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Immunometabolism and GLP-1 Signaling in Rheumatic Diseases: Molecular Mechanisms, Clinical Implications, and Therapeutic Perspectives

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Abstract

Background

Rheumatic diseases are increasingly recognized as disorders driven not only by immune dysregulation but also by profound alterations in cellular metabolism. Emerging evidence indicates that metabolic reprogramming of immune and stromal cells critically contributes to chronic inflammation, tissue damage, and disease progression. At the same time, glucagon-like

peptide-1 receptor agonists (GLP-1RAs), initially developed for the treatment of type 2 diabetes and obesity, have demonstrated pleiotropic effects extending beyond metabolic control. However, the intersection between immunometabolism and GLP-1 signaling in rheumatic diseases remains incompletely understood.

Aim

This review aimed to integrate current evidence on the interplay between immunometabolic pathways and GLP-1 signaling in rheumatic diseases, with a particular focus on molecular mechanisms, translational relevance, and emerging therapeutic opportunities.

Material and methods

A narrative review was conducted using PubMed, Scopus, and Web of Science databases. Original studies, randomized controlled trials, observational studies, systematic reviews, and meta-analyses published between 2010 and 2026 were included. The search strategy focused on immunometabolism, GLP-1 receptor agonists, rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus, psoriatic disease, obesity, and immune-mediated inflammatory pathways.

Results

Current evidence demonstrates that dysregulated glycolysis, mitochondrial dysfunction, altered lipid metabolism, and hypoxia-driven signaling orchestrate the activation of T lymphocytes, macrophages, fibroblast-like synoviocytes, and chondrocytes in rheumatic diseases. Central immunometabolic regulators, including AMP-activated protein kinase, mammalian target of rapamycin, hypoxia-inducible factor-1 α , and the NLRP3 inflammasome, link cellular metabolism to immune activation and tissue remodeling. Beyond their glucose-lowering effects, GLP-1 receptor agonists modulate innate and adaptive immune responses, promote anti-inflammatory macrophage polarization, attenuate pro-inflammatory cytokine production, and improve cardiometabolic outcomes. Emerging clinical and epidemiological studies further suggest beneficial effects of GLP-1-based therapies in rheumatoid arthritis, osteoarthritis, psoriasis, and other immune-mediated disorders.

Conclusions

Immunometabolism has emerged as a promising therapeutic frontier in rheumatology, positioning GLP-1 signaling at the interface between metabolic regulation and immune homeostasis. Although accumulating evidence supports the immunomodulatory potential of GLP-1 receptor agonists, further mechanistic studies and adequately powered clinical trials are required to establish their long-term efficacy and therapeutic role in rheumatic diseases.

Keywords: immunometabolism; GLP-1 receptor agonists; rheumatic diseases; rheumatoid arthritis; inflammation; metabolic reprogramming.

1. Introduction

The conceptual framework of rheumatic diseases has undergone a profound transformation over the past two decades. Although these disorders have traditionally been viewed through the prism of immune dysregulation and autoimmunity, accumulating evidence indicates that chronic inflammation is inseparably linked to alterations in cellular metabolism. Immune activation and metabolic adaptation are now recognized as interdependent processes that collectively determine disease susceptibility, tissue damage, and therapeutic response. This paradigm shift has positioned immunometabolism at the forefront of contemporary rheumatology [1-5].

Immunometabolism encompasses the bidirectional relationship between metabolic pathways and immune function. Far from serving solely as a source of energy, cellular metabolism actively governs immune-cell differentiation, cytokine production, epigenetic remodeling, and tissue homeostasis. Activation of T lymphocytes, macrophages, B cells, fibroblast-like synoviocytes, and chondrocytes is accompanied by profound metabolic reprogramming involving glycolysis, oxidative phosphorylation, mitochondrial dynamics, lipid metabolism, amino acid utilization, and redox signaling. Increasing evidence suggests that these alterations are not merely secondary consequences of inflammation but fundamental drivers of disease initiation, persistence, and progression [1,2,6,7].

