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WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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EDITORIAL

Influence of gut bacteria on type 2 diabetes: Mechanisms and therapeutic strategy

Xue Wen, Lu-Ming Qi, Kui Zhao

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Abstract

The onset and progression of type 2 diabetes mellitus (T2DM) are strongly associated with imbalances in gut bacteria, making the gut microbiome a new potential therapeutic focus. This commentary examines the recent publication in *World Journal of Diabetes*. The article explores the association between T2DM and gut microbiota, with a focus on the pathophysiological changes related to dysbiosis. It proposes innovative microbiome-targeted therapeutic strategies and evaluates the challenges and future directions of such approaches. This editorial summarizes the key points of their discussion of the role of the gut microbiome in T2DM and elaborates on the influence of specific gut microbial species on the disease through the host–microbiota metabolic axis. It provides new insights for future research on gut-microbiota-based interventions for T2DM.

Key Words: Type 2 diabetes; Intestinal microbiome; Intestinal axis; Biological pathways; Treatment; Short-chain fatty acids

Core Tip: Our editorial uncovers the pivotal role of the gut microbiome in type 2 diabetes mellitus (T2DM), pinpointing microbial imbalances as therapeutic targets. It explores the mechanisms behind the cross-tissue effects of gut bacteria on T2DM and its complications, suggesting that probiotics, prebiotics or fecal transplantation may offer a promising new path to combat this escalating global health issue.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a prevalent metabolic condition resulting from a mix of genetic, environmental and nutritional influences. Even with growing studies on the causes and treatments of T2DM, the global rates of the disease keep climbing. Increasing research suggests a strong connection between gut microbiota imbalance and the onset and progression of T2DM. This imbalance in gut microbiota can affect the host's immune response and metabolic processes for glucose and lipids, contributing significantly to the development of diabetes. Within this framework, the gut microbiome has been identified as a new therapeutic target for managing T2DM[1].

Jeyaraman *et al*[2] discovered that the gut microbiome of individuals with T2DM, in contrast to healthy people, exhibited an increase in harmful pathogens and a reduction in helpful bacteria, significantly influencing the body's metabolic functions and disease conditions. The increase in bacterial families like *Proteobacteria* and *Firmicutes*, coupled with a decline in advantageous bacteria such as *Bifidobacterium* and *Bacteroides*[3-5], paints a multifaceted image of gut microbiota imbalance in individuals with T2DM. These microbial changes not only directly participate in the production of key metabolites but also indirectly regulate physiological processes such as insulin secretion, glycogen synthesis and appetite control. The dysbiosis in the gut microbiota of T2DM patients may exacerbate inflammatory responses and damage to pancreatic β cells by increasing intestinal permeability and promoting endotoxin release[6,7].

Organ-targeted therapy has great advantages in improving curative effect and reducing stress[8]. Fecal microbiota transplantation (FMT) is a groundbreaking approach in recent medical advances for restoring intestinal flora. In 2012, a clinical trial showed that FMT using healthy donor microbiota improved insulin sensitivity and increased butyrate-producing bacteria in metabolic syndrome patients after 6 weeks[9]. Similar results were seen in T2DM patients, with an increase in butyrate producers in their fecal microbiota[10]. Probiotics offer an alternative to FMT for a healthy gut microbiota. A study found that T2DM patients who took *Lactobacillus* casei daily for 8 weeks had higher sirtuin 1 levels, lower fetuin-A levels, and improved blood glucose compared to the placebo group[11]. Another trial showed that combining multistrain probiotics with metformin for 12 weeks increased beneficial bacteria such as *Bifidobacterium* and reduced proinflammatory bacteria, leading to lower fasting blood glucose and insulin resistance in T2DM patients[12].

Approaches targeting gut microbiota offer promising avenues for T2DM treatment, such as using probiotics to re-establish microbial equilibrium, using FMT to rebuild a healthy gut environment, making dietary changes to encourage beneficial bacteria, and utilizing traditional Chinese medicine to influence gut flora and metabolic processes. These approaches collectively act on the gut microenvironment to improve the condition of T2DM and its complications. Therefore, the regulation and intervention of gut microbiota have become an emerging focus in the field of T2DM treatment.

