Review

Type 2 Diabetes Mellitus and the Gut Microbiota: Charting New Territory for Sodium-Glucose Co-Transporter 2 Inhibitors

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Abstract

The gut microbiome is a dynamic microecosystem within us that actively influences health beyond digestion. It impacts energy regulation, the immune response, and even drug metabolism. People with type 2 diabetes mellitus (T2DM) exhibit variations in the gut microbiota, linking gut dysbiosis to metabolic dysfunction. In the pursuit of novel therapeutic strategies for T2DM, the intricate interplay between sodium-glucose co-transporter 2 (SGLT2) inhibitors and the gut microbiota emerges as a promising frontier. Renowned for their effectiveness in glycemic control, SGLT2 inhibitors have a range of benefits, including renoprotection, weight loss, blood pressure reduction, and cardiovascular protection. Although the exact mechanisms responsible for these multifaceted advantages remain unclear, recent evidence indicates that SGLT2 inhibitors potentially affect the gut microbiota. This review sheds light on the potential benefits of SGLT2 inhibitors mediated by their influence on the gut microbiota in the management of T2DM by examining the current understanding and developments in this field of research.

Keywords: Type 2 diabetes mellitus, gut microbiota, sodium-glucose co-transporter-2 (SGLT2) inhibitors, treatment, prevention

Type 2 diabetes mellitus (T2DM) is a global epidemic that affects millions of people and places a significant burden on healthcare systems worldwide.[1–3] Addressing this disease has proven challenging due to its multifactorial nature; its development is associated with an intricate interplay among genetic, lifestyle, and environmental factors and is compounded by numerous comorbidities.[4–6] Despite the strides made in diabetes research and medical innovations, a definitive treatment for T2DM has remained elusive, necessitating ongoing exploration of novel therapeutic avenues.[2, 7] Amid this persistent challenge, a promising frontier has emerged in the form of sodium-glucose co-transporter 2 (SGLT2) inhibitors, which represent a paradigm shift in T2DM management. SGLT2 inhibitors modulate renal glucose reabsorption and have demonstrated remarkable efficacy in improving glycemic control addressing renal and cardiovascular risk factors.[8, 9] However, the story does not end with their direct impact on glucose metabolism; an intriguing and relatively uncharted path is revealed when we consider the interplay between SGLT2 inhibitors and the human gut microbiota.

Amid the quest for novel therapeutic interventions, attention has increasingly turned to the human gut microbiota, a dynamic and intricate community of microorganisms residing in the gastrointestinal tract. From 2013 to 2017, there was a notable surge in the number of publications devoted to gut microbiota studies—a staggering 12,900 publications.[10] This surge accounted for a remarkable four-fifths of all research conducted on this topic over the preceding 40 years and reflected a paradigm shift and an expansive exploration of uncharted territory in microbiome re-

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search.[10] This heightened interest underscores a profound commitment among researchers to delve into the untapped potential of manipulating the gut microbiome, not only for the treatment of various diseases but also to unravel the intricate ways in which pharmaceutical agents, such as SGLT2 inhibitors, can modulate and interact with the microbiota.

As the scientific community directs its focus toward deciphering the complex relationship between the gut microbiota and T2DM [11, 12], the exploration of how SGLT2 inhibitors may impact this microbial community represents a pivotal intersection in the pursuit of comprehensive and effective therapeutic strategies. This review delves into the evolving landscape of research surrounding the interactions between SGLT2 inhibitors and the gut microbiota, providing insight into potential mechanisms, metabolic implications, and therapeutic opportunities that may redefine our approach to managing T2DM.

