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Decoding The Gut-Brain-Microbiome Axis In GLP-1 Signaling

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Abstract

The treatment of type 2 diabetes and obesity has been reshaped by glucagon-like peptide-1 receptor agonists (GLP-1RAs), which produce substantial weight loss along with clear metabolic benefits. Increasing evidence shows that these drugs act beyond classical endocrine pathways, engaging interconnected biological systems that link the gut microbiome with the gastrointestinal tract, immune system, and brain. However, much of the existing research on GLP-1RA-induced microbiome changes remain largely associative, and the mechanisms through which these microbial shifts influence neuroendocrine regulation, adipose tissue remodeling, and preservation of lean mass are still poorly understood. This review integrates findings from preclinical and clinical studies to examine how GLP-1RAs alter gut microbial composition and how microbial metabolites shape hormone secretion, immune balance, gut–brain communication, and tissue-specific metabolic responses. Across studies, GLP-1RAs consistently promote short-chain fatty acid–producing bacteria while suppressing pro-inflammatory taxa. By framing the gut microbiome as an active partner in GLP-1-mediated effects rather than a passive bystander, this review highlights new opportunities for developing more personalized and durable metabolic therapies.

Keywords: GLP-1 receptor agonists; gut microbiome; gut-brain axis; short-chain fatty acids; adipose tissue remodeling; neuroendocrine signaling; sarcopenia

Introduction

The main therapies for type 2 diabetes (T2D) and obesity today consist of glucagon-like peptide-1 receptor agonists (GLP-1RAs), which not only effectively control blood glucose levels but also encourage considerable weight loss and reduce cardiovascular risk [1-4]. The metabolic impacts of GLP-1RAs go beyond their conventional functions, as they operate through a variety of interconnected systems linking the gastrointestinal (GI) tract, central nervous system (CNS), and immune system [5-7]. This integrated signaling network, now acknowledged as the gut-brain-microbiome axis, manages nutrient detection, appetite regulation, inflammation, and energy equilibrium, highlighting that GLP-1 acts at the convergence of metabolic and neuroendocrine control [8-10]. Treatment with GLP-1RAs during the initial year typically results in weight loss ranging from 15% to 25% [11,12]. However, the long-term sustainability of these effects remains uncertain, as many patients tend to regain weight upon discontinuation of therapy. The need for enduring and effective interventions is further underscored by the prevalence of GI side effects and rare but serious complications, such as pancreatitis and bowel obstruction, alongside the critical importance of preserving lean body mass [13,14]. While most studies indicate that fat loss is more pronounced than skeletal muscle loss, the biological mechanisms governing tissue-specific remodeling during GLP-1-induced weight loss remain insufficiently understood [15].

Importantly, the gut microbiome functions as an adaptive system that controls metabolism, immune reactions, and neuroendocrine signaling in the host [16-18]. GLP-1RAs affect microbial populations by encouraging the proliferation of bacteria that produce short-chain fatty acids (SCFAs), such as Akkermansia, Bifidobacterium, Roseburia, and Faecalibacterium, while inhibiting pro-inflammatory and unbalanced species [19-21]. Microbial byproducts, such as butyrate and propionate, strengthen the intestinal barrier, enhance insulin sensitivity, modulate appetite regulation, and decrease systemic inflammation [22,23]. These byproducts also activate intestinal L cells, boosting the secretion of endogenous GLP-1 and creating a reciprocal feedback mechanism between the host and its microbes [24,25]. Overall, these results indicate that the gut microbiome acts not just as a passive responder but as an active player in mediating the effectiveness of GLP-1.

Despite these advancement, notable gaps still exist. The majority of research is correlational, which restricts our ability to understand how alterations in the microbiome affect metabolic and neurobehavioral results. The microbial gene signatures that predict

responses to GLP-1 vary inconsistently across various drug formulations and research designs, which reflects differences in treatment duration, dietary management, initial metabolic conditions, and additional medications [26,27]. Although independent relationships have been identified between GLP-1 therapy, gut microbiota composition, and skeletal muscle, direct evidence does not exist to show that microbial changes induced by GLP-1 provide protection against muscle loss during weight reduction caused by pharmacological means. This concern is especially relevant due to the potential risk of sarcopenia and loss of function during significant weight loss. 28 Similarly, the ways in which microbial signals influence brain insulin and leptin sensitivity, neuroinflammation, and the circuitry of the hypothalamus are still largely uncharted, as the integration of microbiome research with studies of the CNS has yet to be fully realized [29,30]. Additionally, our capacity to monitor temporal changes and establish causal relationships across the gut-brain-microbiome axis is further complicated by the absence of longitudinal, mechanistic, and multi-omics studies [31,32].