MECHANISMS OF CROSS-TISSUE INFLUENCE OF GUT MICROBIOTIA ON T2DM AND ITS COMPLICATIONS

Given the influence of gut microbiota on T2DM complications, we explore how the host–microbiota metabolic axis mediates these effects. In T2DM, the signaling mechanism, involving direct chemical interactions between gut bacteria and the host, influences various organs, including the kidneys, muscles and brain. This aspect is crucial for understanding how gut microbiota can influence and potentially treat T2DM and its complications.

There are similarities and correlations between the physiological and pathological aspects of the skin and gut, with the skin microbiota and skin condition being closely related to the gut microbiota[13]. Probiotic intervention shows promising potential in the treatment of diabetic ulcers. Mohtashami *et al*[14] created a diabetic ulcer model in Wistar rats and treated them with probiotics, which led to faster wound recovery in the group receiving probiotics, indicating that probiotics may enhance the healing of diabetic wounds. Probiotics curb the proliferation of harmful bacteria by emitting bioactive compounds, disrupt the communication system of pathogens, and cluster with them, aiding in their elimination from the skin *via* peristaltic movement. Furthermore, probiotics can outcompete harmful microorganisms by strongly attaching to epithelial cell receptors.

Research has found that *Bifidobacterium* may be related to cognitive function in T2DM patients, and it has also been observed that calcium signaling and the renin–angiotensin system may influence cognitive function in T2DM patients by affecting the metabolism of gut microbiota[15]. Imbalance in gut microbiota can influence the gut–brain connection, affecting glucose regulation and resulting in T2DM. Certain molecules engage directly with enteroendocrine cells and the mucosal immune system, whereas others might traverse the intestinal barrier, enter the bloodstream, and possibly pass through the blood–brain barrier (BBB)[16-18]. Enteroendocrine cells are regarded as crucial elements linking the intestinal microbiota with the nervous system.

In 2011, Meijers and Evenepoel[19] introduced the idea of the gut–kidney axis, demonstrating that changes in gut bacteria might affect the development of diabetic nephropathy by modulating metabolic byproducts. Gut microbiota dysbiosis, coupled with increased intestinal permeability, facilitates the entry of metabolic waste and pathogens into the bloodstream, exacerbating insulin resistance and promoting the progression of diabetes. This is linked to the onset of several long-term illnesses like obesity and metabolic syndrome, which in turn harm nephrons, lower the estimated glomerular filtration rate (eGFR), and impair kidney function[20]. Kidney damage leads to the excessive accumulation of circulating metabolic waste, which, by entering the gut lumen through the impaired gut wall, further aggravates gut dysbiosis, forming a vicious cycle between the gut and kidneys, and worsening diabetic nephropathy. In Figure 1, the left part is the previous author's opinion, and the right part is our opinion.

MECHANISMS OF SPECIFIC GUT MICROBIOTA SPECIES IN INFLUENCING T2DM

Studies indicate that *Lactobacillus*, *Bifidobacterium* and *Faecalibacterium* are inversely associated with the onset of T2DM, whereas *Ruminococcus* and *Clostridium* show a direct correlation with the condition. Beneficial bacteria associated with T2DM include *Bacteroides*, *Bifidobacterium* and *Faecalibacterium*, whereas harmful bacteria include *Clostridium* and *Ruminococcus*[21]. Comprehending how these particular gut microbiota species affect T2DM can facilitate focused research on gut microbiota for T2DM prevention and therapy.

Lactobacillus and *Lactococcus* can alleviate diabetic symptoms by improving the function of the intestinal mucosal barrier[22], enhancing immune function[23], and improving insulin resistance, thereby promoting glucose utilization in target organs[24]. Given its few side effects and nontoxic nature, *Lactobacillus* presents a new method for future diabetes prevention and treatment. As one of the gut microbiota that plays a positive role in the intestines, *Bifidobacterium* supplementation can stabilize the gut microecology and enhance the intestinal barrier function, thereby reducing bacterial translocation[25].

Faecalibacterium prausnitzii (*F. prausnitzii*), a core strain of *Faecalibacterium*, has been found to be significantly reduced in abundance in both T1DM and T2DM[26]. *F. prausnitzii* has been proposed as a marker of a healthy gut. It can convert acetate into butyrate *via* the butyryl-coenzyme A transferase pathway, thus providing a balanced potential of hydrogen environment in the gut[27].