At the cellular level, pathogenic metabolic reprogramming affects virtually every component of the inflamed joint and systemic immune compartment. In rheumatoid arthritis, fibroblast-like synoviocytes acquire an aggressive phenotype characterized by enhanced glycolysis, mitochondrial dysfunction, altered bioenergetics, and resistance to apoptosis, whereas

macrophages and T cells undergo metabolic adaptations that perpetuate synovial inflammation and disrupt immune tolerance. Similar immunometabolic signatures have been identified in osteoarthritis, psoriatic disease, systemic lupus erythematosus, and other immune-mediated rheumatic disorders, suggesting that metabolic dysregulation represents a shared pathogenic axis across clinically diverse diseases [7-13].

These processes are orchestrated by evolutionarily conserved signaling pathways, including AMP-activated protein kinase (AMPK), mammalian target of rapamycin (mTOR), hypoxia-inducible factor-1 α (HIF-1 α), and the NLRP3 inflammasome. Acting as molecular sensors of nutrient availability, mitochondrial stress, and inflammatory stimuli, these pathways integrate environmental and metabolic cues with immune responses, thereby regulating cytokine production, cell proliferation, tissue remodeling, and immune tolerance. Consequently, targeting immunometabolism has emerged as one of the most promising therapeutic frontiers in rheumatology [3,4,14].

In parallel with these advances, glucagon-like peptide-1 receptor agonists (GLP-1RAs) have revolutionized the treatment of obesity and type 2 diabetes mellitus. However, the rapidly expanding field of incretin biology has revealed that GLP-1 signaling extends far beyond metabolic regulation. Experimental and clinical studies increasingly support the concept that GLP-1 receptor activation modulates innate and adaptive immunity, influences macrophage polarization, attenuates inflammasome activation, and interacts with key immunometabolic pathways, including AMPK and mTOR signaling [15-22].

These observations are particularly relevant given the growing prevalence of obesity and metabolic syndrome among patients with rheumatic diseases. Adipose tissue is now recognized as an immunologically active organ capable of amplifying chronic low-grade inflammation through the release of adipokines, cytokines, and metabolites that shape immune-cell behavior. Beyond their established effects on weight reduction and glycemic control, GLP-1 receptor agonists may therefore represent a unique therapeutic strategy targeting the intersection of metabolic dysfunction, cardiovascular risk, and chronic inflammation [15-17,22,23].

Despite remarkable progress in both immunometabolism and incretin biology, the mechanistic links between these fields remain incompletely understood. Clarifying how GLP-1 signaling influences immune-cell metabolism may refine current concepts of rheumatic disease pathogenesis and identify novel therapeutic targets [4,15,21].

By bridging the rapidly evolving fields of immunometabolism and incretin biology, this review proposes a unifying framework through which GLP-1 signaling may reshape contemporary concepts of disease mechanisms and therapeutic intervention in rheumatic diseases.

Research Objective

The primary objective of this review is to provide an integrative and critical analysis of the emerging interplay between immunometabolic dysregulation and glucagon-like peptide-1 (GLP-1) signaling in rheumatic diseases. Specifically, this review aims to elucidate the molecular mechanisms through which metabolic pathways shape immune-cell function and inflammatory responses, to examine the immunomodulatory and metabolic effects of GLP-1 receptor agonists (GLP-1RAs), and to evaluate their potential to redefine current therapeutic strategies in rheumatology.

Furthermore, this review seeks to establish a conceptual framework linking metabolic reprogramming, chronic inflammation, and incretin biology across rheumatoid arthritis, osteoarthritis, psoriatic disease, and systemic autoimmune disorders.

Research Problems

1. How does immunometabolic reprogramming contribute to the initiation, persistence, and progression of rheumatic diseases?
2. Which metabolic pathways and intracellular signaling networks regulate interactions between immune and stromal cells within chronically inflamed tissues?
3. Through which mechanisms does GLP-1 signaling modulate key immunometabolic regulators, including AMPK, mTOR, HIF-1 α , mitochondrial homeostasis, oxidative stress, and inflammasome activation?
4. To what extent are the potential benefits of GLP-1 receptor agonists in rheumatic diseases mediated by weight reduction and improved metabolic status, and to what extent do they reflect direct immunomodulatory effects?
5. What is the current strength of clinical evidence supporting the use of GLP-1 receptor agonists in rheumatoid arthritis, psoriatic arthritis, osteoarthritis, and systemic lupus erythematosus?

6. Can the integration of immunometabolism and incretin biology establish a new therapeutic paradigm focused on restoring immunometabolic resilience in rheumatic diseases?