This review thus consolidates existing preclinical and clinical studies to investigate the relationships between GLP1-RAs, the gut microbiome, and the gut–brain axis (GBA). The first parts present findings that show how different GLP-1 analogs affect microbial diversity, composition, and metabolic function. Following this, the review discusses how alterations in the gut microbiome due to GLP-1RA influence neuroendocrine signaling, aid in correcting immune imbalances, and promote overall metabolic equilibrium. The article also explores how these effects impact the remodeling of adipose tissue (AT) and emphasizes the potential danger of muscle loss, such as sarcopenia, which has become a notable concern with GLP-1 analog therapy. By identifying the gut microbiome as an active player in the effects mediated by GLP-1 instead of a mere passive factor, this review puts forth a conceptual framework designed to clarify the variability in therapeutic responses and to inform the creation of personalized GLP-1 strategies that take the microbiome into account.

Impact of GLP-1 Analogs on Gut Microbiota: Preclinical and Clinical Insights

GLP-1RAs, such as liraglutide, semaglutide, and dulaglutide, are increasingly acknowledged for their potential to affect gut microbiota in addition to their well-known functions in regulating blood glucose levels and aiding in weight loss [1-4]. Initial studies in animals suggest that these agonists effectively contribute to maintaining microbiome equilibrium by fostering optimal conditions for the proliferation of beneficial microorganisms like Akkermansia muciniphila, Bacteroides, Lactobacillus, Roseburia, and Faecalibacterium prausnitzii [33,34]. Certain microorganisms excel at generating SCFAs, such as butyrate and propionate, which have demonstrated the ability to improve insulin sensitivity, bolster the intestinal barrier, and decrease systemic inflammation [23,24]. In terms of mechanism, GLP-1RAs may improve gut health by influencing gut motility, altering luminal pH, and changing bile acid metabolism, thereby encouraging the growth of beneficial bacteria and supporting the gut-brain-microbiome connection [7,21,22,24,25,35].

The evidence presented in Table 1 [36-66] substantiates these effects. Liraglutide significantly influences the microbiota by increasing the relative abundance of Akkermansia, Bacteroides, Lactobacillus, Parabacteroides, and Oscillospira across various rodent models [36-38]. In models following a methionine- and choline-deficient (MCD) diet, liraglutide not only restores Bacteroides populations but also alters the Erysipelotrichaceae composition from Allobaculum to Turicibacter, indicating its potential to prevent diet-induced dysbiosis in the context of liver disease [39,40]. In male db/db mice, an increase in short-chain fatty acid (SCFA)-producing bacteria (such as Parabacteroides, Oscillibacter, and Prevotellaceae) coincides with a reduction in pro-inflammatory genera (like Anaerotruncus and Lachnospiraceae) and a positive change in alanine aminotransferase/aspartate aminotransferase (ALT/AST) levels, thereby establishing a clear connection between changes in the microbiome and metabolic as well as liver health benefits [41-43].

Table 1: GLP-1 Analog Effects on Gut Microbiota.

GLP-1 Analog	Model / Study Type	Microbiota Changes (Composition / Diversity)	Functional / Metabolic Outcomes
Liraglutide	Animal (rodent models)	↑ Beneficial genera (e.g., ***Akkermansia***, ***Bacteroides***, ***Lactobacillus***, ***Parabacteroides***,	Enhanced glucose metabolism, reduced weight gain, improved lipid profiles [36-

