D [80, 81]. Taken together, this evidence suggests that gut-derived endotoxin plays a significant role in how the gut microbiota influences inflammation-related metabolic processes. The concept of a "metabolic infection" is gaining traction in understanding the link between gut microbiota and chronic, low-grade inflammation associated with obesity and insulin resistance [82]. In adipose tissue, the primary source of inflammatory cytokines in obesity, cytokine expression is significantly higher compared to the liver [114, 115]. This suggests a potential role for gut bacteria in initiating inflammation. Burcelin et al. propose that metabolic infection might be a culprit, with gut bacteria translocating from the intestines to the bloodstream and adipose tissue early in the development of insulin resistance [83, 84, 85]. This translocation could trigger low-grade inflammation in these tissues. Supporting this concept, human studies using 16S ribosomal DNA sequencing have shown elevated levels of specific bacterial DNA (primarily from Proteobacteria) blood of pre-diabetic individuals [116]. Furthermore, a recent study found an association between increased blood levels of Proteobacteria and cardiovascular complications in patients with diabetes [117, 118]. The detection of bacterial DNA in various tissues like blood, liver, and adipose tissue offers a new perspective on how metabolic inflammation, including inflammation in adipose tissue, might develop (Figure 2).

THE GUT AS A REGULATOR OF EARLY INFLAMMATION IN T1D

Intriguingly, the gut emerges as a potential regulator of early inflammation in type 1 diabetes (T1D [29, 30]. While autoimmune destruction of insulin-producing pancreatic beta cells remains the primary theory, the gut's influence is supported by several lines of evidence. Firstly, dietary manipulations in animal models can alter the course of T1D development [30]. This suggests a link between gut processes and the immune response. Secondly, research has revealed an immunological connection between the pancreas and the intestine [31, 32]. Studies have shown that T cells activated within the digestive system can migrate to the islets of Langerhans in the pancreas, which express a specific homing receptor (MadCAM-1) [31]. Additionally, the processing of dietary antigens appears to involve the pancreatic lymph nodes, as demonstrated in a mouse model with engineered T cells specific for ovalbumin (OVA) [32]. When exposed to oral OVA, these mice exhibited T cell proliferation not only in the expected mesenteric lymph nodes, but also within the pancreatic lymph nodes, highlighting a potential gut-pancreas connection. This section emphasizes the growing body of evidence, citing relevant studies [30, 31, 32], that suggests the gut plays a regulatory role in beta-cell autoimmunity by influencing T1D development.

The Gut Permeability as a Regulator of Type 1 Diabetes

The intestinal lining acts as a barrier between the gut and the bloodstream. Tight junctions between epithelial cells control this permeability, with proteins like occludin, claudin, and zonulin playing a key

role [33]. Specialized M-cells can also transport antigens across the barrier, while dendritic cells sample antigens for presentation to T cells. A growing body of evidence suggests a link between increased gut permeability ("leaky gut") and T1D development in both animal models and humans [34–37]. Studies in biobreeding rats, for example, showed structural changes and higher permeability in the intestine of diabetes-prone rats compared to resistant ones [34–36]. Interestingly, early transient permeability increases were observed in both prone and resistant rats, while only prone rats exhibited lasting inflammation [36].

Similar findings were reported in non-obese diabetic (NOD) mice, where increased permeability preceded diabetes onset [38]. Intriguingly, infection with a specific bacteria strain *(Citrobacterium rodentum)* that disrupts the intestinal barrier in young NOD mice accelerated diabetes development [38]. This suggests a potential link between early gut infections, leaky guts, and T1D.