The Gut Microbiome: A Hidden Universe Within Us

The human gut harbors a complex community of trillions of microorganisms, collectively known as the gut microbiome.[13, 14] This thriving microecosystem is not just a passive bystander; it plays an active role in maintaining health.[13] Over the past decade, extensive research has revealed the profound influence of the gut microbiome, which extends far beyond its primary role in digestion.[13, 15, 16] The resident microorganisms collaborate not only with each other but also with other bodily systems in complex ways.[16, 17] This collaborative activity encompasses crucial functions, including aiding in food breakdown, facilitating nutrient absorption, metabolizing bile acids, maintaining intestinal barrier integrity, regulating energy balance and the immune system, as well as influencing drug metabolism (Fig. 1).
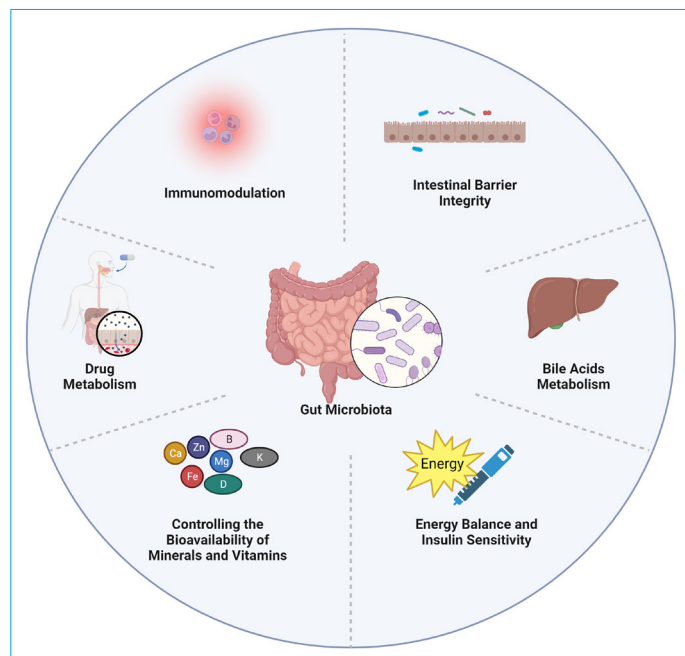

Figure 1. The multifaceted functions that the gut microbiota contribute to in a collaborative manner. Created with BioRender.com.

The gut microbiota actively participates in the metabolism of dietary components, producing short-chain fatty acids (SCFAs) and modulating energy extraction from indigestible polysaccharides.[18, 19] A harmonious interaction between the gut microbiome and the immune system is essential for maintaining a robust and well-balanced immune response.[10, 20, 21] Commensal bacteria help educate the immune system to tolerate beneficial microbes and elicit an appropriate response against pathogens. This immunomodulatory role of the gut microbiome is essential for preventing inappropriate inflammatory reactions and autoimmune diseases.[20, 21] Moreover, the gut microbiota is now recognized as a vital partner of human cells, as it is intricately linked to nearly all aspects of human physiology.[10] This connection extends to metabolic processes with the gut microbiota influencing the host's metabolism and energy regulation.[19, 21, 22] Gut microbes contribute to the fermentation of undigested dietary components, producing metabolites (e.g., SCFAs) that impact the host's energy balance and insulin sensitivity.[19, 23] Imbalances in the gut microbiota have been associated with metabolic disorders, including obesity and T2DM.[22, 24] Certain bacteria within the gut microbiome are capable of synthesizing vitamins and other essential nutrients, such as B12 and folate, and thus contribute to the overall nutritional status of the host.[21, 25, 26] Additionally, the gut microbiome plays a crucial role in the maintenance of the intestinal barrier, which prevents the translocation of harmful substances from the gut into the bloodstream.[20, 21, 26, 27] This barrier is also crucial for the prevention of inflammation and for maintaining overall gut health.[20, 21, 27] Furthermore, the gut microbiota can impact drug metabolism through various mechanisms, resulting in inter-individual differences in drug efficacy and toxicity.[28]

It is important to note that the composition and diversity of the gut microbiome can vary significantly from person to person, influenced by a complex interplay of factors including geography, genetics, dietary habits, medications, lifestyle, and environmental conditions.[29, 30]

The complex communication network that links the gut microbiota to various organs plays a pivotal role in the diverse ways that the gut microbiota impacts host health. Through intricate signaling pathways, such as the gut–brain and gut–kidney axes, the gut microbiome communicates with distant organs.[13, 20, 21] This communication involves signaling metabolites, including lipopolysaccharide (LPS), bile acids, SCFAs, and trimethylamine[10, 13, 20, 21, 26] and ultimately influences the host's overall health (Fig. 2).

