Advances in Obesity, Endocrinology, and Diabetes

Volume 3 Issue 2 (July-Dec 2026) | **ISSN**: 3049-0715

GLP-1 receptor agonists and the immune microbiome infection axis: a narrative review

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Abstract

Background:

Obesity and type 2 diabetes mellitus (T2DM) are associated with chronic inflammation, immune dysfunction, and as a result increased risk of infections. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as key therapeutic agents with potential pleiotropic effects beyond glycemic control.

Objective:

This narrative review summarizes current evidence on the role of GLP-1 receptor agonists in modulating the immune–microbiome–infection axis and their potential impact on infection risk.

Methods:

A narrative review of recent experimental, clinical, and meta-analytic studies was performed focusing on immune regulation, inflammatory biomarkers, gut microbiota, and infectious outcomes.

Results:

GLP-1 RAs are associated with reduced systemic inflammation and oxidative stress, along with immunomodulatory effects including macrophage polarization and cytokine regulation. Emerging evidence suggests beneficial modulation of gut microbiota composition and improved intestinal barrier function. Studies have shown a reduction in infections, especially respiratory and systemic infections.

Conclusion:

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GLP-1 receptor agonists may act as immunometabolic modulators linking metabolic health with immune and microbial homeostasis. Further mechanistic studies are required to clarify their role in infection susceptibility.

Introduction

The global prevalence of obesity and type 2 diabetes mellitus (T2DM) has increased substantially over recent decades, representing a major challenge for healthcare systems worldwide. In addition to their metabolic consequences, both conditions are associated with impaired immune responses, chronic low-grade inflammation, and an increased susceptibility to infectious diseases. Patients with diabetes or obesity are more likely to develop severe infections and often experience poorer clinical outcomes, contributing significantly to morbidity and mortality on a global scale. (1,2)

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as a cornerstone in the management of T2DM and obesity. Originally developed as glucose-lowering agents, these drugs have demonstrated substantial benefits beyond glycemic control, including significant weight reduction, improvement of cardiovascular risk factors, enhancement of endothelial function, and favorable effects on metabolic health. As a result, the clinical use of GLP-1 receptor agonists has expanded rapidly in recent years, particularly with the widespread adoption of semaglutide and related agents. (3,4,5)

Beyond their established metabolic and cardiovascular benefits, increasing attention has been directed toward the pleiotropic effects of GLP-1 receptor agonists. A growing body of evidence suggests that these agents may exert anti-inflammatory properties and influence immune regulation through mechanisms that extend beyond glucose lowering. A meta-analysis of randomized controlled trials demonstrated significant reductions in inflammatory and oxidative stress biomarkers among patients receiving GLP-1 receptor agonist therapy, while more recent evidence has shown a consistent anti-inflammatory effect of semaglutide across different patient populations and treatment regimens. (6,7)

Experimental studies further support a direct interaction between GLP-1 signaling and the immune system. GLP-1 and its analogues have been shown to regulate the function of innate immune cells, particularly macrophages, promoting polarization toward an anti-inflammatory M2 phenotype. In addition, GLP-1 receptors have been identified on eosinophils, neutrophils, and invariant natural killer T (iNKT) cells, suggesting a broader role in immune modulation. These findings indicate that GLP-1 receptor agonists may act as immunometabolic regulators capable of influencing both inflammatory and host defense pathways. (8,9,10,11)

The immune–microbiome–infection axis describes a bidirectional biological network in which gut microbial homeostasis shapes immune tone, immune activity in turn modulates microbial ecology, and the dynamic equilibrium between these two systems ultimately determines host susceptibility or resilience to infection.