Research Hypotheses

Hypothesis 1. Immunometabolic dysregulation constitutes a fundamental pathogenic mechanism that actively shapes immune responses, perpetuates chronic inflammation, and drives tissue damage across rheumatic diseases.

Hypothesis 2. The biological effects of GLP-1 receptor agonists extend substantially beyond glucose homeostasis and include the modulation of innate and adaptive immune responses, mitochondrial homeostasis, and cellular adaptation to metabolic stress.

Hypothesis 3. Interactions between GLP-1 signaling and major immunometabolic pathways—including AMPK, mTOR, HIF-1 α , mitochondrial metabolism, and the NLRP3 inflammasome—provide a mechanistic link between metabolic homeostasis and immune regulation.

Hypothesis 4. The beneficial effects of GLP-1 receptor agonists in rheumatic diseases result not only from weight reduction and improvements in metabolic status but also from direct immunometabolic mechanisms that influence inflammation and tissue adaptation.

Hypothesis 5. Therapeutic strategies targeting the interface between metabolism and immunity may complement existing anti-rheumatic therapies and improve inflammatory, metabolic, and cardiovascular outcomes.

Hypothesis 6. The convergence of immunometabolism and incretin biology has the potential to establish a new therapeutic paradigm in rheumatology focused on restoring immunometabolic resilience rather than exclusively suppressing immune activation.

2. Methodology

Review design

This study was conducted as an integrative review aimed at critically synthesizing current evidence regarding the interplay between immunometabolism and glucagon-like peptide-1 (GLP-1) signaling in rheumatic diseases. The review was designed to bridge mechanistic, translational, and clinical perspectives by integrating findings from basic science, experimental models, and human studies. Particular emphasis was placed on the molecular pathways linking metabolic

regulation to immune-cell function, as well as on the emerging therapeutic implications of GLP-1 receptor agonists (GLP-1RAs) in rheumatology.

Literature search

A comprehensive literature search was performed using the PubMed, Scopus, and Web of Science databases to identify relevant publications published between January 2010 and June 2026. To ensure the inclusion of the most influential and clinically relevant evidence, an additional manual search of the reference lists of eligible articles and key reviews was conducted. The search strategy combined Medical Subject Headings (MeSH) and free-text terms related to immunometabolism, incretin biology, and rheumatic diseases. Search terms included, but were not limited to, “*immunometabolism*”, “*metabolic reprogramming*”, “*glucagon-like peptide-1*”, “*GLP-1 receptor agonists*”, “*rheumatic diseases*”, “*rheumatoid arthritis*”, “*osteoarthritis*”, “*psoriatic arthritis*”, “*systemic lupus erythematosus*”, “*obesity*”, “*inflammation*”, “*AMPK*”, “*mTOR*”, “*HIF-1 α* ”, “*mitochondrial dysfunction*”, and “*NLRP3 inflammasome*”.

Study selection and eligibility criteria

Original research articles, randomized controlled trials, observational studies, systematic reviews, meta-analyses, and landmark review articles published in English were considered eligible for inclusion. Particular priority was given to recent high-impact publications and seminal studies that substantially advanced the current understanding of immunometabolic regulation and GLP-1-mediated signaling.

Studies were included if they:

- investigated immunometabolic mechanisms involved in the pathogenesis of rheumatic diseases;
- explored the effects of GLP-1 receptor agonists on immune or stromal cells;
- examined the relationship between metabolic dysregulation and chronic inflammation;
- assessed the clinical and translational relevance of GLP-1-based therapies in rheumatic diseases;
- addressed the role of obesity and cardiometabolic dysfunction in immune-mediated inflammatory disorders.

Publications lacking peer review, conference abstracts, editorials, letters to the editor, and studies outside the scope of rheumatology or immunometabolism were excluded.

Data synthesis

The retrieved evidence was analyzed and synthesized narratively, with particular emphasis on identifying shared immunometabolic pathways across different rheumatic diseases and elucidating the mechanisms through which GLP-1 signaling may influence immune regulation. The findings were interpreted within the broader context of contemporary rheumatology, immunology, and metabolic medicine.