Microbial diversity shifts in T2DM and implications for metabolic dysfunction. Numerous studies have highlighted that the composition and abundance of gut microbial communities vary between individuals with T2DM and those with normoglycemia.[31–34] Noteworthy changes include a decrease in butyrate-producing bacteria, such as *Faecalibacterium prausnitzii* and *Roseburia* spp., depletion of the genera *Akkermansia* and *Clostridium*, and increases in the *Ruminococcus* and Streptococcus genera observed in T2DM patients.[31, 34–37] Reductions in *Akkermansia muciniphila (A. muciniphila)*, a mucin-degrading bacterium associated with improved metabolic health, have been observed in T2DM patients, suggesting a potential role in the disease pathogenesis.[38]
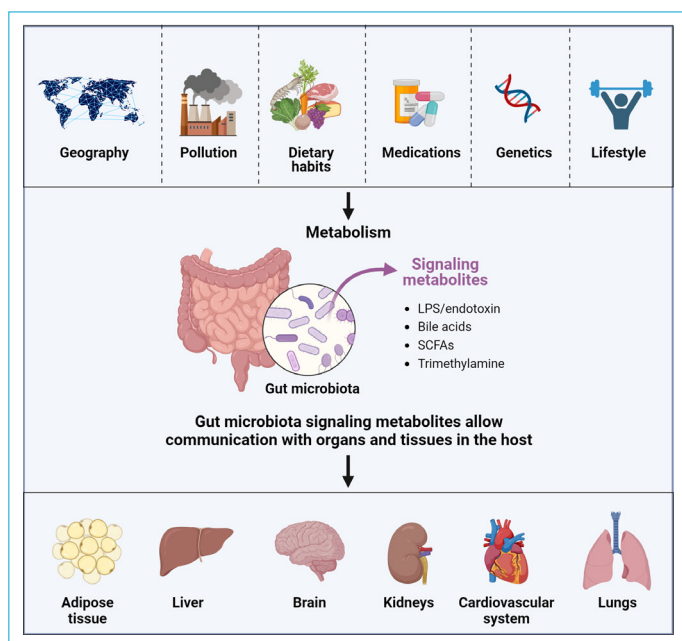
Figure 2. The gut microbiota's communication network with the body's organs. Created with BioRender.com.

LPS: lipopolysaccharide; SCFA: short-chain fatty acids.

Simultaneously, an increase in opportunistic pathogens, such as *Escherichia coli*, has been observed, which potentially exacerbates the inflammatory milieu associated with T2DM.[39] The Firmicutes to Bacteroidetes ratio, a widely recognized marker of gut microbiota composition, is frequently altered in T2DM patients.[31, 36, 37] Although the significance of this ratio remains under investigation, studies have reported an elevated Firmicutes to Bacteroidetes ratio in T2DM patients that correlates with insulin resistance and metabolic dysfunction.[31, 36, 37]

These observed reductions in microbial diversity and shifts in the relative abundance of specific taxa in T2DM patients suggest a potential link between gut dysbiosis and metabolic dysfunction.[23, 37, 38] The altered microbial profile is hypothesized to contribute significantly to inflammation, impair gut barrier function, and influence host metabolism—which are all key factors in the pathophysiology of T2DM.[22–24] For example, metabolites produced by gut microbes, such as SCFAs, secondary bile acids, and indoles, have been implicated in the regulation of insulin sensitivity and glucose metabolism.[19, 20, 24, 40] Particularly, SCFAs, with butyrate taking a prominent role, contribute to maintaining the integrity of the gut barrier and exhibit anti-inflammatory effects; thus, they potentially alleviate inflammation associated with T2DM.[19, 23, 38, 40] Conversely, the decrease in butyrate-producing bacteria observed in T2DM leads to the disruption of the integrity of the gut barrier and "leaky gut," and it is also associated with chronic low-grade inflammation.[20, 22, 24, 38]

Furthermore, the impact that the gut microbiota has on lipid metabolism in T2DM adds a significant layer to the complex T2DM–gut microbiota relationship.[37, 41] The gut microbiome, through its engagement in lipid metabolism, actively influences lipid absorption, synthesis, and storage.[42] Thus, the gut dysbiosis observed in T2DM may contribute to disturbances in lipid metabolism and thereby exacerbate the overall metabolic dysregulation associated with this condition.[23, 37, 38, 41] This multifaceted interplay between gut dysbiosis, insulin sensitivity, metabolic dysfunction, and lipid metabolism underscores the intricate nature of the relationship between the gut microbiota and T2DM.

