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DIFFERENCES IN GUT MICROBIOTA MODULATION BY SEMAGLUTIDE, LIRAGLUTIDE AND TIRZEPATIDE

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ABSTRACT

Introduction and purpose: Gut microbiota has emerged as a key regulator of metabolic homeostasis. Incretin-based therapies such as semaglutide, liraglutide and tirzepatide not only improve glycemic control and promote weight loss, but may also exert systemic effects through microbiota modulation. This narrative review aims to compare the gut microbiota-related effects of these agents based on current preclinical and clinical evidence.
Material and method: A systematic search of PubMed and Web of Science databases was conducted for full-text studies published between 2020 and 2025. Inclusion criteria encompassed original research in humans and animals evaluating the impact of semaglutide, liraglutide or tirzepatide on gut microbiota. From 136 initial results, 30 eligible studies were included after removing duplicates and applying inclusion criteria.
Results: All three agents promoted increases in beneficial taxa such as Akkermansia muciniphila and SCFA-producing bacteria, and reduced pro-inflammatory genera. Semaglutide was associated with neuroimmune modulation, liraglutide with renal and hepatic benefits, while tirzepatide induced broader taxonomic shifts and diversity restoration, likely due to dual receptor agonism. Most findings derive from animal models, with limited human data available.
Conclusions: Semaglutide, liraglutide and tirzepatide demonstrate both shared and distinct microbiota-modulating properties, which may partly mediate their therapeutic effects. Further clinical studies integrating microbiota profiling and metabolic outcomes are needed to validate these findings and support microbiota-informed treatment strategies.

KEYWORDS

GLP-1 Receptor Agonists, Tirzepatide, Semaglutide, Liraglutide, Gut Microbiota, Metabolic Diseases

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1. Introduction

The human gut microbiota is increasingly recognized as a central regulator of host metabolic, immune, and neuroendocrine homeostasis. This intricate microbial ecosystem, composed predominantly of bacteria, plays a critical role in the digestion of nutrients, production of short-chain fatty acids (SCFAs), maintenance of intestinal barrier function, and modulation of systemic inflammation. Dysbiosis a disruption of microbial diversity and stability has been associated with the development of metabolic disorders such as obesity, type 2 diabetes mellitus (T2DM), and non-alcoholic fatty liver disease [1–3].

The introduction of incretin-based therapies, particularly glucagon-like peptide-1 receptor agonists (GLP-1 RAs), has transformed the clinical landscape of T2DM and obesity management. Agents such as liraglutide and semaglutide both selective GLP-1 Ras and tirzepatide, a dual GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist, offer not only superior glycemic and weight-reduction benefits but also show potential cardiometabolic and anti-inflammatory effects [4–6].

Recent evidence indicates that these agents may exert part of their systemic effects through modulation of the gut microbiota. Proposed mechanisms include direct interaction with intestinal GLP-1 receptors, improvement of mucosal barrier integrity, alteration of bile acid metabolism, and secondary shifts resulting from weight loss and metabolic normalization [7–9]. However, the extent and direction of gut microbiota modulation appear to differ across these agents, potentially due to variation in receptor targeting profiles, pharmacokinetic properties, and the presence of GIP co-agonism in the case of tirzepatide [10–12].

Despite growing interest, no comprehensive comparative review has yet evaluated the distinct effects of semaglutide, liraglutide, and tirzepatide on gut microbiota composition and function. This narrative review aims to synthesize available preclinical and clinical data published between 2020 and 2025 to critically compare how these three agents influence the gut microbiome. Only full-text, peer-reviewed publications in English were included to ensure high methodological consistency. The overarching goal is to clarify potential microbiota-related mechanisms of action and their relevance to future therapeutic strategies.

2. Methods

This narrative review was designed to synthesize and compare the effects of semaglutide, liraglutide, and tirzepatide on gut microbiota composition and function, based exclusively on full-text, peer-reviewed publications available in English. The review followed a structured approach to ensure methodological transparency and reproducibility.

2.1 Search Strategy and Data Sources

A systematic search was conducted in two major biomedical databases: PubMed and Web of Science. The search query used was:

("semaglutide" OR "liraglutide" OR "tirzepatide") AND ("gut microbiota" OR "intestinal microbiota" OR "gut microbiome" OR "intestinal flora"), limited to articles published between January 1, 2020, and June 30, 2025. Only original research articles with full-text availability in English were considered eligible.

2.2 Inclusion and Exclusion Criteria

Studies were included if they:

- Investigated semaglutide, liraglutide, or tirzepatide;
- Reported microbiota-related outcomes;
- Were conducted in humans or animal models (in vivo);
- Were published as full-text peer-reviewed articles in English.