Another emerging area of interest involves the interaction between GLP-1 receptor agonists and the gut microbiome. Gut microbial alterations have been implicated in obesity, insulin resistance, chronic inflammation, and immune dysfunction. Similar to metformin, emerging evidence

suggests that GLP-1 receptor agonists may beneficially modulate gut microbiota composition and function. Specifically, GLP-1 RA therapy has been associated with increased abundance of beneficial taxa such as Bacteroides, alongside a reduction in obesity-associated Bacillota. These changes are linked to enhanced production of short-chain fatty acids, including butyrate and propionate, which support metabolic regulation and mucosal immune homeostasis. In addition, GLP-1 signaling may improve intestinal barrier integrity through modulation of tight junction proteins and suppression of proinflammatory cytokine activity, thereby reducing lipopolysaccharide (LPS) translocation into the systemic circulation. Totally, these microbiome and barrier-mediated effects may represent an important mechanistic pathway linking GLP-1 receptor agonists to host immune regulation and infection risk. (12)

Recent clinical evidence has also highlighted a potential association between GLP-1 receptor agonist therapy and infectious disease outcomes. A large systematic review and meta-analysis reported that GLP-1 RA use was associated with a reduced risk of serious infections, particularly those involving the respiratory, skin, musculoskeletal, vascular systems, and COVID-19-related complications. These benefits appeared to be partially mediated by weight reduction and improved glycemic control, although the underlying biological mechanisms remain incompletely understood. (13)

However, these effects remain fragmented across metabolic, immunological, and microbiome-focused studies, limiting an integrated understanding of their clinical relevance.
Despite the growing literature on the metabolic, immunological, and microbiome-related effects of GLP-1 receptor agonists, their impact on host immunity, microbial homeostasis, and susceptibility to infections has not been comprehensively evaluated. Understanding the complex interactions among GLP-1 signaling, immune regulation, gut microbiota, and infection risk may provide important insights into the broader clinical implications of these agents. Therefore, this narrative review aims to summarize current evidence regarding the

immune–microbiome–infection axis in patients receiving GLP-1 receptor agonist therapy and to explore the potential mechanisms through which these agents may influence infection-related outcomes.

GLP-1 receptor signaling: physiological roles and pleiotropic mechanisms

GLP-1 is an incretin hormone secreted by intestinal L-cells in response to eating. It exerts its physiological actions via the GLP-1 receptor (GLP-1R), a class B G-protein-coupled receptor expressed in pancreatic β-cells, the central nervous system, and the gastrointestinal tract. Activation of GLP-1R enhances glucose-dependent insulin secretion, suppresses glucagon release, delays gastric emptying, and promotes satiety, forming the basis of its glucose-lowering and weight-reducing effects in type 2 diabetes and obesity. (14,15)
Beyond its classical metabolic role, GLP-1 signaling exerts broad pleiotropic effects on cardiovascular and systemic physiology. Clinical trials of GLP-1 receptor agonists have demonstrated reductions in major adverse cardiovascular events, body weight, and improvements in cardiometabolic risk profiles. These benefits extend beyond glycemic control, suggesting systemic biological actions of GLP-1R activation.(16,3,4)

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At the intracellular level, GLP-1 receptor activation stimulates adenylate cyclase, increasing cyclic AMP (cAMP) production and activating protein kinase A (PKA) and exchange protein activated by cAMP (EPAC) signaling pathways. These pathways regulate insulin secretion and cellular metabolism, but also modulate inflammatory signaling cascades. In particular, cAMP-dependent inhibition of nuclear factor-kappa B (NF-κB) reduces transcription of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). (15,17)

Emerging evidence indicates that GLP-1 receptor signaling also interacts with the immune system. GLP-1 receptors have been identified on innate immune cells, including macrophages, neutrophils, eosinophils, and invariant natural killer T (iNKT) cells. Experimental studies suggest that GLP-1 receptor activation promotes macrophage polarization toward an anti-inflammatory M2 phenotype and suppresses activation of eosinophils and other immune effector cells, indicating a direct immunomodulatory role.(11,8,9,10)

Collectively, GLP-1 receptor signaling represents an immunometabolic regulatory pathway linking energy homeostasis with inflammatory control. In metabolic diseases such as obesity and type 2 diabetes, chronic low-grade inflammation contributes to immune dysregulation and disease progression. GLP-1 receptor activation may counteract these processes through combined metabolic improvement and suppression of inflammatory signaling pathways, providing a biological framework for its potential influence on infection susceptibility. (14,11,7)