The Gut Microbiota and Antidiabetic Medications: Bidirectional Interactions in T2DM Treatment

The bidirectional relationship between antidiabetic medications and the gut microbiota is complex and has far-reaching implications for T2DM treatment. Ongoing research, encompassing in vitro and animal studies, endeavors to elucidate the intricate mechanisms that underlie drug–microbe interactions and their potential consequences for drug efficacy and safety.[43, 44] While the adverse effects of antibiotics on the gut microbiome are well-acknowledged,[45, 46] recent insights underscore that non-antibiotic drugs can also instigate substantial changes in gut microbiota composition.[44, 47] Moreover, individual drugs, drug combinations, and the cumulative effects of drugs have been shown to alter the metabolome and microbiome and ultimately influence gut health.[43, 44, 47] This bidirectional drug–microbe relationship extends to antidiabetic medications, adding a dynamic layer to T2DM treatment.

Antidiabetic medications, from oral hypoglycemic agents to injectable therapies, have been shown to influence the composition and function of the gut microbiota.[48] For instance, a recent systematic review demonstrated that the interplay between the gut microbiome and glucose-lowering medications is a key factor that contributes to the variability observed in T2DM progression and treatment outcomes.[49] This relationship is bidirectional and can have both positive and negative consequences for T2DM management, which underscores the imperative for personalized treatment approaches.[48, 49] On one hand, enzymatic activity in the gut microbiome can influence the metabolism and efficacy of glucose-lowering drugs. On the other hand, these drugs can alter the composition and function of the gut microbial community, thereby reshaping the gut microenvironment and impacting microbial metabolism.[49]

The most robust evidence of the impact of antidiabetic medications on the gut microbiota composition has been derived from studies with metformin.[50–52] Metformin usage has been demonstrated to foster the proliferation of various healthy bacteria that produce SCFAs.[50, 51] In a double-blinded randomized controlled trial conducted by Wu et al., treatment-naïve T2DM patients were assigned to receive either metformin or a placebo for four months.[53] The results indicated that receiving metformin for four months, compared to the placebo, increased the abundance of SCFA-producing bacteria such as *Blautia, Bacteroides, Butyricoccus, Bifidobacterium, Prevotella, Megasphaera, and Butyrivibrio* spp., as well as Proteobacteria and Firmicutes genera.[53] Metformin has also been shown to increase mucin-degrading bacteria such as *A. muciniphila*.[51, 52, 54]

Incretin-based therapies, which involve glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors, represent another dimension to the intricate relationship between antidiabetic medications and the gut microbiome, potentially influence the gut microbiota composition and impact metabolic outcomes.[50, 51, 55] For example, the GLP-1 receptor agonist liraglutide has the capacity to reduce weight by modifying the structure of the gut microbiota.[56] Similarly, DPP-4 inhibitors have been shown to affect the composition of the gut microbiota.[50, 51, 55] Notably, the administration of sitagliptin led to an increase in 24 genera, with 75% being Bacteroidetes, while 87.5% of the decreased genera were Firmicutes, resulting in an elevated Bacteroidetes to Firmicutes ratio.[57] Despite these intriguing findings, a 12-week randomized placebo-controlled trial involving adults with T2DM failed to reveal any discernible impact on the composition of the intestinal microbiota from either liraglutide or sitagliptin.[58] This absence of observable changes underscores the complexity and variability in the interactions between antidiabetic medications and the gut microbiome. Further examination of the specific mechanisms involved and potential long-term impacts, and the identification of interventions, will undoubtedly play a pivotal role in shaping the future landscape of T2DM management.