Exclusion criteria:

- Review articles, conference abstracts, editorials, or protocols;
- In vitro studies or those not reporting any microbiota data;
- Non-English publications or incomplete records.

Screening and Selection

The initial search yielded 136 records: 47 from PubMed and 89 from Web of Science. After removing duplicates, 90 unique articles remained. Titles and abstracts were screened manually for relevance to gut microbiota and the specified GLP-1-based agents. 47 studies were retained for full-text review, and ultimately 30 studies met the inclusion criteria and were incorporated into this narrative analysis.

2.3 Data Organization

All included studies were qualitatively assessed and categorized by:

- Investigated compound (semaglutide, liraglutide, tirzepatide);
- Model type (human vs. animal);
- Method of microbiota analysis (e.g., 16S rRNA sequencing, SCFA quantification);
- Key findings related to microbial shifts, metabolic changes, and intestinal barrier integrity.

No meta-analytic synthesis was performed, as the heterogeneity in experimental design, endpoints, and microbiota analysis precluded quantitative pooling. Instead, data were narratively compared to highlight shared and unique microbiota-related effects across agents.

3. Effects of Semaglutide on Gut Microbiota

3.1. Preclinical Studies

Several preclinical studies have investigated the impact of semaglutide on gut microbiota using mouse models of diet-induced obesity, type 2 diabetes, cognitive impairment, and depression. These models have consistently shown that semaglutide treatment leads to significant shifts in microbial diversity and composition. In high-fat diet (HFD)-fed mice, semaglutide was associated with a notable increase in Akkermansia muciniphila, a bacterium linked to improved mucosal integrity and metabolic homeostasis [2,13,14]. Other commonly enriched genera included Bacteroides, Blautia, and Parabacteroides, taxa associated with SCFA production and anti-inflammatory properties [1,14].

In murine models of neuroinflammation and cognitive decline, semaglutide reversed dysbiosis by reducing pro-inflammatory genera such as Desulfovibrio and increasing beneficial taxa like Faecalibaculum and Lactobacillus [15–17]. These microbial changes were accompanied by decreased levels of systemic cytokines (e.g., IL-6, TNF-α), suggesting a gut-brain-immunometabolic axis potentially modulated by semaglutide.

3.2. Clinical Studies

Data from human studies remain limited. One small randomized controlled trial (RCT) in patients with obesity did not find significant taxonomic changes after 12 weeks of semaglutide treatment; however, subtle alterations in microbial metabolite profiles were reported [10]. Another observational study found increased Akkermansia and Bacteroides abundance in patients achieving ≥10% weight loss on semaglutide, although causality was not established [11].

The scarcity of human microbiota studies highlights a major research gap, especially given semaglutide's widespread clinical use and superior metabolic efficacy.

3.3. Microbial Taxonomic Changes

Across preclinical models, semaglutide consistently reduced the Firmicutes/Bacteroidetes ratio, a shift often associated with improved metabolic profiles [13,18]. Decreases in potentially pathogenic genera such as Helicobacter, Desulfovibrio, and Klebsiella were observed, alongside enrichment of commensal and probiotic taxa [16,19].

Of particular interest is the reproducible increase in Akkermansia muciniphila, which may mediate semaglutide's effects on gut barrier integrity and inflammation. Several studies also noted increased abundance of SCFA-producing genera, including Blautia and Faecalibaculum, suggesting a functional reconfiguration of the gut ecosystem toward anti-inflammatory and metabolically favorable states [14,20].

3.4. Functional and Metabolic Effects

Semaglutide-induced microbiota changes were functionally linked to improved insulin sensitivity, reduced endotoxemia, and enhanced intestinal barrier function. Markers such as serum lipopolysaccharide (LPS) levels, tight junction protein expression (e.g., ZO-1, occludin), and fecal SCFA concentrations were positively affected in treated animals [7,8,21].

Additionally, neurobehavioral improvements in depressive and cognitive models were accompanied by microbiota shifts, supporting a potential gut–brain interaction pathway. While these mechanisms remain hypothetical in humans, they offer intriguing directions for future translational research.

3.5. Summary and Limitations

In summary, preclinical evidence strongly supports the notion that semaglutide alters gut microbiota composition and function in a manner consistent with metabolic and anti-inflammatory benefits. Key microbial signatures include increases in Akkermansia, SCFA-producing genera, and reductions in pro-inflammatory taxa. However, human data are scarce, and causality remains speculative.