Section 3: GLP-1 RA and immune modulation

3.1 Innate immunity: macrophages and myeloid cells

Emerging evidence suggests that glucagon-like peptide-1 receptor agonists (GLP-1 RAs) exert direct modulatory effects on innate immune responses. Experimental studies have demonstrated that GLP-1 signaling influences macrophage polarization, shifting cells from a pro-inflammatory M1 phenotype toward an anti-inflammatory M2 phenotype. This shift is mediated, at least in part, through STAT3-dependent signaling pathways and is associated with reduced production of pro-inflammatory cytokines and enhanced resolution of inflammation. (8,17)

In addition to macrophages, GLP-1 receptor expression has been identified in human monocytes and other myeloid-derived cells, supporting a broader role in innate immune regulation. These findings suggest that GLP-1 signaling may not only modulate metabolic pathways but also directly influence innate immune cell behavior, thereby shaping systemic inflammatory tone. (8,11)

3.2 Neutrophils and eosinophils

Beyond macrophages, GLP-1 receptor expression has also been identified on neutrophils and eosinophils, indicating that GLP-1 signaling may regulate multiple arms of innate immunity. In eosinophils, GLP-1 receptor activation has been shown to reduce cellular activation markers and

decrease the production of key cytokines including IL-4, IL-8, and IL-13. These effects suggest a potential role for GLP-1 signaling in modulating allergic and inflammatory responses. (9)

Although data on neutrophil-specific functional outcomes remain limited, available evidence supports a broader immunoregulatory role of GLP-1 signaling in innate immune effector cells, potentially contributing to controlled inflammatory responses during infection. (9,17)

3.3 Adaptive immunity: T cells and iNKT cells

Evidence also suggests that GLP-1 signaling may influence adaptive immune responses. Invariant natural killer T (iNKT) cells, which play a key role in bridging innate and adaptive immunity, have been shown to express GLP-1 receptors. Experimental studies indicate that GLP-1 signaling can modulate iNKT cell activity, particularly in metabolic inflammatory states such as obesity and diabetes. (10)

This interaction may contribute to altered cytokine production and immune regulation in chronic inflammatory diseases. Although direct evidence on classical CD4+ and CD8+ T cell modulation by GLP-1 receptor agonists is still limited, the presence of GLP-1R in immune-related pathways suggests potential downstream effects on adaptive immune homeostasis. (10)

3.4 Cytokine modulation and systemic inflammation

One of the most consistent immunological effects of GLP-1 receptor agonists is the reduction of systemic inflammatory markers. Clinical and translational studies have shown reductions in circulating levels of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) following GLP-1 RA therapy. (6,7,17) These changes reflect a broader attenuation of chronic low-grade inflammation, which is a hallmark of obesity and type 2 diabetes.

The anti-inflammatory effects of GLP-1 receptor agonists are thought to be mediated through both direct immune cell signaling and indirect metabolic improvements, including weight reduction and improved glycemic control. This dual mechanism may be particularly relevant in reducing infection susceptibility, as chronic inflammation is known to impair effective immune responses. (6,7)

3.5 Integrated immunometabolic interpretation

Collectively, current evidence supports the concept that GLP-1 receptor agonists act as immunometabolic regulators rather than purely glucose-lowering agents. By modulating innate and adaptive immune cell function, reducing pro-inflammatory cytokine production, and improving systemic metabolic status, GLP-1 signaling may contribute to restoration of immune homeostasis.

This immunomodulatory profile provides a mechanistic basis for the observed clinical associations between GLP-1 RA therapy and infection-related outcomes, suggesting that their effects extend beyond metabolic regulation to include systemic immune modulation. (11,17)

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Section 4: GLP-1 receptor agonists and the gut microbiome

4.1 Alterations in microbial composition

Emerging evidence indicates that GLP-1 receptor agonists (GLP-1 RAs) may influence gut microbial composition in both experimental and clinical settings. Although findings remain heterogeneous across studies, several consistent patterns have been reported, particularly in relation to obesity and type 2 diabetes populations.