		Oscillospira); ↓ harmful taxa; ↓ *Firmicutes:Bacteroidetes* ratio in some models	38]
	Animal (MCD diet: methionine-choline deficient)	Restored normal *Bacteroides* levels; shifted *Erysipelotrichaceae* from *Allobaculum* → *Turicibacter*; overall altered gut microbiota disrupted by MCD diet	Potential mitigation of diet-induced dysbiosis; supports metabolic homeostasis in liver disease model [39,40]
	Animal (Male db/db mice)	↑ SCFA-producing/anti-inflammatory taxa (*Parabacteroides, Oscillibacter, Prevotellaceae)*; ↓ *Anaerotruncus, Lachnospiraceae*; correlated with ALT/AST	Anti-inflammatory effects via SCFAs; improved liver markers [41-44]
	Human (T2D patients)	↑ *Akkermansia* vs metformin; no consistent alpha/beta diversity change in RCTs	Correlate with improved gut-barrier taxa; clinical significance unclear [45]
Semaglutide	Animal (obesity / high-fat diet)	↑ *Akkermansia*, *Faecalibaculum*, *Allobaculum*; restored dysbiotic taxa; often times reduced diversity	Reduced weight gain, enhanced glucose tolerance, improved gut-barrier integrity [46.47]
	Animal (PCOS model)	↑ *Helicobacter* (negatively correlated with body weight)	Weight loss correlated with microbiome shift [48,49]
	Animal (C57BL/6 mice, neurobehavioral model)	Modulates gut microbiota	Reduces hippocampal neuroinflammation; promotes neurogenesis via insulin/GLP-1 pathway; potential antidepressant and anxiolytic effects [50,51]
Dulaglutide	Animal models	↑ *Bacteroides*, *Akkermansia*, *Ruminococcus*	Improved metabolic patterns (SCFA, gut barrier support) [52,53]
	Human studies	Limited data; some ↑ *Lactobacillus*; no significant changes after 1 week, but microbial abundance decreased after 48 weeks in newly diagnosed T2D patients	Metabolic effects observed; microbial effects underpowered; long-term microbiota modulation [54,55]
Exenatide / Exendin-4	Animal models	↑ *Akkermansia*, *Barnesiella, Ruminococcus*; ↓ dysbiotic taxa	Improved metabolic parameters associated with microbiota shifts [56,57]
	Human observations	↑ *Coprococcus*, *Bifidobacterium* in small cohorts; otherwise, inconsistent	Limited clinical evidence for direct microbiota mediation [58]
GLP-1Ras (general)	Mixed clinical observations	Some ↑ *Akkermansia*, *Roseburia*, *Faecalibacterium*; SCFA-producing genera enriched; human diversity often unchanged	Suggestive links to glucose tolerance and inflammation regulation; causality not confirmed [59,60]
	Observational (Human patients)	Increased abundance of *Faecalibacterium prausnitzii*, negatively correlated with fasting blood glucose levels.	Improved glycemic control; suggests microbiota influences drug responsiveness [61,62]
	Observational (Human cohort)	Higher abundance of *Roseburia* associated with reduced obesity and dyslipidemia; *Prevotella/Bacteroides* ratio positively associated with obesity, with *Prevotella* linked to insulin resistance.	Improved metabolism [63,64]
Inflammatory / extra-metabolic models	Animal inflammatory models	Shifts toward more beneficial taxa (SCFA-producing *Firmicutes*); ↓ pathogenic taxa like Staphylococcus	Enhanced anti-inflammatory activity (IL-22), improved gut barrier; causality in humans unproven to date [65,66]

Abbreviations: GLP-1: Glucagon-Like Peptide-1; HFD: High-Fat Diet; T2D: Type 2 Diabetes; MCD: Methionine-Choline Deficient; SCFA: Short-Chain Fatty Acids; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; PCOS: Polycystic Ovary Syndrome; IL-22: Interleukin-22.

Moreover, high-resolution taxonomic data as shown in Table 2 [69-93], reveal that liraglutide not only boosts but also maintains the levels of SCFA-producing genera within Bacteroidota (Bacteroides, Alistipes, Parabacteroides, Butyricimonas) and Bacillota (Lactobacillus, Allobaculum, Clostridium, Oscillospira) [36]. At the same time, liraglutide decreases the occurrence of potentially harmful taxa such as Staphylococcus, Anaerotruncus, and Flavonifractor. Importantly, the notable decline in Prevotella_9 is particularly significant given the known link between microbiota dominated by Prevotella and insulin resistance (IR). This highlights the metabolic consequences of the microbial changes induced by GLP-1Ras [67,68].

Table 2: Liraglutide-driven changes in gut microbial taxa.