Studies in human infants also provide suggestive evidence. We observed altered antibody responses to cow's milk proteins in early life in children who later developed T1D, potentially reflecting an underlying intestinal maturation defect or increased permeability [39]. Additionally, several studies using lactulose-mannitol tests have shown increased gut permeability in T1D patients [40]. Notably, an Italian study suggests this increased permeability may even precede clinical symptoms, with all at-risk individuals displaying signs of a compromised gut barrier [41]. A leaky gut in T1D patients could allow increased access of luminal antigens to the gut, potentially contributing to the intestinal inflammation observed in these individuals [42–44]. Studies in Italian and Finnish children with T1D revealed activation of small intestinal T cells, suggesting an ongoing immune response [43, 44]. However, unlike celiac disease, infiltration of regulatory T cells (FOXP3+) was not observed [44]. These activated T cells, as seen in animal models, might migrate to the pancreatic lymph nodes and contribute to beta-cell destruction. It is important to note that most studies supporting the gut-T1D connection involve children, and the observed alterations are not present in all patients (around half). Further research on gene-environmental interactions is needed to identify individuals who might benefit from interventions targeting the gut immune system.

The Gut Microbiota Modulates Autoimmune Diabetes

The intestinal microbiome is not just a bystander in T1D; it appears to play a modulatory role. Here's how:

1. *Barrier function:* Gut microbes, through components like lipopolysaccharide and bacterial DNA, can interact with Toll-like receptors (TLRs) on epithelial cells, potentially influencing barrier function [45]. Studies using Lactobacillus plantarum have shown promise; it increased expression of tight junction proteins in human volunteers and cell lines, suggesting a potential for promoting gut barrier integrity [45].
2. *Immune modulation:* Microbes not only affect permeability but also have direct immune effects. Pattern-recognition receptors on immune cells like dendritic cells and regulatory T-cells recognize microbial antigens [46]. Commensal bacterial signals can induce regulatory cytokines (IL-10, TGF-β) in dendritic cells, potentially promoting tolerance mechanisms [46]. Animal models support the role of gut microbiota in establishing oral tolerance [47, 48].
3. *T1D development:* Differences in gut microbiota have been linked to T1D development. Biobreeding diabetes-prone rats displayed distinct fecal microbiota compared to resistant rats, even before diabetes onset [49]. Additionally, antibiotic treatment, reducing gut bacteria, protected these rats from autoimmune diabetes [49]. Selective changes in microbiota composition were observed in diabetes-prone rats, suggesting potential immune-mediated targeting of specific bacteria [50]. Interestingly, NOD mice exhibited T-cell responses towards commensal microbes, hinting that not just altered microbiota, but also tolerance failure towards commensals, might be involved in T1D [51].
4. *Protective microbes:* Studies suggest the possibility of identifying diabetes-protective gut bacteria. In NOD mice lacking MyD88 (a TLR signaling molecule), germ-free status prevented

diabetes, highlighting the importance of microbial stimulation [52]. Notably, fecal transfer from protected mice attenuated diabetes in germ-free recipients, suggesting a protective microbiota composition [52]. Similarly, *Lactobacillus johnsonii*, isolated from diabetes-resistant rats, delayed diabetes onset in biobreeding-prone rats when administered after weaning [53]. Mechanistically, *L. johnsonii* skewed immune response in mesenteric lymph nodes towards Th17 cells, which may explain its protective effect [54]. However, it is important to note that Th17 immunity, while protective in the gut, can be detrimental to pancreatic beta-cells [55]. Human T1D also shows signs of Th17 activation [56, 59], but the link to gut microbiota remains elusive.

5. *Human studies:* While evidence for gut microbiota involvement in human T1D is limited, a preliminary study observed changes in microbiota composition in children who seroconverted to beta-cell autoantibodies [60]. These children exhibited reduced bacterial diversity compared to healthy controls, suggesting a potential link between less diverse microbiota and autoimmunity. Further research is needed to explore this intriguing connection. The rise in T1D might be partly attributed to modern lifestyle changes impacting gut microbiomes. Future research in this area holds significant promise for understanding T1D development and potentially developing preventive or therapeutic strategies [61].