Well-designed, longitudinal studies in humans combining microbiome sequencing with metabolic, inflammatory, and neurocognitive endpoints are urgently needed to confirm the translational relevance of these findings.

4. Effects of Liraglutide on Gut Microbiota

4.1. Preclinical Studies

Liraglutide has been extensively evaluated in animal models of obesity, type 2 diabetes mellitus, nephropathy, non-alcoholic steatohepatitis (NASH), and inflammation. In murine studies, liraglutide consistently modified gut microbial composition toward increased abundance of beneficial taxa. Several studies reported enrichment of genera such as Lactobacillus, Bacteroides, and Ruminococcus, and a reduction in Desulfovibrio and Helicobacter, which are often linked to inflammation and metabolic dysregulation [13,22,23].

Additionally, liraglutide treatment was associated with improved intestinal morphology, tighter epithelial junctions, and a decrease in circulating endotoxins, indicating enhanced gut barrier integrity. These microbial and histological changes were frequently accompanied by reductions in pro-inflammatory cytokines and markers of oxidative stress [8,18,24].

4.2. Clinical Studies

Clinical evidence regarding liraglutide's effects on gut microbiota remains limited. In one pilot study, patients with obesity showed increased relative abundance of Lactobacillus and decreased Escherichia/Shigella following liraglutide administration [19]. Another study involving patients with diabetic nephropathy revealed microbiota shifts toward SCFA-producing bacteria and reductions in potentially pathogenic taxa [25].

While these data are promising, variations in study design, microbiota analysis methods, and small sample sizes limit generalizability. No large-scale randomized controlled trials have yet been published with microbiota as a primary endpoint in liraglutide-treated patients.

4.3. Microbial Taxonomic Changes

Liraglutide consistently promoted the expansion of health-associated genera across preclinical models. Increases in Lactobacillus, Bifidobacterium, and Blautia have been reported, often correlating with favorable metabolic parameters [13,22]. Reductions in Desulfovibrio, Klebsiella, and Helicobacter were associated with decreased gut permeability and systemic inflammation [18,23].

Importantly, some studies noted increases in microbial diversity (Shannon index), suggesting liraglutide may restore eubiosis in dysbiotic hosts [14,26].

4.4. Functional and Metabolic Effects

Beyond taxonomic shifts, liraglutide-induced microbiota changes were linked to functional outcomes. Increased SCFA production, particularly butyrate and propionate, was observed in several models and correlated with improved glucose tolerance, insulin sensitivity, and lipid profiles [7,8,20].

In models of nephropathy and NASH, liraglutide modulated gut microbiota in ways that may have contributed to reduced renal fibrosis, hepatic steatosis, and inflammation, potentially through modulation of the gut liver and gut kidney axes [22,25].

4.5. Summary and Limitations

In summary, liraglutide exerts reproducible effects on the gut microbiota in animal models, leading to increased abundance of probiotic taxa and reduction of pathogenic bacteria. These changes are associated with improved metabolic, inflammatory, and histological outcomes. However, clinical data remain scarce, and existing studies are limited by small sample sizes and heterogeneous designs.

Future research should focus on human RCTs integrating microbiota, metabolomic, and clinical endpoints to clarify liraglutide's gut-mediated mechanisms of action.

5. Effects of Tirzepatide on Gut Microbiota

5.1. Preclinical Studies

Tirzepatide, a dual GIP and GLP-1 receptor agonist, has been primarily evaluated in murine models of obesity, type 2 diabetes, and metabolic dysfunction. Across multiple studies, tirzepatide administration resulted in significant remodeling of gut microbiota composition, typically characterized by increases in Akkermansia muciniphila, Bifidobacterium, and Parabacteroides, and a decrease in pro-inflammatory genera such as Desulfovibrio and Helicobacter [4,13,27].

In HFD-fed mice and ovariectomized models simulating postmenopausal metabolic derangement, tirzepatide improved microbial richness and diversity while reducing systemic inflammation and endotoxemia [15,28]. Notably, it restored the integrity of intestinal tight junctions and enhanced SCFA production, particularly of acetate and butyrate.

5.2. Clinical Studies

As of mid-2025, there are no published randomized controlled trials directly evaluating the impact of tirzepatide on gut microbiota in humans. One small observational study involving patients with obesity and prediabetes suggested beneficial microbial shifts namely, an increase in Akkermansia after tirzepatide use, but these findings were preliminary and lacked mechanistic exploration [6].

This significant gap in clinical data limits the translatability of preclinical findings and underscores the need for human-focused microbiome investigations.

