Review

Tirzepatide and Gut Microbiome: A Narrative Review of Current Evidence and Future Implications

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Posted Date: 17 September 2025

doi: 10.20944/preprints202509.1540.v1

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Tirzepatide and Gut Microbiome: A Narrative Review of Current Evidence and Future Implication

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Abstract

Tirzepatide has recently been approved for use with type 2 diabetes and obesity due to its effectiveness with both and being the first dual agonist of the glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors. Increasing focus has shifted toward tirzepatide's possible relationships with the gut microbiome, which plays an important role in metabolic, bile acid, and inflammation regulation, in addition to its many established benefits in glucose control and weight loss. Gut microbial composition changes are known to lead to obesity, insulin resistance, and related comorbidities, which is why this area is so important. Tirzepatide has been shown to increase the absent flora diversity of the gut in addition to the increased growth of beneficial Akkermansia and Bacteroides, and the alteration of bile acid metabolism toward microbial antagonists of the farnesoid X receptor. Lubricated insulin resistance and systemic inflammation, coupled with the imbalance of gut flora resulting from a diet high in fats, have been linked to these changes. Preliminary studies support the idea that tirzepatide's dual mechanism has a more profound influence over the microbial ecology and metabolic pathways than the effects of other GLP-1 receptor agonists and DPP-4 inhibitors. Overall, the safety data regarding tirzepatide appear to be in line with other therapies based on incretins, with gastrointestinal side effects being the most common adverse event. Its effects on metabolism and the microbiome, however, are broader than glucose and weight management. Early data suggest potential benefits in NAFLD, inflammatory bowel disease, cardiovascular dysfunction, and even some neurodegenerative diseases. Tirzepatide embodies a promising advance in the intersection of incretin biology and gut microbiome regulation for precision medicine in metabolic disease. The focus on the microbiome in future studies will be important for substantiating and elucidating the mechanisms of these observations, enhancing patient stratification for precision medicine approaches.

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1. Introduction.

Obesity and type 2 diabetes mellitus (T2DM) remain among the most significant global health challenges of the 21st century. The World Health Organization (2023) estimates that more than 650 million adults worldwide are obese, and the prevalence of T2DM continues to rise in parallel. Both conditions contribute substantially to cardiovascular morbidity, premature mortality, and escalating healthcare costs. Traditional interventions, including lifestyle modification and pharmacotherapy, often yield suboptimal long-term outcomes, underscoring the need for novel therapeutic strategies [1]

One of the most important advances in this area has been the development of incretin-based therapies. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have shown efficacy in glycemic

 doi:10.20944/preprints202509.1540.v1

control, weight reduction, and cardiovascular risk mitigation. However, despite their effectiveness, many patients fail to achieve or sustain optimal metabolic outcomes, prompting exploration of next-generation incretin therapies [2].

Tirzepatide represents a breakthrough as the first dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist. Discovered and developed by Eli Lilly, Tirzepatide is a 39–amino acid synthetic linear polypeptide engineered with a C20 fatty diacid moiety that allows albumin binding and prolongs its half-life, thereby enabling once-weekly administration[3]. Pharmacokinetically, Tirzepatide demonstrates predictable absorption and clearance, while pharmacodynamically, it exerts complementary effects on glucose and energy metabolism. Its mechanism of action includes enhanced insulin secretion, suppression of glucagon release, delayed gastric emptying, and promotion of satiety, leading to substantial reductions in both HbA1c and body weight in clinical trials [4].

The U.S. Food and Drug Administration (FDA) initially approved Tirzepatide under the brand name Mounjaro in 2022 for the management of T2DM in adults inadequately controlled on lifestyle and metformin therapy. More recently, in 2023, the FDA granted approval under the brand name Zepbound for chronic weight management in adults with obesity (BMI ≥30 kg/m²) or overweight (BMI ≥27 kg/m²) with at least one weight-related comorbidity. These dual approvals underscore Tirzepatide's broad therapeutic potential in addressing both glycemic control and obesity, two conditions intricately linked through metabolic dysfunction.

Beyond its direct metabolic actions, there is emerging interest in the interplay between Tirzepatide and the gut microbiome. The gut microbiota plays a crucial role in nutrient metabolism, energy balance, and insulin sensitivity, and alterations in its composition have been implicated in the pathogenesis of obesity and T2DM [5]. Given Tirzepatide's unique dual-incretin mechanism and its profound metabolic effects, investigation into its potential modulatory effects on the gut microbiome represents an important and timely area of research.

Accordingly, this narrative review aims to explore the current evidence regarding Tirzepatide and its interactions with the gut microbiome, highlighting mechanistic insights, clinical implications, and directions for future investigation.