Phylum	Genus	Change with Liraglutide	Functional/Metabolic Relevance
Bacteroidota	*Bacteroides*	↑ Increased / Maintained	SCFA production; glucose homeostasis and gut barrier support [69,70]
	Alistipes	↑ Increased / Maintained	Acetate/propionate production; improved insulin sensitivity [71,72]
	Parabacteroides	↑ Increased / Maintained	SCFA production; anti-inflammatory, insulin-sensitizing [73,74]
	Butyricimonas	↑ Increased / Maintained	Butyrate producer; intestinal and metabolic health [75,76]
Bacillota (Firmicutes)	*Lactobacillus*	↑ Increased / Maintained	Gut barrier integrity; metabolic signaling (species-dependent) [77-79]
	Allobaculum	↑ Increased /Maintained	Linked to leanness and improved insulin sensitivity [80,81]
	Clostridium	↑ Increased / Maintained	Butyrate-producing taxa; gut barrier and anti-inflammatory effects [82,83]
	Oscillospira	↑Increased / Maintained	Associated with leanness and favorable metabolic profile [84,85]
Bacillota	*Staphylococcus*	↓ Decreased	Opportunistic genus; dysbiosis and inflammation [86,87]
	Anaerotruncus	↓ Decreased	Associated with metabolic dysfunction and inflammation [88,89]
	Flavonifractor	↓ Decreased	Pro-inflammatory; linked to insulin resistance [90,91]
Bacteroidota	*Prevotella_9*	↓ Markedly Decreased	Prevotella dominance associated with insulin resistance [92,93]

In addition to its function in regulating metabolism, GLP-1 signaling has a notable impact on anti-inflammatory mechanisms and cytoprotection in the gut. When GLP-1 receptors (GLP-1Rs) on intraepithelial lymphocytes (IELs) are activated, there is a decrease in pro-inflammatory cytokine levels, a reduction in the expression of interferon-stimulated genes (ISGs), and a lower rate of apoptosis in epithelial cells [94,95]. In an experiment with mice administered anti-CD3, treatment with exenatide results in a significant drop in levels of interferon gamma (IFNG) and ISG expression in intestinal epithelial cells (IECs), as well as a decrease in crypt cell apoptosis; these outcomes are not observed in mice lacking GLP-1R [96]. These results highlight the crucial importance of GLP-1R signaling in immune cells for sustaining gut homeostasis. In models of colitis, liraglutide successfully diminishes inflammation, maintains crypt structure, and restricts leukocyte infiltration, thus showcasing the protective benefits of GLP-1RAs on intestinal health [97,98].

Furthermore, semaglutide (Table 1) shows distinct microbial profiles, featuring Akkermansia, Faecalibaculum, and Allobaculum, along with improved glucose tolerance and enhanced gut barrier integrity [46,47]. Certain research outcomes are notable, indicating a decrease in microbial diversity, which implies that functional remodeling may play a more significant role than diversity metrics in influencing therapeutic effectiveness. Changes in the microbiome in models of polycystic ovary syndrome (PCOS) have been linked to weight reduction, while studies on neurobehavioral effects have revealed lower inflammation in the hippocampus and increased neurogenesis, thereby supporting the involvement of GLP-1RAs in the GBA [48-51].

More importantly, clinical observations align closely with these preliminary findings. Short-term treatment with liraglutide positively impacts the microbiome, while prolonged dulaglutide treatment leads to gradual changes in the microbial community, mirroring the slow and steady progress in glycemic control, weight loss, and reduction of inflammation [99,100]. It's important to recognize that the baseline composition of the microbiome affects treatment outcomes: a greater presence of Bacteroides dorei and Roseburia inulinivorans is linked to more pronounced decreases in HbA1c, while an increase in Prevotella copri may hinder treatment success [26,101]. Multiple clinical studies consistently show a rise in key strains that produce SCFAs, such as Faecalibacterium prausnitzii and Roseburia, which are inversely related to fasting glucose levels and dyslipidemia [102,103].

Interestingly, research from retrospective studies suggests that GLP-1RAs not only assist but also improve the quality of life for individuals with inflammatory bowel disease (IBD), especially those who have T2D, underscoring the drugs' dual role in metabolic and immune modulation [104,105]. In studies involving mouse models of inflammation, GLP-1RAs facilitate the proliferation of Firmicutes that produce SCFAs and generate Interleukin-22 (IL-22), while also suppressing harmful bacteria like Staphylococcus, which aligns with the observed reduction in epithelial cell death and the activation of the interferon signaling pathway [106,107].