5.3. Microbial Taxonomic Changes

Preclinical studies showed consistent expansion of microbial taxa associated with metabolic homeostasis. Increases in Akkermansia, Bifidobacterium, Blautia, and Faecalibaculum were repeatedly observed, alongside declines in Desulfovibrio and other endotoxin-producing genera [4,12,13].

The reduction of the Firmicutes/Bacteroidetes ratio and restoration of alpha-diversity metrics suggest tirzepatide may reverse obesity-associated dysbiosis more robustly than GLP-1 monotherapy [13,28].

5.4. Functional and Metabolic Effects

Tirzepatide-associated microbiota shifts were linked to reduced intestinal permeability, decreased circulating LPS levels, and enhanced SCFA output. Improvements in glycemic control, lipid metabolism, and inflammatory markers were observed in parallel with microbial changes, particularly in models mimicking postmenopausal and insulin-resistant states [15,27,28].

In some studies, tirzepatide also modulated bile acid profiles and signaling via FXR and TGR5 pathways, which may mediate both gut and systemic metabolic effects [13,29].

5.5. Summary and Limitations

Tirzepatide has demonstrated consistent, favorable modulation of gut microbiota in preclinical models, exceeding some effects seen with semaglutide or liraglutide. Key features include increased Akkermansia and Bifidobacterium, higher SCFA levels, and improved barrier integrity. These effects are aligned with the dual incretin mechanism of action and may contribute to its superior clinical efficacy.

However, the absence of controlled human trials with microbiota outcomes remains a major limitation. Translational studies in humans are urgently needed to validate whether tirzepatide's microbiota-modulating effects have clinically meaningful implications.

6. Comparative Analysis and Discussion

6.1. Overview of Shared Microbiota Effects

Semaglutide, liraglutide, and tirzepatide, though pharmacologically distinct, exhibit several overlapping effects on gut microbiota across preclinical models. All three agents consistently increase the abundance of Akkermansia muciniphila, a bacterium associated with mucosal integrity and improved glucose metabolism [4,13,27,28]. Additionally, there is repeated enrichment of SCFA-producing genera such as Blautia, Bacteroides, and Faecalibaculum, which are linked to anti-inflammatory effects and energy homeostasis [8,14,20,24]. Concurrently, a reduction in genera implicated in systemic inflammation such as Desulfovibrio, Klebsiella, and Helicobacter is commonly observed [16,18,19]. These taxonomic shifts frequently coincide with improved insulin sensitivity, reduced circulating endotoxins, and enhanced intestinal barrier function [8,22,25].

6.2. Distinctive Features of Each Agent

Despite these commonalities, each agent also presents unique microbial signatures that may reflect differences in receptor affinity, pharmacodynamics, or downstream metabolic signaling. Semaglutide appears to exert a more pronounced influence on the gut–brain–immune axis, with studies in models of cognitive impairment and depression highlighting modulation of neuroinflammatory-related taxa [2,15,17]. Liraglutide shows distinct effects in models of nephropathy and non-alcoholic steatohepatitis, with microbiota changes correlating with improved renal and hepatic histology [18,24,25]. Tirzepatide, by contrast, demonstrates the most profound reshaping of the gut microbiota, including restoration of alpha-diversity and shifts in bile acid metabolism. These more robust effects may stem from its dual agonist action on both GIP and GLP-1 receptors[4,13,29].

6.3. Mechanistic Considerations

An ongoing challenge in interpreting these findings is the difficulty in distinguishing drug-induced microbiota changes from those secondary to weight loss, altered dietary intake, or metabolic improvement. For instance, it remains uncertain whether increases in Akkermansia or improvements in Firmicutes/Bacteroidetes ratio are a direct result of drug action or a consequence of reduced caloric intake and weight loss [11,28]. Many of the reviewed studies did not control for these confounders, making it challenging to determine causality [7,10]. Furthermore, alterations in microbial composition may in part reflect downstream effects of improved glucose metabolism or appetite suppression, rather than direct interactions between the drugs and the microbiota.

6.4. Translational Relevance and Limitations

While preclinical studies provide robust evidence of gut microbiota modulation by incretin-based therapies, clinical translation remains limited. Human studies evaluating semaglutide and liraglutide offer only preliminary insights, often constrained by small sample sizes, short duration, or methodological heterogeneity [6,19,25]. No randomized controlled trials have yet assessed tirzepatide's impact on human microbiota, despite promising preclinical data [13,28]. Moreover, few studies included functional analyses such as fecal metabolomics or gut permeability markers, and none employed causality-establishing techniques such as fecal microbiota transplantation [18,24]. These gaps underscore the need for rigorously designed human studies that integrate microbial, metabolic, and clinical endpoints to clarify the clinical relevance of these findings.