Limitations

Several limitations should be acknowledged. As an integrative review, this study is subject to potential selection bias and heterogeneity among the included publications. Moreover, the rapidly evolving nature of both immunometabolism and incretin biology may affect the long-term applicability of current evidence. Nevertheless, priority was given to high-quality systematic reviews, randomized clinical trials, and landmark mechanistic studies to provide a comprehensive and up-to-date overview of this emerging field.

3. Results

3.1. Immunometabolism: redefining the pathogenesis of rheumatic diseases

Despite remarkable advances in biologic therapies and targeted synthetic disease-modifying agents, rheumatic diseases continue to impose a substantial clinical burden owing to their heterogeneity, incomplete therapeutic responses, persistent structural damage, and disproportionately high rates of cardiovascular and metabolic comorbidity. Although major progress has been achieved through the identification of pathogenic cytokines and immune pathways, conventional models centered exclusively on immune dysregulation fail to fully explain the complexity of disease phenotypes, interindividual variability, and the intimate relationship between chronic inflammation, metabolic dysfunction, and accelerated ageing [3-5]. Over the past decade, the emergence of immunometabolism has profoundly transformed the conceptual landscape of rheumatology. Initially regarded as a field primarily concerned with the

energetic requirements of activated immune cells, immunometabolism has evolved into a broader biological framework that recognizes metabolism as a fundamental regulator of immune-cell identity, tissue adaptation, and disease susceptibility. Cellular metabolism is now understood not simply as a downstream consequence of inflammation but as an active determinant of immune competence, operating alongside cytokine networks, transcriptional programs, and epigenetic mechanisms [1-4,6].

This paradigm shift has been driven by a series of discoveries demonstrating that immune and stromal cells continuously adjust their metabolic programs in response to environmental cues, nutrient availability, and inflammatory stress. Far beyond ATP generation, metabolic pathways govern cellular differentiation, cytokine synthesis, migration, proliferation, and survival. Dynamic changes in glycolysis, oxidative phosphorylation, fatty-acid oxidation, amino acid utilization, mitochondrial function, and redox homeostasis collectively shape inflammatory outcomes and influence the trajectory of disease [1,2,6,8,9].

A central concept emerging from contemporary immunometabolic research is that immune function depends on the maintenance of metabolic fitness - a dynamic state encompassing mitochondrial integrity, energetic flexibility, biosynthetic capacity, and resilience to environmental stressors. In healthy tissues, these mechanisms ensure the precise coordination of immune responses and preserve tissue homeostasis. In rheumatic diseases, however, growing evidence suggests that the progressive loss of metabolic fitness disrupts immune tolerance and promotes chronic inflammation [1-3,11].

Rheumatoid arthritis is increasingly recognized as a disorder characterized not only by aberrant immune activation but also by profound disturbances in cellular bioenergetics and adaptive capacity. Altered glucose metabolism, impaired nucleotide biosynthesis, defective mitochondrial function, and dysregulated redox balance collectively contribute to premature immune ageing, persistent inflammation, and inadequate tissue repair. These observations challenge the traditional view of rheumatoid arthritis as an isolated synovial disease and instead support a broader model in which immune dysfunction reflects the breakdown of coordinated immunometabolic adaptation [4,5,7,8].

Importantly, immunometabolic dysregulation extends beyond rheumatoid arthritis and has been increasingly recognized in osteoarthritis, psoriatic arthritis, systemic lupus erythematosus, and other immune-mediated rheumatic disorders. Across these conditions, abnormalities in nutrient

sensing, mitochondrial homeostasis, oxidative stress, and intermediary metabolism converge to shape disease progression and clinical outcomes. Such findings suggest that apparently distinct rheumatic diseases may share a common pathogenic architecture rooted in disrupted immunometabolic resilience [4,11-13].

This evolving framework has also transformed the understanding of the inflamed synovium. The rheumatoid synovium is increasingly recognized as a metabolically specialized tissue characterized by persistent hypoxia, nutrient competition, mitochondrial stress, and extensive communication between immune and stromal compartments. Fibroblast-like synoviocytes acquire a highly invasive phenotype associated with enhanced glycolysis, altered glutamine metabolism, resistance to apoptosis, and increased production of inflammatory mediators. Rather than serving merely as a passive target of immune-cell infiltration, the synovium behaves as a dynamic immunometabolic organ that actively sustains inflammation and tissue destruction [7-10,13].