Preclinical and clinical studies suggest that GLP-1 RA therapy is associated with an increased abundance of beneficial microbial taxa, including Akkermansia, Bacteroides, and members of the Lachnospiraceae family. These taxa are generally linked to improved metabolic profiles and reduced intestinal inflammation. Conversely, reductions in potentially pro-inflammatory or dysbiosis-associated groups, including certain Proteobacteria and an altered Firmicutes-to-Bacteroidetes ratio, have also been observed. (18,21)

Systematic reviews of gut hormone–microbiome interactions have highlighted that GLP-1-based therapies may partially reverse high-fat diet–induced dysbiosis, although inter-study variability remains significant due to differences in host phenotype, diet, and study design. (19,21)

4.2 Short-chain fatty acids and microbial metabolites

GLP-1 receptor agonist–induced microbiome changes are functionally associated with altered production of microbial metabolites, particularly short-chain fatty acids (SCFAs) such as butyrate and propionate. These metabolites play a critical role in maintaining intestinal epithelial integrity, regulating energy metabolism, and modulating mucosal immune responses.

SCFAs exert anti-inflammatory effects through multiple mechanisms, including inhibition of histone deacetylases and activation of G-protein–coupled receptors (e.g., GPR41 and GPR43), which are involved in immune and metabolic signaling pathways. Increased SCFA availability has been linked to improved insulin sensitivity and reduced systemic inflammation, suggesting a mechanistic link between microbiome modulation and metabolic benefit observed with GLP-1 RA therapy. (22,20)

4.3 Gut barrier integrity and endotoxin translocation

A key mechanistic pathway linking GLP-1 receptor signaling to host immunity involves modulation of intestinal barrier function. Experimental evidence suggests that GLP-1 signaling contributes to the maintenance of epithelial integrity through regulation of tight junction proteins and reduction of inflammatory signaling in intestinal epithelial cells. (19,20)

Improved barrier function reduces translocation of microbial products such as lipopolysaccharide (LPS) into the systemic circulation, thereby limiting metabolic endotoxemia. This reduction in

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endotoxin burden may contribute to decreased chronic low-grade inflammation observed in metabolic disease states.

In addition, incretin signaling pathways have been implicated in gut–liver axis regulation, further supporting a systemic role for GLP-1 in maintaining mucosal and metabolic homeostasis. (14,20)

4.4 Microbiome–immune–metabolic integration

Collectively, current evidence supports the concept that GLP-1 receptor agonists influence host physiology through an integrated microbiome–immune–metabolic network. Changes in microbial composition, increased SCFA production, and improved gut barrier integrity may act in concert to modulate systemic immune tone.

This integrated framework provides a mechanistic explanation for observed reductions in inflammatory biomarkers and suggests that GLP-1 RA therapy may indirectly influence infection susceptibility through microbiome-mediated immune modulation. However, causality remains to be established, and human interventional studies with standardized microbiome profiling are still limited. (18,19,21)

Section 5: Clinical evidence regarding infection outcomes

5.1 Overall infection risk

A growing body of clinical evidence has evaluated the association between GLP-1 receptor agonist therapy and infectious disease outcomes. Contrary to initial concerns regarding potential immunosuppressive effects, large-scale randomized clinical trials and meta-analyses have consistently demonstrated that GLP-1 receptor agonists are not associated with an increased risk of infections. In fact, some analyses suggest a modest reduction in overall infectious events. (13,24)

A recent comprehensive meta-analysis including over 160,000 participants from randomized controlled trials demonstrated that GLP-1 receptor agonist use was associated with a significant reduction in serious infections, non-serious infections, and total infections compared with control therapies. These findings suggest a neutral-to-protective safety profile with respect to infection risk. (13) A summary of the key studies evaluating infection outcomes in GLP-1 RA users is presented in Table 1.