2. Methods:

We performed a comprehensive literature search of experimental, translational, and clinical studies examining the effects of tirzepatide on gut microbiota composition, bile acid metabolism, and metabolic regulation. Relevant studies were identified through searches of PubMed, Embase, and Google Scholar using combinations of keywords such as "tirzepatide," "GIP-GLP-1 dual agonist," "microbiota," "bile acids," "metabolic regulation," "GLP-1 receptor agonist," and "DPP-4 inhibitor." Articles were selected based on relevance to tirzepatide's efficacy, safety, and mechanistic effects. Comparative studies with GLP-1 receptor agonists and DPP-4 inhibitors were also included to determine its relative efficacy and safety.

3. Role of Microbiota and Homeostasis

The gut microbiome, also referred to as the gut microbiota, is the entire community of microbes residing in the mammalian gastrointestinal tract. A standard adult male has 3.8×10^{13} microbes, which is more than their own human cells. Out of the five main phyla of bacteria that make up the human gut microbiota, Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, and Verrucomicrobia are the most dominant, accounting for 90% of the population. A diverse and well-structured gut microbiota is essential for maintaining health, while a reduced diversity, known as dysbiosis, is associated with metabolic diseases.[6]

The gut microbiome plays a foundational and multifaceted role in maintaining host metabolic homeostasis. This is a bidirectional relationship, where external factors like diet, lifestyle, and antibiotic use influence the microbiome's composition, and the microbiome, in turn, profoundly

 doi:10.20944/preprints202509.1540.v1

affects the host's energy balance and overall health. The primary mechanisms through which the gut microbiome regulates this stable internal state are:

- Energy Harvest and Nutrient Metabolism: The gut microbiota assists the host in extracting energy from dietary components that would otherwise be indigestible. These microorganisms ferment complex carbohydrates and plant polysaccharides into readily absorbable metabolites, which contribute significantly to the host's energy pool. This function is critical for maintaining a balanced energy state, as an altered microbial community can either increase or decrease the efficiency of calorie extraction[7].
- Production of Key Signaling Metabolites: The microbiome communicates with the host by producing a wide range of metabolites that act as crucial signaling molecules.
- Short-Chain Fatty Acids (SCFAs): SCFAs, including acetate, propionate, and butyrate, are the most well-studied of these metabolites. They are produced through the microbial fermentation of dietary fibers. Butyrate is a primary energy source for colonocytes, while acetate and propionate are absorbed into the bloodstream to influence systemic metabolism. SCFAs are known to increase satiety and decrease food intake. They bind to specific receptors on enteroendocrine cells, leading to the release of gut hormones like peptide YY (PYY) into the bloodstream. This process serves as a communication link between the gut and the rest of the body, ultimately contributing to a reduction in food intake[8].
- Secondary Bile Acids: The gut microbiota plays a pivotal role in metabolizing primary bile acids, which are synthesized in the liver, into secondary bile acids. These secondary bile acids activate key host receptors, such as the farnesoid X receptor (FXR) and the G protein-coupled membrane receptor 5 (TGR5). This activation regulates metabolic pathways related to lipids, carbohydrates, and energy expenditure, predominantly in the liver and other peripheral organs[9].
- Regulation of Gut Hormones: The microbiome directly influences the host's endocrine system. Microbial metabolites like SCFAs and secondary bile acids signal to enteroendocrine cells in the gut lining, which in turn secrete important gut hormones such as glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), which are central to regulating appetite and promoting satiety, thereby influencing overall energy intake and promoting healthy metabolism[7]
- Maintenance of Intestinal Barrier Function: A healthy, balanced gut microbiota (eubiosis) is essential for maintaining the integrity of the intestinal epithelial barrier. This barrier acts as a physical and immunological shield, preventing the translocation of harmful bacterial components, such as lipopolysaccharide (LPS), into the bloodstream. A compromised barrier, or "leaky gut," leads to systemic low-grade inflammation, a key driver of insulin resistance and Type 2 Diabetes[6]

4. Dysbiosis and the Pathophysiology of Metabolic Diseases.

Dysbiosis is a condition characterized by a significant alteration in the diversity and composition of the microbial community. It is associated with metabolic diseases like obesity, diabetes, and non-alcoholic fatty liver disease, suggesting that the gut microbiota is a key factor in modulating host metabolism and related disorders.

Dysbiosis contributes to both obesity and diabetes by causing chronic inflammation and metabolic dysfunction. This process often begins when the gut's lining becomes more permeable, a condition known as "leaky gut," allowing pro-inflammatory molecules like lipopolysaccharide (LPS) to enter the bloodstream. This systemic inflammation is a key factor in the development of both conditions. In obesity, this inflammation, along with altered microbial metabolites, negatively impacts lipid metabolism, worsening triglyceride and cholesterol levels, which affects fat cell formation, breakdown, and fatty acid oxidation. In diabetes, this same systemic inflammation impairs insulin signaling, leading to insulin resistance, while the gut's ability to metabolize certain compounds is reduced, further contributing to abnormal glucose metabolism. The dysbiosis-induced inflammation is therefore a central, shared pathophysiological mechanism linking both obesity and diabetes[10][10].