Lastly, GLP-1RAs activate a bidirectional regulatory system that interlinks host metabolism with the immune response in the intestines and the ecology of gut bacteria. The metabolic byproducts produced by bacteria, such as SCFAs, enhance the release of natural GLP-1, while GLP-1RAs alter signaling pathways, acid responses, immune reactions, and the composition of gut microorganisms, leading to increasingly robust therapeutic feedback mechanisms

[108,109]. Studies suggest that the gut microbiome acts not merely as a passive entity but as an active biological influencer of GLP-1RA effectiveness, providing compelling support for microbiome-targeted precision therapies for conditions such as T2D and IBD [110,111].

The Gut Microbiome as A Modulator Of GLP-1-Driven Neuroendocrine Signaling

Signals originating from the gut microbiome have a significant effect on neuroendocrine function via several interconnected pathways that correspond with the known mechanisms of GLP-1Ras [112-114]. These pathways include the modulation of gut hormone release, neural communication between the gut and brain, immune system signaling, and metabolic networks in the host. Metabolites that derive from the microbiota, especially SCFAs and secondary bile acids, activate G-protein-coupled receptors such as free fatty acid receptor 2 (FFAR2) and free fatty acid receptor 3 (FFAR3), as well as Takeda G-protein-coupled receptor 5 (TGR5), which are expressed by enteroendocrine L cells [115,116]. Activating these receptors leads to the release of endogenous GLP-1 and other hormones that regulate appetite, including peptide YY (PYY) and serotonin, which in turn impact appetite, glucose regulation, and energy balance [117,118]. Additionally, SCFAs are vital in determining the differentiation, quantity, and secretory capabilities of enteroendocrine cells, which affects both the baseline and stimulus-induced neuroendocrine responses [119,120].

In addition to hormone release, signals from the microbiome influence GBA via vagal afferent pathways that connect to the brainstem and hypothalamic areas responsible for feeding behavior, reward processing, and metabolic control—neural circuits that largely overlap with networks responsive to GLP-1 [121,122]. Evidence supporting this relationship comes from studies on mice treated with antibiotics, which demonstrate that the disruption of gut microbiota leads to increased GLP-1 levels in circulation along with decreased locomotor activity [123,124]. Interestingly, this reduced movement phenotype can be restored by blocking the GLP-1R pharmacologically or by disrupting subdiaphragmatic vagal signaling [123]. On the other hand, directly stimulating GLP-1R in brain regions that send signals through the vagus nerve is enough to trigger reduced locomotor activity, offering practical evidence for a microbiome-GLP-1-vagal pathway in the regulation of neurobehavior [123,125]. Reintroducing specific commensal species, such as Lactobacillus reuteri and Bacteroides thetaiotaomicron, into mice lacking gut microbiota lowers elevated GLP-1 levels and normalizes locomotor activity, thereby establishing a direct connection between microbial composition and GLP-1-related neuroendocrine effects.

Together, these results further support the idea that certain microbial taxa are closely associated with neuroendocrine functions related to GLP-1. For example, specific taxa in the Bacteroidetes phylum, especially Bacteroides species, have been found to affect GLP-1 secretion through the generation of SCFAs like acetate and propionate [126,127]. These metabolites promote the activity of enteroendocrine L-cells via the signaling pathways of free fatty acid receptors 2 and 3 (FFAR2/3), establishing a mechanistic connection between microbial metabolism and the regulation of gut hormones in the host [128,129]. Conversely, some Firmicutes, including butyrate-producing species like Faecalibacterium, Roseburia, and Eubacterium, are known to enhance the function of enteroendocrine cells and maintain barrier integrity, which in turn has an indirect effect on GLP-1 secretion and neuroendocrine activity [130,131]. Additionally, Lactobacilli have been shown to affect bile acid metabolism and vagal signaling, which further influences GLP-1 secretion and associated behavioral patterns [132,133]. The rise in specific microbial species, particularly Akkermansia muciniphila, has been linked to positive metabolic characteristics and increased secretion of gut hormones such as GLP-1, with stronger associations noted in both human and animal research [134,135].

In essence, the overall results indicate that specific microbial communities and functional groups, instead of overall microbial diversity, are crucial in modulating GLP-1-related neuroendocrine activities. This underscores the significance of microbial composition in governing brain-gut interactions through GLP-1-mediated pathways concerning the management of physiological responses. In this regard, Figure 1 shows that certain gut microbes produce metabolites that stimulate L cells to release GLP-1, PYY (Peptide YY), and serotonin, helping regulate appetite, metabolism, and energy balance while sending signals to the brain via the vagus nerve. These effects are shaped by specific microbial taxa rather than overall diversity, highlighting how targeted changes in the microbiome can influence gut-brain communication.