Table 1. Summary of clinical studies evaluating infection outcomes with GLP-1 receptor agonist therapy

Study (ref)	Study type	Population	Infection outcome	Main finding	Limitation
Han et al., 2025 (13)	SR & MA	T2DM/obesity; >160,000 participants from RCTs	Serious, non-serious & total infections; respiratory;	↓ serious infections, ↓ respiratory	Secondary endpoints; heterogeneous

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Study (ref)	Study type	Population	Infection outcome	Main finding	Limitation
			skin; COVID-19	infections, ↓ skin & soft tissue infections	infection definitions
Xie et al., 2025 (25)	Real-world cohort	US Veterans Affairs; >1,000,000 individuals	175 health outcomes incl. respiratory, systemic & COVID-19 infections	↓ risk across multiple infectious domains; pleiotropic systemic effects	Residual confounding; indication bias; mostly male population
Zeng et al., 2026 (24)	Network MA	T2DM; GLP-1 RA vs SGLT2i vs placebo	Overall infections; infectious complications across drug classes	→ No increase in infection risk vs comparators; neutral–to–protective profile	Indirect comparisons; variable follow-up duration
Marso et al. (SUSTAIN-6), 2016 (16)	RCT	T2DM with high CV risk; n=3,297; 104 weeks	Infections as adverse events (secondary); diabetic retinopathy	→ No significant difference in infection rates; CV benefit confirmed	Not powered for infectious endpoints; short follow-up
Bray et al., 2021 (6)	SR & MA of RCTs	T2DM/obesity; multiple RCTs	Inflammatory biomarkers (CRP, IL-6, TNF-α) as surrogate infection risk markers	↓ CRP, ↓ IL–6, ↓ oxidative stress — indirect support for ↓ infection susceptibility	Surrogate endpoints only; no direct infection outcomes

Study (ref)	Study type	Population	Infection outcome	Main finding	Limitation
Masson et al., 2024 (7)	SR & MA	T2DM/obesity; semaglutide-focused	Anti-inflammatory effect (CRP, IL-6) as proxy for immune modulation	↓ systemic inflammation across diverse populations; consistent across doses	Surrogate endpoints; publication bias possible

Abbreviations: SR, systematic review; MA, meta-analysis; RCT, randomised controlled trial; T2DM, type 2 diabetes mellitus; CV, cardiovascular; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium–glucose cotransporter-2 inhibitor; CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha. ↓ reduced; → neutral/no significant difference.

Similarly, a network meta-analysis evaluating GLP-1 receptor agonists and SGLT2 inhibitors found no overall increase in infectious complications, further supporting the infectious safety profile of this drug class across multiple populations and study designs. (24)

5.2 Respiratory infections and COVID-19

Respiratory tract infections represent a major concern in patients with metabolic diseases due to impaired immune responses and chronic inflammation. Evidence from large meta-analyses indicates that GLP-1 receptor agonist therapy is associated with a reduced risk of respiratory infections.

In the largest available synthesis of randomized trials, GLP-1 RA use was associated with a statistically significant reduction in serious respiratory infections. This protective association was also observed during the COVID-19 pandemic period, suggesting that metabolic and anti-inflammatory effects of GLP-1 signaling may contribute to improved respiratory outcomes. (13)

These findings are consistent with broader observational data indicating that GLP-1 receptor agonists may reduce inflammation-driven complications in respiratory viral infections, although causality remains to be fully established. (25)

5.3 Skin, soft tissue, and vascular infections

Infections involving the skin, soft tissues, and vascular system are common complications in patients with diabetes and obesity due to impaired immune function and microvascular dysfunction.

Meta-analytic evidence suggests that GLP-1 receptor agonists are associated with a reduced incidence of these infection subtypes. In particular, reductions in skin and subcutaneous

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infections, musculoskeletal infections, and vascular-related infectious complications have been reported in randomized controlled trial populations.

These effects may reflect improvements in glycemic control, weight reduction, and systemic inflammatory status rather than direct antimicrobial or immunosuppressive actions. (13,17)

5.4 Evidence from real-world population data

Large-scale real-world evidence has further expanded understanding of the clinical safety profile of GLP-1 receptor agonists. A landmark population-based study using US Veterans Affairs databases (Nature Medicine) evaluated over one million individuals and assessed 175 health outcomes associated with GLP-1 receptor agonist use.