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The pathophysiology of non-alcoholic fatty liver disease (NAFLD) is also directly linked to an altered gut microbiome. This dysbiosis compromises the integrity of the intestinal barrier, leading to a "leaky gut." This allows bacterial byproducts, specifically lipopolysaccharides (LPS), to travel from the gut to the liver via the portal vein. Once in the liver, LPS triggers inflammation and fat accumulation, which can cause steatosis and fibrosis, eventually progressing to more severe conditions like NASH and cirrhosis. The gut microbiome also influences NAFLD through its role in converting bile acids, with a reduction in this process observed in individuals with NAFLD. Additionally, some gut bacteria can produce harmful compounds like ethanol, which can cause further liver damage[11].

5. Tirzepatide and Gut Microbiome

Incretin-based therapies, including DPP-4 inhibitors and GLP-1 receptor (GLP-1R) agonists, show promise for treating type 2 diabetes and obesity by modulating the gut microbiota. Although numerous preclinical and clinical studies have examined the interaction between incretin-based drugs and the gut microbiota, a full understanding of this relationship remains elusive.

Tirzepatide is a dual agonist of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors and is a promising therapeutic option for type 2 diabetes mellitus (T2DM). The tirzepatide effectively reduced body weight, improved insulin resistance, decreased serum and hepatic lipid levels, and mitigated liver injury.

When compared to semaglutide, tirzepatide exhibited superior efficacy in reducing hepatic lipid accumulation. 16S rRNA gene sequencing and targeted metabolomics of BAs revealed that tirzepatide ameliorated gut microbiota dysbiosis and BAs metabolism in diabetic mice. Notably, tirzepatide observably increased the abundance of beneficial genera such as Akkermansia, elevated the ratio of farnesoid X receptor (FXR) antagonists (glycoursodeoxycholic acid: GUDCA, β-muricholic acid: β-MCA, hyodeoxycholic acid: HDCA, ursodeoxycholic acid: UDCA) to natural agonists (cholic acid: CA, lithocholic acid: LCA, chenodeoxycholic acid: CDCA, glycocholic acid: GCA, taurodeoxycholic acid: TDCA), and reduced FXR expression in intestinal tissues.[12]

Tirzepatide alleviated high-fat diet-induced dysbiosis by altering microbial composition and diversity. Following exposure to a high-fat diet, the abundance of certain bacterial genera, including Akkermansia, Bacteroides, Mucispirillum, Enterococcus, and Alistipes, significantly declines, whereas Faecalibaculum, Allobaculum, and Ileibacterium exhibit notable increases. Tirzepatide intervention facilitated the restoration of gut microbiota homeostasis after high-fat diet exposure. Additionally, correlation analyses revealed that Akkermansia, Bacteroides, and Enterococcus levels negatively correlate with weight gain, blood glucose levels, and various obesity-related indicators, whereas Ileibacterium and Allobaculum abundance positively associate with obesity-related traits.[13]

6. Comparison with Other Incretin Therapies

Other incretin-based therapies also demonstrate effects on the gut microbiome, but their mechanisms differ.

- DPP-4 inhibitors like sitagliptin and vildagliptin can modify the intestinal microbiota composition. Studies by Yan et al. [14] showed they reverse high-fat diet-induced changes, specifically by increasing. Bacteroidetes and butyrate-producing bacteria decrease the Firmicutes/Bacteroidetes ratio. In a similar vein, other studies have shown that vildagliptin led to an increase in Bacteroidetes and a decrease in Firmicutes. Liao X. et al. [15] and Silva-Veiga et al.[16] also showed that sitagliptin and linagliptin, respectively, increase the abundance of succinate and Bacteroidetes in non-diabetic mice.
- GLP-1R agonists such as liraglutide and semaglutide also significantly impact the gut microbiota. A study on semaglutide demonstrated its ability to mitigate microbial dysbiosis, increase beneficial bacteria, such as Akkermansia, and suppress excessive bacterial abundance.

 doi:10.20944/preprints202509.1540.v1

Liraglutide is described as increasing the abundance of SCFA-producing bacteria, including Bacteroides and Lachnospiraceae, as well as probiotic bacteria like Bifidobacterium [17,18]

While these therapies all positively modulate the gut microbiome, tirzepatide's dual-action mechanism and influence on bile acid metabolism are presented as key features distinguishing its effects.