At the molecular level, the interface between metabolism and immunity is orchestrated by highly conserved signaling networks, including AMP-activated protein kinase (AMPK), mammalian target of rapamycin (mTOR), hypoxia-inducible factor-1 α (HIF-1 α), mitochondrial signaling pathways, and the NLRP3 inflammasome. Acting as sensors of nutrient availability, oxidative stress, and inflammatory stimuli, these pathways integrate metabolic and environmental information to regulate immune-cell activation, tissue remodeling, and immune tolerance. Importantly, these signaling circuits do not operate independently but constitute an interconnected regulatory system that determines whether tissues adapt successfully to inflammatory stress or transition toward chronic disease [3,4,14].

The clinical relevance of immunometabolism is further underscored by the increasing prevalence of obesity, insulin resistance, sarcopenia, and cardiovascular disease among patients with rheumatic disorders. Adipose tissue is now recognized as an active immunological organ capable of shaping systemic inflammation through the secretion of adipokines, cytokines, and bioactive metabolites. Consequently, joint inflammation, metabolic dysfunction, cardiovascular complications, and accelerated biological ageing are increasingly understood as interconnected manifestations of a shared immunometabolic disturbance rather than as isolated comorbidities [15-17,24].

Within this context, glucagon-like peptide-1 receptor agonists (GLP-1RAs) have emerged as particularly compelling therapeutic candidates. Originally developed for the treatment of obesity and type 2 diabetes mellitus, these agents are now recognized to exert pleiotropic effects extending far beyond glycaemic control. Experimental and clinical evidence indicate that GLP-1 signaling influences mitochondrial function, macrophage polarization, oxidative stress, and key immunometabolic pathways, including AMPK, mTOR, and inflammasome activation. Consequently, GLP-1 receptor agonists may represent one of the first clinically available therapeutic strategies capable of simultaneously targeting metabolic dysfunction, chronic inflammation, cardiovascular risk, and accelerated ageing [15-23].

Taken together, these observations support a fundamental reinterpretation of rheumatic diseases. Rather than representing disorders driven solely by aberrant immunity, they may increasingly be viewed as diseases arising from the failure of coordinated immunometabolic adaptation across immune and stromal compartments. Understanding the molecular mechanisms underlying this process may therefore provide the conceptual foundation for the next generation of precision therapies in rheumatology.

3.2. Failure of immunometabolic resilience: a systems-level model of rheumatic diseases

The growing recognition of immunometabolism has fundamentally altered the conceptual framework through which rheumatic diseases are understood. Although chronic inflammation has traditionally been attributed to dysregulated cytokine signaling and aberrant immune activation, accumulating evidence indicates that immune dysfunction cannot be fully explained without considering the profound metabolic disturbances that accompany - and often precede - the onset of overt disease. Rather than representing isolated defects in immune regulation, rheumatic diseases increasingly appear to arise from the progressive failure of coordinated immunometabolic adaptation across immune and stromal compartments [1-5,13].

This emerging paradigm challenges the long-standing distinction between inflammation and metabolism. Cellular energetics, nutrient sensing, mitochondrial homeostasis, and redox balance are no longer viewed as passive processes supporting immune activation but as integral determinants of immune competence and tissue integrity. Consequently, chronic inflammatory diseases may be conceptualized as disorders of impaired immunometabolic resilience, in which

the inability to appropriately adapt to environmental stress, nutrient fluctuations, and inflammatory stimuli drives pathological immune responses [1,2,6,13].

3.2.1. Metabolic fitness as a prerequisite for immune homeostasis

One of the most influential concepts introduced by contemporary immunometabolic research is that effective immune responses depend on the preservation of metabolic fitness. Beyond energy production alone, metabolic fitness encompasses mitochondrial integrity, biosynthetic capacity, redox regulation, nutrient sensing, and the ability to dynamically switch between distinct metabolic programs according to cellular demands [1,2,6].

Immune cells in rheumatoid arthritis exhibit profound metabolic abnormalities that extend far beyond classical inflammatory activation. Altered glucose utilization, impaired pentose phosphate pathway activity, disrupted nucleotide biosynthesis, and defective ATP generation collectively compromise immune resilience and promote persistent inflammatory responses. These metabolic disturbances affect not only immune-cell activation but also cellular differentiation, tissue adaptation, and long-term disease progression [4,7,25].