This study demonstrated that GLP-1 receptor agonist therapy was associated with reduced risk across multiple disease domains, including cardiometabolic disorders, neuropsychiatric outcomes, and selected infectious diseases. These findings support the hypothesis that GLP-1 receptor agonists may exert systemic effects beyond glucose lowering, potentially influencing host susceptibility to infection through immunometabolic pathways. (25)

5.5 Interpretation of infection outcomes

Taken together, current evidence from randomized trials, meta-analyses, and large real-world cohorts consistently indicates that GLP-1 receptor agonist therapy does not increase infection risk. Instead, a neutral or modestly protective association has been observed across multiple infection categories.

These findings are particularly important given the high baseline susceptibility to infections in patients with obesity and type 2 diabetes. However, most available studies were not primarily designed to evaluate infectious endpoints, and heterogeneity in definitions of infection outcomes remains a limitation. (13,24)

Therefore, while current evidence is reassuring, further mechanistic and prospective studies are required to clarify whether observed reductions in infection risk are primarily driven by metabolic improvements, immunomodulation, or microbiome-mediated effects.

Section 6: Proposed mechanistic framework — the immune–microbiome–infection axis

6.1 Conceptual integration of the axis

The immune–microbiome–infection axis represents an integrated biological framework in which host immunity, gut microbial ecology, and infectious susceptibility are dynamically interconnected. Rather than functioning as independent systems, the gut microbiome continuously shapes immune tone through microbial metabolites and antigenic signaling, while the immune system reciprocally regulates microbial composition and epithelial barrier integrity. Disruption of this bidirectional homeostasis contributes to dysbiosis, chronic inflammation, and

increased susceptibility to infectious diseases, particularly in metabolic disorders such as obesity and type 2 diabetes mellitus. (23,26)

6.2 GLP-1 signaling as an upstream immunometabolic regulator

Within this framework, GLP-1 receptor agonists can be conceptualized as upstream immunometabolic modulators that simultaneously influence metabolic, inflammatory, and microbial pathways. By improving glycemic control and reducing adiposity, GLP-1 RA therapy attenuates metabolic stress–driven inflammation, which is a key driver of immune dysfunction in obesity and diabetes. (14,15) Beyond metabolic effects, GLP-1 signaling directly modulates innate immune cell activity, including macrophage polarization and cytokine production, thereby reshaping systemic inflammatory tone. (11,17)

6.3 Microbiome-mediated immune reprogramming

A central component of this axis is the gut microbiome, which acts as a functional intermediary between GLP-1 signaling and host immunity. GLP-1 receptor agonist therapy has been associated with shifts in microbial composition toward taxa linked to metabolic health, alongside increased production of short-chain fatty acids such as butyrate and propionate. These microbial metabolites regulate immune homeostasis by enhancing regulatory immune pathways, suppressing pro-inflammatory signaling, and reinforcing epithelial barrier integrity. (22,23)

Strengthening of the intestinal barrier reduces lipopolysaccharide (LPS) translocation, thereby decreasing metabolic endotoxemia and systemic immune activation. This microbiome–barrier interface provides a plausible mechanistic link between GLP-1 therapy and reduced inflammatory burden. (19,20)

6.4 From immunomodulation to infection susceptibility

The downstream consequence of this integrated network is modulation of host susceptibility to infection. Chronic low-grade inflammation and immune dysregulation are key determinants of infection severity in metabolic disease. By attenuating inflammatory cytokine signaling, restoring immune cell balance, and improving gut barrier function, GLP-1 receptor agonists may reduce the biological vulnerability to infectious diseases.