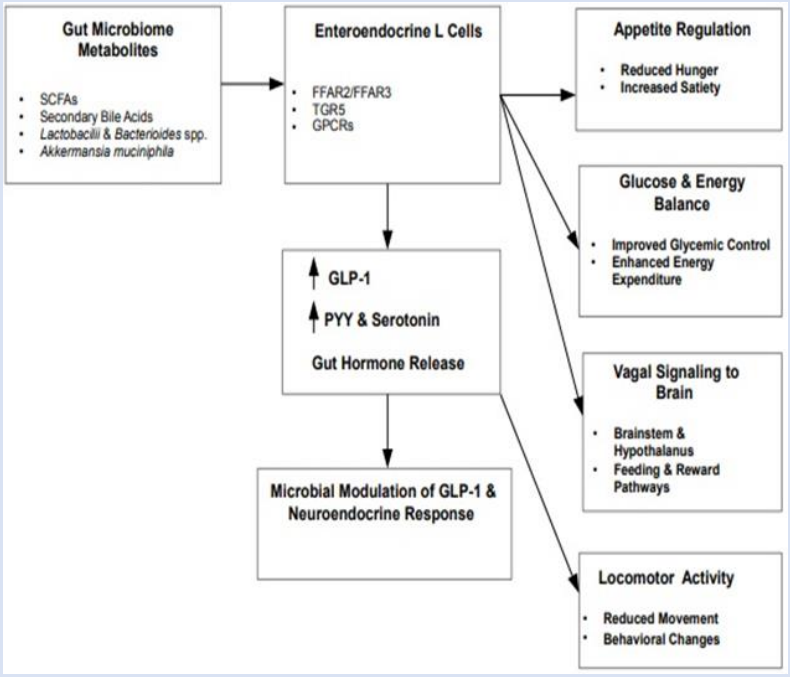

Figure 1: Gut microbiome modulation of GLP-1–driven neuroendocrine signaling. The gut microbiome generates a range of bioactive metabolites, including short-chain fatty acids (SCFAs) and secondary bile acids, which can act on enteroendocrine L cells via specific G-protein-coupled receptors, notably free fatty acid receptors 2 and 3 (FFAR2/3) and Takeda G-protein-coupled receptor 5 (TGR5). Activation of these signaling pathways promotes the secretion of gut-derived hormones such as glucagon-like peptide-1 (GLP-1), peptide YY (PYY), and serotonin. Collectively, these hormones regulate appetite, glucose homeostasis, and whole-body energy balance, while also influencing central neuroendocrine processes. In parallel, microbiome-derived signals engage vagal afferent pathways that relay information from the gut to the brainstem and hypothalamus, thereby integrating peripheral metabolic cues with neural circuits governing feeding behavior, reward processing, and locomotor activity. The figure illustrates how specific microbial metabolites and defined microbial taxa, rather than overall microbial diversity, contribute to brain–gut communication through GLP-1-mediated neuroendocrine signaling pathways.

GLP-1 and Microbiota: Linking the Brain and Adipose Tissue

The GLP-1RAs demonstrate strong impacts on all body metabolic functions. The treatment of GLP-1RA alters the composition of gut microbes. The treatment increases the beneficial microbial groups, which include Roseburia, Faecalibacterium prausnitzii, and Akkermansia [19]. Additionally, the treatment decreases the harmful obesity-related gut bacteria pattern, which shows high Firmicutes-to-Bacteroidetes ratios. The changes in gut bacteria lead to increased production of SCFAs such as acetate, propionate, and butyrate, which act on adipocytes through free fatty acid receptors 41 and 43 (GPR41/43) [19,136]. SCFAs induce white adipose tissue (WAT) to develop beige fat through increased expression of thermogenic and mitochondrial regulators, which include uncoupling protein 1 (UCP1) and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) [137-139]. In other words, WAT activation results in higher energy expenditure and better metabolic flexibility.