Fusobacterium triggers the release of proinflammatory cytokines such as interleukin (IL)-1β, tumor necrosis factor-α and IL-17, which worsens the inflammation[28,29]. Research indicates that *Fusobacterium nucleatum* enhances the production of 2-hydroxybutyric acid, a significant contributor to insulin resistance and T2DM. Possible biochemical processes include enhanced fat oxidation and oxidative stress, which could result in higher insulin resistance and reduced glucose tolerance [30,31]. Studies have shown a positive link between *Ruminococcus gnavus* (*R. gnavus*) and the occurrence of T2DM[32]. *Ruminococcus* has been shown to help intestinal epithelial cells absorb sugars, which may lead to weight gain in the host [33]. Studies have found that the *R. gnavus* group is specific to T2DM, with high abundance in T2DM rats, while short-chain fatty acids (SCFAs) levels are significantly reduced[34]. SCFAs can stimulate G-protein-coupled receptors that play a role in glucose and fat metabolism, thereby demonstrating inherent regulatory functions[35]. *Ruminococcus* may decrease SCFAs levels in the intestines, disrupting various pathways, which can result in imbalances in lipid and glucose metabolism, ultimately contributing to the onset and advancement of type 2 diabetes.

Probiotics such as *Lactobacillus*, *Bifidobacterium* and *Propionibacterium acnes* exert antioxidant effects through the action of antioxidant enzymes like catalase[36], inhibit the cleavage of inhibitory molecules like IkB[37], and reduce the expression of IL-8 to alleviate skin inflammation. Additionally, they can increase the levels of glucagon-like peptide-1 and insulinotropic hormones, enhancing insulin sensitivity[38], thereby mitigating vascular hardening and improving local ischemia. Probiotic soy milk can ameliorate renal oxidative stress, including urinary protein, serum creatinine, and eGFR, and can also reduce the production of serum p-cresol sulfate[39]. *Lactobacillus* promotes the activation of astrocytes[40], improves the BDNF/TrkB/CREB signaling pathway, and reduces the level of neuronal apoptosis[41,42]. *Lactobacillus* and others can increase SCFAs, which in turn induce the interaction of intestinal hormones with brain receptors.

In contrast, harmful bacteria such as *Fusobacterium* and *Ruminococcus* primarily affect the skin, brain, and kidneys by releasing lipopolysaccharides and reducing SCFAs (Table 1)[22-34]. *Ruminococcus* may regulate immune responses by affecting gut-associated lymphoid tissue, thereby influencing the skin's reactivity and inflammatory state in response to external stimuli[43]. The reduction of SCFAs can lead to increased glutathione peroxidase activity[44] and promote the production of transforming growth factor β1, exacerbating renal fibrosis[45]. SCFAs can also regulate the integrity of the BBB, thereby alleviating neuroinflammation and the maturation of microglia (Figure 2)[46].

KEY POINTS FROM THE SELECTED ARTICLE

This research was chosen for editorial comment as it explores the complex connection between the gut microbiota and T2DM, emphasizing its potential for treatment[2]. The global surge in T2DM is affected by genetic predispositions and environmental conditions, with the gut microbiome playing a pivotal role in the development of the disease. The persistent dysbiosis observed in T2DM patients presents opportunities for innovative treatment approaches.

The research outlines changes in gut microbiota in T2DM, highlighting the disrupted *Firmicutes*/*Bacteroidetes* ratio and identifying particular bacterial species linked to metabolic issues. These results highlight the possibility of using probiotics, prebiotics, and fecal microbiota transplants to reestablish a balanced gut ecosystem. These measures might provide new ways to enhance insulin responsiveness and lessen the issues linked to T2DM.

Table 1 Mechanisms of specific gut microbiota species in influencing type 2 diabetes

Specific bacterial species		Influence path	Ref.
Beneficial bacteria	*Lactobacillus*	Improve the intestinal mucosal barrier function, enhance the immune function of the body, and promote the utilization of glucose by target organs	[22-24]
	Bifidobacterium	Maintain intestinal barrier function, reduce bacterial translocation, improve metabolic endotoxemia and reduce low level chronic inflammation	[25]
	Faecalibacterium prausnitzii	Produce butyrate, provide a balanced potential of hydrogen for the intestine	[26, 27]
Harmful bacteria	*Fusobacterium*	Exacerbating the inflammatory state, produces 2HB	[28-31]
	Ruminococcus	Reduced short-chain fatty acids, helps the intestinal epithelial cells absorb sugar	[32-34]