This mechanistic framework is supported by clinical evidence demonstrating a neutral or reduced risk of infections in GLP-1 RA users across large randomized trials and population-based studies. These include reductions in respiratory infections, skin and soft tissue infections, and COVID-19-related complications, suggesting that immunometabolic improvement translates into clinically relevant infectious outcomes.
(13,25)

6.5 Integrated pathway model (conceptual synthesis)

Collectively, the available evidence supports a unified mechanistic model:

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GLP-1 receptor activation → metabolic improvement → reduced systemic inflammation → immune cell reprogramming → microbiome modulation → enhanced gut barrier integrity → decreased microbial translocation → improved immune homeostasis → reduced infection susceptibility

This model positions GLP-1 receptor agonists not only as antidiabetic and anti-obesity agents but also as systemic immunometabolic modulators operating through the immune–microbiome–infection axis. However, causality remains incompletely established, and future mechanistic and longitudinal interventional studies are required to validate this proposed framework. (11,7,14)

Section 7: Future directions and research gaps

7.1 Need for mechanistic human studies

Although accumulating evidence suggests that GLP-1 receptor agonists may influence immune pathways and gut microbiome composition, most mechanistic data are derived from preclinical models or indirect clinical biomarkers. Direct human studies linking GLP-1 signaling to immune cell function, microbiome dynamics, and infection susceptibility in an integrated manner remain limited. (13,25)

Future studies should incorporate multi-omics approaches (metagenomics, metabolomics, and immunophenotyping) to delineate causal pathways within the proposed immune–microbiome–infection axis. Longitudinal cohort studies with serial microbiome and immune profiling are particularly needed to establish temporal relationships between GLP-1 therapy and immune reprogramming.

7.2 Infection-specific endpoint limitation in current trials

Most randomized clinical trials evaluating GLP-1 receptor agonists were designed primarily to assess metabolic and cardiovascular outcomes. As a result, infection-related endpoints were often secondary, non-standardized, or underpowered for robust inference.

Although large meta-analyses suggest a neutral-to-protective effect on infections, these findings should be interpreted cautiously due to heterogeneity in infection definitions, reporting bias, and lack of pathogen-specific analyses. Future randomized trials should include predefined infectious disease endpoints with standardized classification systems.

7.3 High-risk populations: immunocompromised and elderly patients

Data on GLP-1 receptor agonist effects in immunocompromised populations remain scarce. Patients with malignancy, organ transplantation, HIV infection, or chronic immunosuppressive therapy were largely excluded from major trials.

Given that immune function is already altered in these populations, it remains unclear whether GLP-1–mediated immunomodulation confers benefit, neutrality, or potential risk. Similarly, elderly populations with immunosenescence represent an important subgroup requiring targeted evaluation.

Future observational and interventional studies should specifically address infection outcomes in these high-risk cohorts.

7.4 Vaccine response and adaptive immunity

An important unanswered question is whether GLP-1 receptor agonists influence vaccine immunogenicity. Given their effects on innate immune cells, cytokine signaling, and T-cell–related pathways, it is biologically plausible that GLP-1 signaling could modulate vaccine responses.

However, no large-scale clinical studies have yet systematically evaluated humoral or cellular immune responses to vaccines (including influenza, pneumococcal, or SARS-CoV-2 vaccines) in patients receiving GLP-1 receptor agonists. This represents a critical knowledge gap with direct clinical relevance.

7.5 Microbiome causality and functional validation

Although multiple studies have reported associations between GLP-1 receptor agonist therapy and changes in gut microbiota composition, causality remains unproven. It is unclear whether microbial shifts are a direct pharmacological effect, a secondary consequence of weight loss and dietary changes, or a combined effect of metabolic improvement. (18,19,21)

Future research should employ germ-free animal models, fecal microbiota transplantation studies, and human interventional microbiome trials to establish causal links between GLP-1 signaling and microbial ecology.

Additionally, functional readouts such as short-chain fatty acid production, bile acid metabolism, and microbial gene expression should be prioritized over purely taxonomic descriptions.