6.5. Implications for Future Research and Therapy

The evidence to date suggests that modulation of gut microbiota may partially mediate the metabolic benefits of incretin-based therapies, offering a potential target for treatment optimization. Patients with specific microbial deficiencies—such as low abundance of Akkermansia or SCFA-producing bacteria—may benefit more from agents with stronger microbiome-modulating effects [4,13,27]. Additionally, combining GLP-1 receptor agonists or tirzepatide with microbiota-directed interventions such as probiotics, prebiotics, or postbiotics could enhance therapeutic outcomes [16,22]. Beyond metabolic disorders, the influence of these agents on the gut microbiota raises intriguing possibilities in areas such as neuroinflammation, cardiovascular disease, and aging [15,17].

7. Clinical and Research Implications

Emerging evidence from preclinical studies and limited human trials suggests that the gut microbiota may represent both a mediator and a modifier of the metabolic benefits conferred by GLP-1 receptor agonists and dual GIP/GLP-1 agonists. This insight holds several potential implications for clinical practice and future research.

First, microbiota composition might serve as a predictive biomarker to personalize incretin-based therapies. For example, patients with low levels of Akkermansia muciniphila, Faecalibacterium prausnitzii, or other SCFA-producing bacteria could derive greater benefit from agents that promote their expansion [4,13,27]. If validated, this approach could inform baseline screening of microbiota profiles to match patients with specific incretin agents.

Second, future treatment strategies may involve co-administration of microbiota-targeting adjuncts such as probiotics, prebiotics, or postbiotics with GLP-1 receptor agonists or tirzepatide to potentiate their metabolic and anti-inflammatory effect [16,22][30]. Such combinations might enhance gut barrier integrity, reduce endotoxemia, or amplify short-chain fatty acid production, potentially yielding superior clinical outcomes in obesity, type 2 diabetes, and NAFLD.

Third, the absence of randomized clinical trials evaluating tirzepatide's microbiota effects constitutes a significant knowledge gap. Human studies integrating metagenomics, metabolomics, and functional outcomes such as insulin sensitivity, hepatic steatosis, or neuroinflammation are urgently needed. Especially valuable would be mechanistic studies employing fecal microbiota transplantation to establish causality [18,24].

Finally, microbiota-informed approaches may extend beyond glycemic control. Considering the observed effects on gut–brain, gut–liver, and gut–kidney axes, future research should explore whether microbiota modulation contributes to neuroprotective, nephroprotective, or anti-aging benefits of incretin therapies[2,15,17].

In sum, gut microbiota profiling and modulation may become integral components of precision metabolic medicine. However, robust human data are essential to translate the promising findings of this review into therapeutic reality.

8. Conclusions

This narrative review demonstrates that semaglutide, liraglutide, and tirzepatide while pharmacologically distinct share the ability to modulate gut microbiota composition in ways that may contribute to their systemic metabolic effects. Across preclinical models, all three agents consistently promoted the growth of beneficial taxa such as Akkermansia muciniphila and SCFA-producing genera, while reducing pro-inflammatory or pathogenic microbes. These changes were associated with improved glycemic control, reduced systemic inflammation, and enhanced gut barrier integrity.

Each agent also exhibited unique microbial signatures, likely reflecting differences in receptor activity and metabolic pathways. Semaglutide was primarily associated with neuroimmune modulation, liraglutide with hepatorenal benefits, and tirzepatide with the broadest microbial restructuring, possibly due to dual GIP/GLP-1 receptor agonism.

Despite encouraging results, most data derive from animal studies. Clinical trials evaluating microbiota changes particularly for tirzepatide remain scarce. Furthermore, the mechanistic links between microbial shifts and clinical outcomes have yet to be fully elucidated. Therefore, microbiota-informed precision therapy using incretin agents remains a promising but as yet unrealized frontier.

To translate these findings into clinical application, future studies must integrate microbiota profiling with metabolic, immunologic, and neurocognitive endpoints in well-designed human cohorts. If confirmed, gut microbiota may become not only a marker but a modifiable mediator of treatment response in metabolic disease.

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Methodology: JN
Software: JN, MK, MKa, AP
Check: JN, MK, MKa, DB
Formal analysis: JN, PK, MKa, DB
Investigation: JN, PK, PM, DB, DŻ
Resources: JN, PK, PM, BS, DŻ
Writing- rough preparation: JN, TS, PM, BS
Writing- review and editing: JN, TS, AP, BS
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