Enteral Viruses, Gut and Autoimmune Diabetes

Enteral viral infections, particularly those caused by rotavirus and enterovirus, have been investigated as potential triggers for T1D. While some studies support this connection, others yield conflicting results. Rotavirus infection has been linked to T1D through molecular mimicry. A recent study showed human T cells can react to both the rotavirus VP7 protein and islet autoantigens (IA-2 and GAD65), suggesting rotavirus could trigger autoimmunity by mimicking beta-cell antigens [62]. Enter viruses, on the other hand, might directly infect and destroy beta-cells, leading to T1D [63]. Alternatively, they could contribute to a "leaky gut" scenario, increasing intestinal permeability and immune activation. This, in turn, could activate beta-cell autoimmunity in pancreatic lymph nodes, as discussed earlier [41]. Viral effects on permeability might involve antiviral cytokines damaging the barrier or direct viral protein effects [41].

The presence of chronic or recurrent enterovirus infections is suggested by the detection of viral antigens and RNA in small intestinal biopsies of long-term T1D patients [64]. However, recent studies paint a more complex picture. While enterovirus RNA in blood before autoantibody detection showed an increased T1D risk, no evidence for persistent infection or post-seroconversion differences were observed [65]. Similar findings emerged from the DAISY study, where blood but not rectal swab enterovirus RNA correlated with progression to T1D in autoantibody-positive children [66]. Additionally, a Norwegian study found no difference in fecal enterovirus RNA frequency between autoantibody-positive and negative children [67].

These recent studies highlight the inconsistencies surrounding the role of enterovirus infections. While some studies associate them with autoimmunity induction [65], progression from autoantibodies to clinical disease [66], or established T1D [64], most lack evidence for persistent infection or intestinal involvement.

Animal models using NOD mice with pre-existing insulitis offer further insights. Rotavirus infection accelerated diabetes development in these mice, but without infecting the pancreas, suggesting gut-mediated effects [68]. This implies that enteral viral infections might not trigger autoimmunity but rather accelerate beta-cell destruction initiated elsewhere.

Diet as a Regulator of Type 1 Diabetes

Several dietary factors are being investigated for their potential influence on T1D development.

1. *Early life exposures:* Epidemiological studies suggest a link between shorter breastfeeding duration and early introduction of cow's milk formula in infancy with increased T1D risk [30]. This highlights the potential importance of gut maturation during early life. The ongoing TRIGR

study is exploring whether delaying exposure to foreign dietary proteins in high-risk infants (through hydrolyzed casein formula instead of cow's milk) can reduce beta-cell autoimmunity [69]. Preliminary results from the TRIGR pilot study are promising, showing a 40% reduction in autoimmunity risk with delayed cow's milk introduction [70].

2. *Bovine insulin hypothesis:* One theory suggests that immunogenic bovine insulin in cow's milk might trigger insulin-specific immune responses in the gut, potentially leading to beta-cell autoimmunity [70]. The FINDIA study is specifically testing this hypothesis by using a bovine insulin-free whey-based formula in infants at genetic risk. Early results showed a decrease in beta-cell autoantibody appearance by age 3 in this group [71].
3. *Wheat exposure:* Early exposure to dietary wheat has also been linked to T1D risk in some studies [72, 73]. In vitro studies suggest that wheat gliadin can activate T-cells in intestinal biopsies from T1D patients [73]. Further evidence comes from a study showing enhanced T-cell responses to wheat antigens in diabetic patients [74]. Animal models also support a role for wheat proteins in modulating gut immune responses and potentially influencing diabetes development [75–77]. Interestingly, one study found that both wheat-free and gluten-enriched diets, when they started early, prevented diabetes in NOD mice, suggesting a complex interplay between timing and immune regulation [78]. Additionally, Norris et al. proposed a "safe window" for introducing wheat, suggesting that exposure after gut maturation (around 3-4 months) might be ideal, while delayed exposure (beyond 6–7 months) could be detrimental [72].
4. *Dietary effects on gut barrier and microbiota:* Studies suggest that dietary interventions can influence gut barrier function and microbiota composition, potentially impacting T1D risk. In bio breeding rats, a hydrolyzed casein diet (compared to whole protein) resulted in reduced diabetes development, possibly due to improved intestinal barrier function [37]. Similarly, wheat gliadin may increase gut permeability by binding to specific receptors on epithelial cells and T-cells [78]. Dietary changes might also affect gut microbiota; a gluten-free diet in NOD mice was associated with a decrease in certain gut bacteria [79]. A recent study further suggests that an anti-diabetic diet might downregulate gut IL-17 immunity, potentially offering another protective mechanism [51].