7.6 Real-world evidence and long-term infectious outcomes

Recent large-scale real-world studies, including population-based cohort analyses, have suggested potential protective associations between GLP-1 receptor agonist use and infection-related outcomes. However, these studies are subject to residual confounding, indication bias, and heterogeneity in exposure duration. (25,24)

Long-term pharmacoepidemiological studies with robust causal inference methods (e.g., target trial emulation, emulated RCT designs) are needed to confirm whether GLP-1 receptor agonists exert true protective effects against infections over extended follow-up periods.

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7.7 Integrative research agenda

Taken together, future research should move beyond descriptive associations and focus on integrative mechanistic frameworks linking metabolism, immunity, microbiome dynamics, and infectious disease outcomes. A systems biology approach combining clinical data, immune profiling, and microbial ecology will be essential to validate the immune–microbiome–infection axis and clarify the role of GLP-1 receptor agonists within this network.

Section 8: Conclusion

Accumulating evidence suggests that glucagon-like peptide-1 receptor agonists (GLP-1 RAs) extend their therapeutic effects beyond glycemic control and cardiovascular protection, functioning as pleiotropic immunometabolic modulators. In particular, growing data indicate that these agents may influence host inflammatory tone, immune regulation, and infection susceptibility through interconnected metabolic and immune pathways.

A systematic review and meta-analysis demonstrated that GLP-1 receptor agonist therapy is associated with significant reductions in circulating biomarkers of inflammation and oxidative stress, including CRP and related inflammatory mediators. (6) These findings support the concept that GLP-1 RAs attenuate chronic low-grade inflammation, a central pathophysiological feature linking obesity, type 2 diabetes, immune dysfunction, and increased vulnerability to infectious diseases.

Consistent with these findings, semaglutide has been shown to exert robust and reproducible anti-inflammatory effects across diverse populations and treatment settings. (7) The reduction in systemic inflammatory burden may represent a key mechanistic link between metabolic improvement and immune homeostasis, suggesting that GLP-1 signaling may indirectly restore immune balance by modulating inflammatory pathways that are known to impair both innate and adaptive immune responses.

At the clinical level, large-scale real-world evidence further supports a potential role of GLP-1 RAs in modulating infection risk. In a population-based study including more than one million individuals, GLP-1 receptor agonist use was associated with a reduced risk of a broad range of infectious outcomes compared with other glucose-lowering therapies. (25) This association was consistent across respiratory, skin, and systemic infections, and extended to COVID-19-related complications, suggesting a possible system-level effect on host defense mechanisms. Additionally, comprehensive outcome mapping has indicated that GLP-1 RAs exert pleiotropic effects across multiple organ systems, including infectious and respiratory domains, reinforcing their systemic biological impact. (25)

Mechanistically, these clinical observations are supported by experimental evidence demonstrating that GLP-1 signaling directly modulates innate immune function. GLP-1 receptor activation has been shown to influence macrophage polarization toward an anti-inflammatory

phenotype and to regulate cytokine production in immune cells.(11) Furthermore, GLP-1 receptors are expressed on eosinophils, neutrophils, and invariant natural killer T (iNKT) cells, highlighting a broader immunoregulatory role beyond metabolic tissues.(8,10)

In parallel, emerging data suggest that GLP-1 receptor agonists may influence gut microbial composition and function, including enrichment of beneficial taxa and increased production of short-chain fatty acids, which are key mediators of mucosal immune regulation.(18) These microbiome-related effects, together with improved intestinal barrier integrity and reduced lipopolysaccharide translocation, may further contribute to attenuation of systemic immune activation and infection susceptibility.(22)

Taken together, current evidence supports the concept that GLP-1 receptor agonists act as integrated immunometabolic agents operating at the intersection of metabolic regulation, immune modulation, and microbial homeostasis. Their potential neutral or protective effect on infection risk is likely mediated through a combination of reduced systemic inflammation, immune reprogramming, and microbiome-associated mechanisms. However, most available data remain observational or derived from secondary endpoints, and causality cannot yet be firmly established.

Therefore, future mechanistic studies and well-designed prospective clinical trials are required to elucidate the causal pathways linking GLP-1 signaling to immune function and infection outcomes, particularly within the context of the immune–microbiome–infection axis.

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