Microbiota changes induced by GLP-1RA treatment initiate two interlinked effects. These begin with alterations in SCFA signaling and subsequently diverge into bile acid-mediated pathways that modulate farnesoid X receptor (FXR) and Takeda G-protein-coupled receptor 5 (TGR5) activity [19 136]. Through these mechanisms, bile acids regulate hepatic lipid distribution and enhance thermogenic activity in AT. Bile acid-derived signals integrate with microbial metabolites to promote beige adipocyte recruitment, thereby supporting systemic lipid homeostasis [140,141]. Concurrently, intestinal signals are relayed through the GBA, which GLP-1RAs engage via two principal routes: vagal afferent signaling and hypothalamic circuits [142,143]. Together, these pathways coordinate appetite regulation, nutrient sensing, and sympathetic nervous system activity, ultimately shaping energy expenditure and fat storage. The convergence of bile acid-FXR/TGR5 signaling, microbial metabolite-driven adipocyte gene programs, and central neuroendocrine control establishes a microbiota-gut-brain-adipose axis through which GLP-1RAs support healthy AT

remodeling, WAT beiging, and overall metabolic balance [144,145]. This framework highlights that GLP-1RAs exert metabolic benefits extending beyond glucose regulation, acting as a mechanistic bridge between gut microbial dynamics and the integrated control of AT function and whole-body energy homeostasis [146,147]. In the context, Figure 2 shows that GLP-1RA-driven microbiota changes coordinate SCFA and bile acid signaling, promoting WAT beiging and gut-brain axis-mediated energy balance.