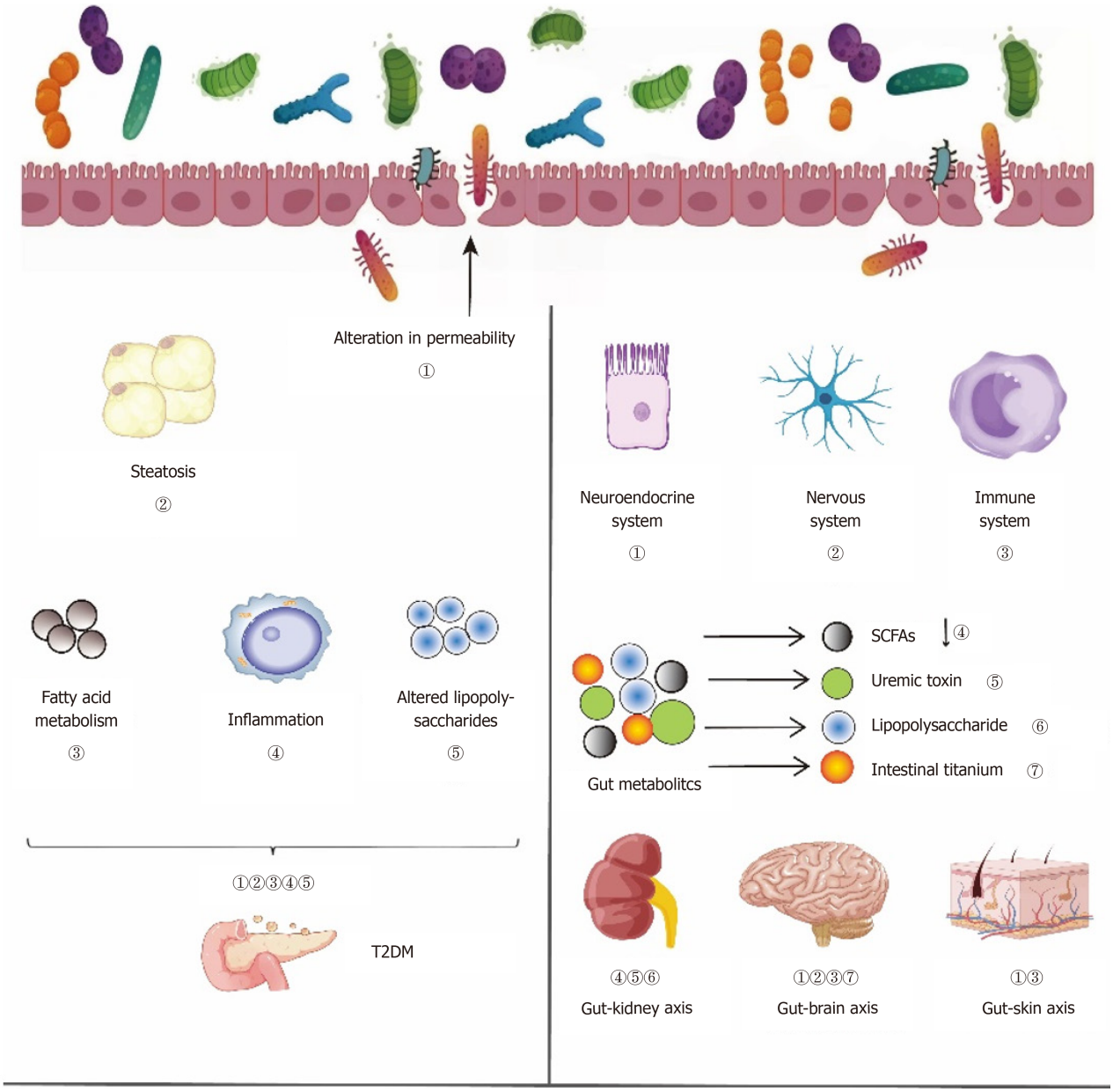

Figure 1 Intestinal bacteria and type 2 diabetes mellitus. TM2D: Type 2 diabetes mellitus.