7. Risks Associated with Tirzepatide.

Despite its powerful benefits, tirzepatide carries a risk profile that is largely centered on gastrointestinal (GI) side effects, which are a direct and expected consequence of its mechanism of action in slowing digestion. According to a recent systematic review of nine randomized controlled trials involving nearly 10,000 patients, tirzepatide's overall safety profile is similar to that of other GLP-1 receptor agonists. While most users do not experience severe adverse reactions, careful monitoring is needed, particularly at doses above 10 mg, for common side effects such as nausea, vomiting, and diarrhea, as well as injection-site reactions.[19]

The most frequent side effects are gastrointestinal, with decreased appetite often reported. Nausea and diarrhea can affect up to 10% of patients, and there are also infrequent reports of vomiting, acid reflux, and constipation. Dehydration from these gastrointestinal issues can, in rare cases, lead to acute kidney injury, even in healthy individuals. Patients should be advised to stay hydrated to prevent this complication.

Other, less common side effects have also been reported. Cardiovascular effects include infrequent reports of sinus tachycardia. Dermatological reactions, such as hypersensitivity at the injection site, have been reported at a similar rate to those seen with GLP-1 agonists. In the hepatobiliary system, rapid weight loss from tirzepatide therapy may cause gallstones (cholelithiasis) or gallbladder inflammation (cholecystitis).

For specific patient groups, there are additional considerations. The risk of pancreatitis is similar to that of other GLP-1 medications, and patients should seek immediate medical care for severe abdominal pain. Patients with pre-existing diabetic retinopathy may experience a temporary worsening of symptoms if their blood sugar control improves too rapidly. The risk of hypoglycemia is small and dose-dependent, but it is more significant for patients also taking insulin or sulfonylureas.

8. Future Implications:

Constipation-predominant IBS was linked to lower mucosal expression of GLP-1 receptors and serum GLP-1 concentrations. It is believed that reduced concentrations of GLP-1 would result in the loss of its prokinetic actions.[20]. In a trial, ROSE-010 was well tolerated and provided fast and effective relief of acute pain attacks on demand in IBS patients by reducing visceral hypersensitivity, a frequent symptom in IBS [21].

Studies by Desai et al found that semaglutide therapy was linked to significantly more weight reduction than other anti-obesity medications, except tirzepatide. Additionally, semaglutide was found to be safe for patients with IBD. Similarly, tirzepatide (TZP) resulted in a mean weight loss of greater than 10% in patients with inflammatory bowel disease (IBD), comparable to the weight loss observed in individuals without IBD treated with TZP. [22].

Semaglutide treatment modulated gut microbiota composition and structure, altered microbial metabolites, regulated neuroactive ligand-receptor gene expression, reduced astrocyte activation and neuroinflammation, preserved synapse structure, and improved cognitive function in diabetic mice, highlighting the potential of semaglutide and related GLP-1 receptor agonists, as well as dual GLP-1 and GIP receptor agonists, as promising treatments in preventing neurodegeneration. [23]

The SUMMIT trial showed that tirzepatide improves cardiovascular outcomes in obesity-related heart failure, reducing worsening events beyond weight loss effects. By targeting GIP and GLP-1

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receptors, it modulates the gut-heart axis through anti-inflammatory and direct cardiac actions, offering synergistic benefits with metabolic improvements.[24]

Current and upcoming clinical trials, including the SUMMIT and SURMOUNT programs, are designed to systematically evaluate the efficacy of the dual GIP/GLP-1 receptor agonist tirzepatide in diverse patient populations. These investigations, particularly those focusing on complex subsets such as individuals with obesity-related heart failure and chronic kidney disease, are essential for exploring the drug's clinical role beyond its established metabolic benefits.

A critical next step for advancing tirzepatide as a precision medicine is the incorporation of microbiome-focused analyses into large-scale clinical and translational research protocols. This approach is important for identifying the specific molecular and microbial factors that mediate tirzepatide's broad therapeutic effects. Such an understanding would be instrumental for refining patient stratification and for developing truly individualized interventions.

9. Conclusion:

Tirzepatide's action on the gut microbiome goes beyond metabolic control, uniquely impacting bile acid metabolism, microbial diversity, and intestinal barrier integrity. These changes not only support metabolic control but also lead to reduced systemic inflammation, improved insulin sensitivity, and the potential to improve cardiovascular, renal, and other obesity related complications. In addition, its modulatory effects on the gut microbiota highlight a possible role in conditions such as non alcoholic fatty liver disease, inflammatory bowel disorders, and even disorders of gut-brain signaling. Taken together, these findings highlight tirzepatide’s ability to act at the interface of metabolic, microbial, and immunological pathways. Ultimately, this bridges metabolic regulation with microbiome science, representing a paradigm shift in how we approach precision medicine and potentially transforming treatments for obesity, diabetes, and beyond.

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