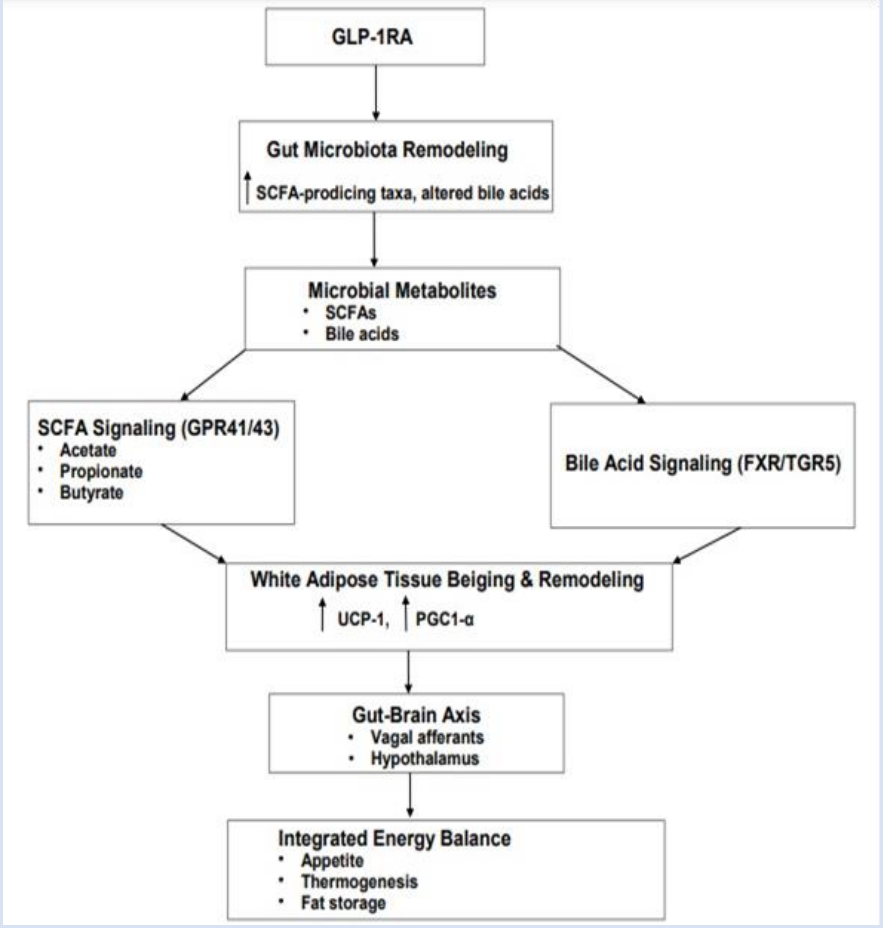

Figure 2: Glucagon-like peptide-1 receptor agonist–mediated microbiota-gut-brain-adipose axis. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) remodel the gut microbiota, increasing short-chain fatty acid (SCFA) production and altering bile acid signaling. SCFAs act on adipocytes via G-protein-coupled receptors 41 and 43 (GPR41/43) to promote white adipose tissue (WAT) beiging and thermogenic gene expression. In parallel, microbiota-modified bile acids activate the farnesoid X receptor (FXR) and Takeda G-protein-coupled receptor 5 (TGR5), regulating hepatic lipid metabolism and enhancing adipose thermogenesis. Intestinal signals are relayed through the gut-brain axis via vagal and hypothalamic pathways, coordinating appetite, energy expenditure, and fat storage. Together, these mechanisms establish an integrated microbiota-gut-brain-adipose axis underlying the metabolic benefits of GLP-1RAs.

GLP-1, Gut Microbiota, and Sarcopenia: Mechanistic Links

GLP-1RAs help preserve skeletal muscle homeostasis by reshaping the intestinal microbiome and its metabolic outputs, offering a novel therapeutic avenue for sarcopenia [148-150]. GLP-1RA treatment alters gut microbial composition, increasing the abundance of beneficial SCFA-producing bacteria such as Roseburia and Faecalibacterium prausnitzii, while reducing dysbiosis-associated taxa [45,47,52,54,59,68]. SCFAs-including acetate, propionate, and butyrate-activate GPR41 and GPR43 receptors expressed on myocytes and engage metabolic signaling pathways such as AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor (PPAR) networks, thereby promoting mitochondrial biogenesis, fatty acid oxidation, and protein synthesis [151-153].

GLP-1RA-induced microbial shifts also attenuate chronic low-grade systemic inflammation by reducing pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), which supports muscle protein integrity and recovery [154,155]. In parallel, microbial bile acid transformation improves insulin sensitivity, enhancing nutrient uptake and metabolic efficiency

in myocytes [156,157]. Activation of the gut-brain-muscle axis occurs as GLP-1 signaling engages dual circuits linking vagal afferent inputs to hypothalamic pathways, coordinating neuroendocrine outputs such as insulin-like growth factor-1 (IGF-1) signaling and sympathetic nervous system (SNS) activity that help maintain muscle mass and strength during aging [158-160].

Collectively, the GLP-1-microbiota-metabolite-gut-brain-muscle network integrates metabolic, inflammatory, and neuroendocrine pathways to support skeletal muscle maintenance, enhance functional strength, and reduce sarcopenia risk, highlighting the potential of GLP-1-based and microbiota-targeted strategies in the management of aging-related and metabolic disorders.

Future Directions

The gut-brain-microbiome axis encompasses interconnected metabolic pathways that converge on central systems regulating energy balance through insulin and leptin signaling. Brain IR is now recognized as a key contributor to obesity, T2D, and cognitive dysfunction, while leptin resistance disrupts hypothalamic satiety pathways and promotes maladaptive eating behaviors. Although microbiome modulation improves peripheral insulin sensitivity and reduces inflammatory burden, evidence for restoration of central insulin and leptin sensitivity remains limited. Microbiota-derived metabolites influence neuroinflammation, blood-brain barrier integrity, vagal signaling, and hypothalamic circuitry, suggesting that enhancing endogenous GLP-1 may complement pharmacologic GLP-1R agonism by engaging both peripheral and central metabolic pathways, warranting more evidence-based mechanistic insights in the future.

Conclusion

GLP-1RAs influence metabolic processes through pathways that integrate gut microbiome dynamics with immune responses, neural signaling, and peripheral metabolic tissues. The evidence presented in this review shows that GLP-1RAs consistently remodel gut microbial communities toward SCFA-producing and anti-inflammatory taxa, strengthening endogenous GLP-1 signaling, supporting gut-brain communication, and promoting healthy AT remodeling. Emerging findings further suggest that microbiome-mediated pathways may help preserve skeletal muscle during pharmacologically induced weight loss, raising important considerations regarding sarcopenia. The originality of this review lies in its unified framework, which positions the gut microbiome as an active biological mediator of GLP-1RA action across interconnected systems spanning the gut, brain, AT, and skeletal muscle. By linking microbial activity to lean mass preservation through integrated neuroendocrine and immune mechanisms, this work provides a foundation for personalized GLP-1–based therapeutic strategies that leverage microbiome insights to improve treatment efficacy and long-term metabolic health.

Declarations

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Conflict of Interest

The authors declare no conflict of interest.

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