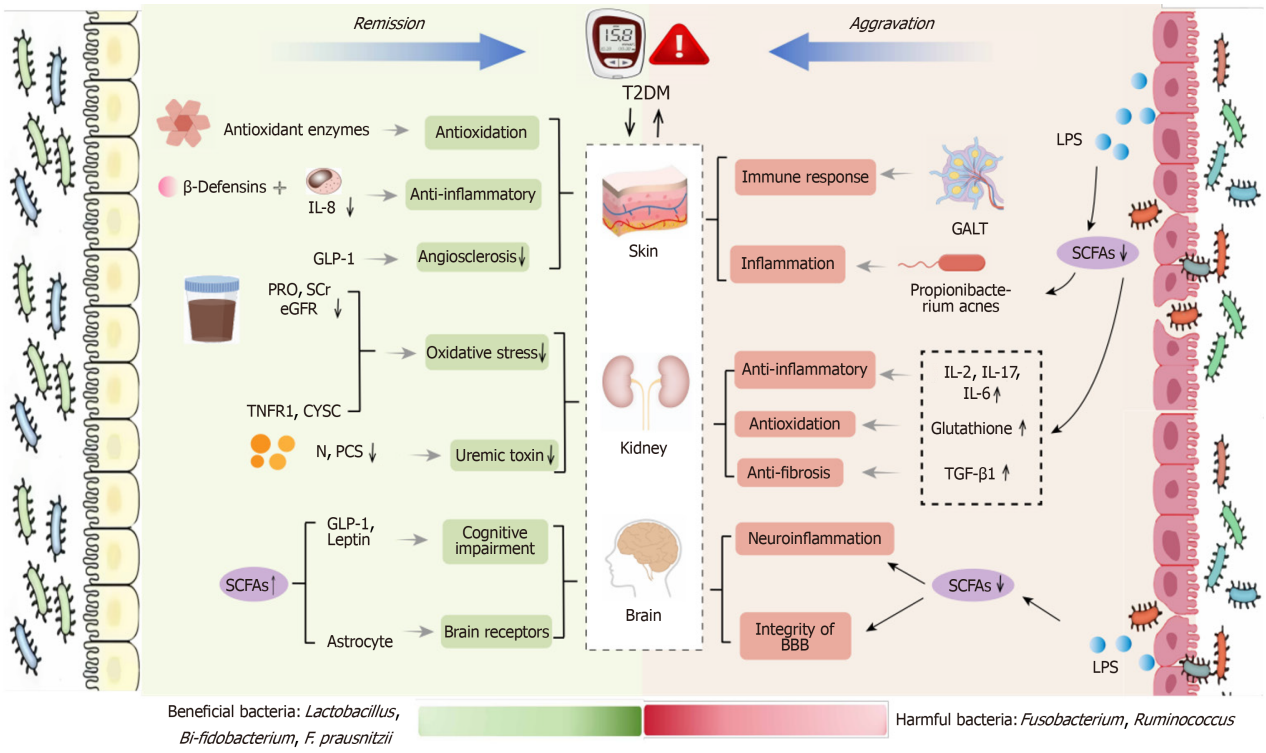

Figure 2 Mechanisms of action of specific gut microbiota affecting various organs. The left side illustrates the mechanisms by which beneficial bacteria, such as *Bifidobacterium*, affect the skin, kidneys, and brain, while the right side shows the impact of harmful bacteria like *Fusobacterium* on these organs. CYSC: Cystatin; EGFR: Estimated glomerular filtration rate; GLP-1: Glucagon-like peptide-1; IL: Interleukin; LPS: Lipopolysaccharide; PRO: Protein; PCS: Phosphatidylcholines; SCr: Sex combs reduced; SCFAs: Short-chain fatty acids; TGF-β1: Transforming growth factor β1; TNFR1: Tumor necrosis factor receptor 1.

Additionally, the review discusses the impact of diabetic medications on gut microbiota, revealing how these drugs can alter microbial composition and influence metabolic outcomes. This insight is crucial for developing more effective, personalized therapeutic strategies that account for individual variations in gut microbiota. The study emphasizes the importance of integrating microbiome research into the broader context of diabetes management to advance the treatment and understanding of T2DM.

CONCLUSION

While studies on the connection between T2DM and gut bacteria are still in their infancy, gut microbiota shows potential as a novel treatment target for T2DM. Exploring the mechanisms by which the host–microbiota metabolic axis influences T2DM, with a focus on specific gut microbiota species, will require extensive future research. In summary, investigating the more reliable connections and mechanisms between gut microbiota and T2DM could pave the way for safer and more effective approaches to the personalized and precision-based prevention, diagnosis and treatment of T2DM.

FOOTNOTES

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