SGLT2 Inhibitors and the Gut Microbiota: A Promising Connection

SGLT2 inhibitors are a class of oral glucose-lowering agents used to treat T2DM.[59, 60] They inhibit the reabsorption of glucose in the kidneys, which increases the urinary excretion of glucose, and thus improve glycemic control.[60, 61] Beyond their primary function of managing blood glucose levels, SGLT2 inhibitors offer additional advantages. These include inducing weight loss, lowering blood pressure, decreasing the likelihood of heart failure-related hospitalizations, reducing cancer risk, and providing cardiovascular and renal protection (Fig. 3).[62–65]

Although the exact mechanisms responsible for these multiple benefits remain unclear, some evidence suggests that these protective effects may be influenced in part by the gut microbiota.[59–61]
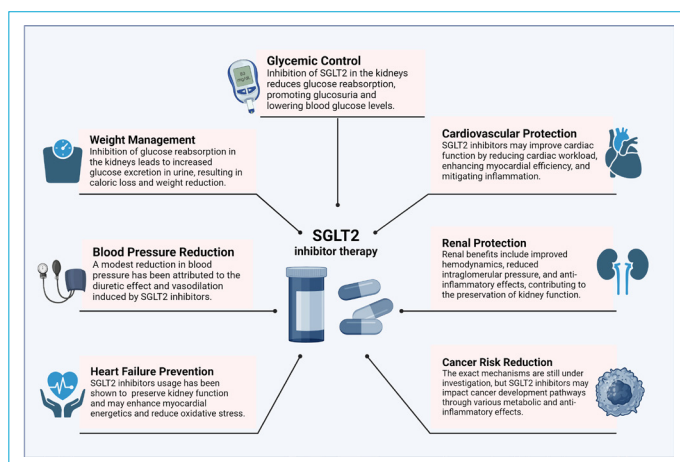
Figure 3. The multifaceted benefits of sodium-glucose co-transporter 2 (SGLT2) inhibitors.[62-65] Created with BioRender.com.

In animal studies, several SGLT2 inhibitors have been shown to induce changes in the composition of the gut microbiota. For example, in experiments with mice with T2DM treated with dapagliflozin, minor positive changes in their gut microbiota were observed.[66] These changes included a decrease in *Oscillospira* spp. and a shift toward a more favorable Firmicutes to Bacteroidetes ratio, as well as an increase in *A. muciniphila*.[66] Similarly, in diabetic mice fed butyrate, a dapagliflozin-treated group showed a trend toward an improved Firmicutes to Bacteroidetes ratio, a decrease in *Adlercreutzia* spp. and *Alistipes* spp., and an increase in *Streptococcus* spp.[67] More recently, a study in db/db mice demonstrated the protective effect of dapagliflozin on diabetic kidney disease, which appears to be associated with a dynamic improvement in gut microbiota over time.[59] This improvement may be related to the effects of dapagliflozin on the bile acid pool and its antioxidant activity.

Empagliflozin has also been demonstrated to ameliorate T2DM-related diabetic nephropathy by altering the gut microbiota by reducing LPS-producing bacteria and increasing SCFA-producing bacteria in T2DM mice.[61]

Furthermore, canagliflozin significantly enhanced the production of SCFAs and reduced plasma levels of p-cresyl sulfate and indoxyl sulfate in the intestines of animal models.[68] Luseogliflozin treatment was also found to increase the quantity of intestinal bacteria involved in the synthesis of SCFAs, leading to improved amino acid metabolism in db/db mice.[69] To further illustrate the impact of SGLT2 inhibitors on the gut microbiota, Table 1 provides a summary of the findings on the alterations induced by various SGLT2 medications generated in animal studies and clinical trials.

While preclinical studies have shown promise in terms of the impact of SGLT2 inhibitors on the fecal microbiome, the limited clinical studies that have been conducted in this area have produced mixed results. In a three-month, randomized, open-label trial with 76 treatment-naïve T2DM patients, empagliflozin demonstrated substantial benefits, including improvements in glucose metabolism, reductions in cardiovascular risk factors, and notable alterations in the gut microbiota.[72] These changes were associated with an increase in beneficial SCFA-producing bacteria and a decrease in harmful bacteria, such as *Escherichia–Shigella, Bilophila, and Hungatella* spp. A study conducted with Japanese T2DM patients found that treatment with an SGLT2 inhibitor was associated with an overall increase in the prevalence of balance-regulating bacteria, including SCFA-producing bacteria.[74] However, conflicting findings also exist: another double-blind randomized trial found no significant impact on microbial diversity or composition in T2DM patients.[75]