THERAPEUTIC INTERVENTIONS TARGETING GUT MICROBIOME IN DIABETES

Type 2 diabetes (T2D) treatment is evolving beyond traditional approaches. Researchers are exploring exciting possibilities by harnessing the power of the gut microbiome. This section delves into various therapeutic interventions that target the gut bacteria composition to improve T2D outcomes. We will explore how dietary modifications, probiotic supplementation, fecal microbiota transplantation (FMT), and even bariatric surgery can influence the gut microbiome and potentially benefit diabetic patients.

Diet

Diet plays a crucial role in shaping the gut microbiota and influencing its impact on diabetes. Studies like the CARDIA study demonstrate how high-fat, low-fiber diets promote weight gain and insulin resistance, while dairy consumption can improve glycemic control [131]. Animal-based diets may even decrease Firmicutes, bacteria that break down plant fibers and produce beneficial Short-Chain Fatty Acids (SCFAs) [132].

Emerging evidence suggests that dietary interventions can directly alter gut bacterial composition. A meta-analysis showed that dietary changes did indeed modify gut microbiota alongside improved blood sugar control (HbA1c) but had minimal effects on other factors like fasting blood sugar, insulin, and inflammation compared to the control group [133]. Another recent study observed that high dietary fiber intake improved HbA1c and increased GLP-1 production, a hormone promoting insulin release. This study also utilized advanced techniques to reveal an increase in SCFA-producing bacteria and a decrease in harmful metabolites like indole and hydrogen sulfide [134].

Therefore, diet offers a powerful tool for influencing gut microbiota composition. However, individual responses can vary significantly. For instance, one study found that baseline abundance of specific Firmicutes species predicted responsiveness to dietary intervention [135]. Large-scale randomized controlled trials are needed to definitively determine if dietary modifications aimed at modulating the gut microbiome can be a viable therapeutic target for preventing and managing Type 2 Diabetes.

Probiotics

Probiotics, defined as live microorganisms with potential health benefits when consumed in adequate amounts [136], offer a promising avenue for Type 2 Diabetes (T2D) management. While the specific bacterial strains in various probiotic products can differ significantly, common ones include *Lactobacillus sp., Enterococcus sp*., *Bifidobacterium sp.,* and *Streptococcus sp.*

One exciting approach involves using genetically modified bacteria to improve glycemic control. Recent research has shown that a modified Lactococcus lactis strain can enhance insulin secretion and improve glucose tolerance in mice [137]. Animal studies provide extensive evidence for the potential benefits of probiotics in T2D. These studies have observed positive effects such as:

1. A reduction in the Firmicutes/Bacteroidetes ratio, often imbalanced in T2D [138].
2. Increased abundance of bacteria that produce beneficial Short-Chain Fatty Acids (SCFAs) [138].
3. Decreased levels of inflammatory molecules like TNFα, IL-1, and IL-6 [139].
4. Increased levels of the gut hormone GLP-1, which promotes insulin release [139].
5. Improved insulin resistance [139].

Beyond these benefits, probiotics also help in the following,

1. Reduce inflammatory processes associated with T2D [140].
2. Improve the function of insulin-producing beta cells [140].
3. Enhance the health of the intestinal wall, reducing its permeability and preventing the translocation of harmful bacterial components [140].

Probiotics even play a role in regulating the immune system. Studies suggest that Bifid bacterium infantis can induce T regulatory cells (Tregs), which help dampen inflammation, and stimulate the production of immune cells that can benefit overall gut health [141]. While animal studies overwhelmingly support the potential of probiotics for Type 2 Diabetes (T2D) management, human trials present a more nuanced picture. Several studies have shown positive effects on glycemic control parameters, but there are also inconsistencies. For example, Ivey et al. observed no improvement in blood sugar levels after a 6-week probiotic intervention in overweight subjects [80]. Another study by Jünger et al. found increased GLP-1 and insulin secretion with *Lactobacillus reuteri* supplementation, but no change in insulin sensitivity [142]. Similarly, Mobini et al. reported improved insulin sensitivity in a subgroup of T2D patients receiving *Lactobacillus reuteri*, but no overall change in HbA1c (glycemic control marker) [143].

Systematic reviews and meta-analyses have yielded mixed results as well. Some suggest potential benefits for glycemic control, while others report inconsistencies in HbA1c reduction, anti-inflammatory effects, and antioxidant properties [144–148].

These inconsistencies can likely be attributed to limitations in current research. Heterogeneity in study populations (ethnicity, metabolic health, medications, diabetes duration), diverse probiotic strains used, short trial durations, varying analysis methods, and small sample sizes all contribute to the inconclusive picture.

The substantial differences in study design and findings, along with individual variations in response to probiotics, highlight the need for well-designed, long-term, multicenter randomized controlled trials (RCTs) with standardized methods. These studies are crucial to definitively determine the potential of probiotics as a preventative or synergistic approach in T2D treatment.

Fecal Transplantation

Fecal microbiota transplantation (FMT) is a novel therapeutic approach that involves transplanting fecal matter from a healthy donor into a recipient, often via endoscopy or enema. This technique has shown remarkable success in treating Clostridium difficile infections when antibiotics fail and holds promise for various other diseases [149].

In the context of Type 2 Diabetes (T2D), only one human study has explored the effects of FMT. This study involved transplanting gut microbiota from healthy subjects to adults with metabolic syndrome. The results were encouraging, with recipients experiencing an increase in stool bacteria that produce butyrate, a beneficial short-chain fatty acid, and improved peripheral insulin sensitivity [150]. However, limitations include the small sample size and lack of data on glycemic control and inflammation markers.

Given the limited current evidence, further research is necessary to fully understand and manage potential adverse effects, such as the transmission of harmful microbes and critically evaluate the risk-benefit ratio of FMT for T2D management.

Bariatric Surgery

Bariatric surgery, a highly effective intervention for severe obesity, offers surprising benefits beyond weight loss in the context of Type 2 Diabetes (T2D) management. These "metabolic surgery" effects include improvements in intestinal glucose metabolism, insulin sensitivity, beta-cell function, bile acid composition, and gut microbiota [151].

A recent review analyzing 12 animals, and 9 clinical studies highlighted these changes in gut microbiota composition following bariatric surgery [152]. The studies observed an increase in bacterial groups like *Bacteroidetes, Fusobacteria, Verrucomicrobia,* and *Proteobacteria.* Conversely, there was a decrease in *Firmicutes, Clostridiaceae, Clostridiales, Blautia,* and *Dorea*. Interestingly, three studies reported a rise in *Akkermansia muciniphila,* a bacterium with potential metabolic benefits.

The exact mechanisms behind these shifts in gut microbiota remain unclear but may involve factors like intestinal remodeling, antibiotic use during surgery, and dietary changes post-surgery. These findings suggest a potential link between bariatric surgery's impact on gut microbiota and its positive effects on T2D, warranting further investigation.

CONCLUSION

This review has explored the growing body of evidence linking the gut microbiome to the development and progression of diabetes, particularly type 1 diabetes (T1D). We have seen how a dysbiotic gut microbiome, characterized by reduced levels of beneficial bacteria like *Akkermansia muciniphila* and *Faecalibacterium prausnitzii,* contributes to metabolic dysfunction and inflammation. Additionally, the gut's role in regulating early inflammation in T1D through mechanisms like gut permeability and immune modulation by the microbiota and dietary factors is becoming increasingly clear.

These findings open exciting avenues for future research and therapeutic interventions. Tailored dietary strategies that promote the growth of beneficial bacteria, the development of safe and effective probiotics, and the continued exploration of fecal microbiota transplantation (FMT) hold immense promises for managing diabetes. Further research into the precise mechanisms by which the gut microbiome influences T1D development and progression will be crucial for refining these therapeutic approaches. Ultimately, harnessing the power of the gut microbiome has the potential to revolutionize the way we prevent, treat, and manage diabetes.

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Conflicts of Interest

The authors declare no conflict of interest.

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