Despite these inconclusive results, the preliminary findings offer hope for people who are facing challenges in managing T2DM, creating the possibility of tailored treatment options. This newfound understanding of the role that the gut microbiota plays raises several questions. How exactly do SGLT2 inhibitors affect the gut microbiota, and can we exploit these changes to improve treatment outcomes in T2DM? Is it possible to optimize SGLT2 inhibitors to specifically target the detrimental microbial changes

Table 1. Impact of sodium-glucose co-transporter 2 (SGLT2) inhibitors on the gut microbiota in type 2 diabetes mellitus (T2DM)

Study	Subjects	Key findings
		Canagliflozin
Wang, et al.[70]	Male C57BL/6J mice	An increase in the Firmicutes to Bacteroidetes ratio (from 230% to 98%) and the relative abundance of *Olsenella*, *Alistipes*, and *Alloprevotella* spp., and a decrease in the abundance of *Helicobacter* and *Mucispirillum* spp.
Wang, et al.[71]	21 treatment-naïve T2DM patients	An increase in the relative abundance of SCFA-producing bacteria, particularly *Lachnospiraceae, Bacteroides*, and *Lachnospiraceae* spp.
		Luseogliflozin
Hata, et al.[69]	Male db/db mice	An increase in the abundance of intestinal SCFA-producing bacteria, leading to improved amino acid metabolism
		Empagliflozin
Deng, et al.[61]	Male C57BL/6J mice	A reduction in LPS-producing bacteria and an increase in SCFA-producing bacteria
Deng, et al.[72]	76 treatment-naïve patients with T2DM and risk factors for CVD	An increase in sphingomyelin, but a reduction in glycochenodeoxycholate, cisaconitate, and uric acid; an elevated level of SCFA-producing bacteria; and a reduced level of harmful bacteria, including *Escherichia–Shigella, Bilophila*, and *Hungatella* spp.
		Dapagliflozin
Wu, et al.[59]	Male db/db mice	An increase in SCFA production; the agent showed anti-inflammatory properties and mitigated kidney damage
Oh, et al.[67]	Male db/db mice	A decreased Firmicutes to Bacteroidetes ratio, a reduction in *Adlercreutzia* and *Alistipes* spp., and an increase in *Streptococcus* spp.
Lee, et al.[66]	Male diabetic mice	An increased abundance of *Akkermansia muciniphila*
Yang, et al.[73]	Rat model of T2DM	Complementary effects on the main beneficial bacteria
Kusunoki, et al.[74]	36 patients with T2DM-related diabetic nephropathy	An increase in the prevalence of balance-regulating bacteria and SCFA-producing bacteria
van Bommel, et al.[75]	44 T2DM patients	No significant effects

CVD: cardiovascular disease; LPS: lipopolysaccharide; SCFA: short-chain fatty acids.

associated with T2DM? Further research is needed to fully explore the complex interplay between SGLT2 inhibitors and the gut microbiota. However, as we continue to explore this fascinating area of research, we must remember that we are still in the very early stages of understanding the full potential of the gut microbiome in the treatment of T2DM. It will take years of dedicated research and clinical trials to determine which interventions are the safest and most effective. In a world where T2DM is a growing health crisis, any promising research approach deserves attention and support.

Conclusion

In the ongoing fight against the global T2DM epidemic, it is imperative to explore new frontiers in search of innovative solutions. The gut microbiome stands out among the unexplored areas—existing research has already provided insights that could revolutionize the prevention and management of T2DM. SGLT2 inhibitors have multifaceted benefits beyond glycemic control, such as weight loss, blood pressure reduction, and cardiovascular and renal protection; their potential influence on the gut microbiota remains a

dynamic and evolving area of research. Current evidence from preclinical studies suggests that various SGLT2 inhibitors induce positive changes in the composition of the gut microbiota, potentially contributing to their therapeutic effects. However, clinical studies have yielded mixed results, underscoring the complexity of this interaction. Substantial research efforts are needed to elucidate the intricate mechanisms involved and optimize interventions for clinical use. While the prospect of tailored treatment options offers hope for T2DM patients, it is essential to approach existing findings with caution and acknowledge that this research field is in its early stages. The outcomes of rigorous clinical trials and dedicated research studies will be pivotal in determining the safety and efficacy of T2DM interventions that target the gut microbiota and involve SGLT2 inhibitors.

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