Importantly, such abnormalities are unlikely to represent merely secondary consequences of chronic inflammation. Increasing evidence suggests that disturbances in metabolic fitness may precede irreversible tissue damage, actively shaping immune-cell behavior and influencing disease susceptibility. This perspective challenges traditional cytokine-centered models of rheumatic disease and instead positions metabolic adaptation as a central regulator of immune homeostasis [3-5,25].

3.2.2. Mitochondrial dysfunction and accelerated immune ageing

Among intracellular organelles, mitochondria have emerged as key orchestrators of immune-cell fate. In addition to ATP production, mitochondria regulate reactive oxygen species generation, calcium signaling, apoptosis, epigenetic remodeling, and innate immune activation. Their function is therefore intimately linked to the maintenance of immune competence and tissue homeostasis [1,6,8].

Rheumatoid arthritis is characterized by profound mitochondrial abnormalities involving defective oxidative metabolism, impaired DNA repair mechanisms, altered redox homeostasis, and reduced energetic reserves. Collectively, these disturbances promote premature

immunosenescence, compromise adaptive immune responses, and impair the capacity of tissues to recover from inflammatory injury [4,8,9,25].

The concept of accelerated immune ageing provides a compelling explanation for clinical phenomena that extend far beyond synovial inflammation. Patients with rheumatoid arthritis exhibit disproportionately high rates of cardiovascular disease, frailty, sarcopenia, and multimorbidity, suggesting that chronic inflammation and biological ageing are closely intertwined processes. Immunosenescence should therefore be regarded not merely as a consequence of chronic disease but as an integral component of its pathophysiology [5,15-17].

These observations have substantially broadened the scope of rheumatology, shifting attention from isolated joint pathology toward systemic mechanisms governing resilience, ageing, and tissue adaptation.

3.2.3. The inflamed synovium as an immunometabolic organ

One of the most important conceptual advances in modern rheumatology has been the recognition that the inflamed synovium represents a metabolically specialized tissue rather than a passive target of immune-cell infiltration. Persistent hypoxia, oxidative stress, nutrient competition, and sustained inflammatory signaling generate a unique microenvironment that continuously reshapes the metabolic behavior of both immune and stromal cells [8-10].

Fibroblast-like synoviocytes undergo extensive metabolic reprogramming characterized by enhanced glycolysis, altered glutamine metabolism, mitochondrial dysfunction, increased lactate production, and resistance to apoptosis. These adaptations confer many of the hallmarks traditionally associated with malignant tissues, including invasive behavior, angiogenesis, extracellular matrix degradation, and sustained proliferative activity [7-10,13].

Importantly, the rheumatoid synovium consists of multiple interconnected metabolic niches in which fibroblasts, macrophages, endothelial cells, and infiltrating lymphocytes compete for nutrients and exchange metabolites that actively shape inflammatory responses. Metabolites such as lactate, succinate, citrate, and reactive oxygen species are increasingly recognized as signaling molecules capable of regulating cytokine production, angiogenesis, inflammasome activation, and epigenetic remodeling [7,9,10,14].

Accordingly, the synovium should no longer be regarded solely as an anatomical site of inflammation but rather as a dynamic immunometabolic organ that actively orchestrates disease progression.

3.2.4. Systemic consequences of immunometabolic failure

The implications of immunometabolic dysfunction extend well beyond the joints. The traditional distinction between rheumatic disease and metabolic comorbidity has become increasingly difficult to sustain in light of evidence demonstrating shared pathogenic mechanisms linking chronic inflammation, obesity, insulin resistance, cardiovascular disease, and accelerated ageing [15-17].

Adipose tissue is now recognized as an active immunological compartment that communicates bidirectionally with the immune system through adipokines, cytokines, and bioactive metabolites. Obesity and metabolic syndrome not only increase the risk of developing rheumatic diseases but also influence disease activity, therapeutic responsiveness, and long-term outcomes [15-17,24].

Moreover, systemic metabolic disturbances contribute to endothelial dysfunction, vascular inflammation, skeletal muscle loss, and frailty, thereby establishing a mechanistic connection between chronic inflammatory disease and age-related comorbidity. Cardiovascular complications, sarcopenia, and immunosenescence increasingly appear to represent distinct manifestations of a shared failure of immunometabolic adaptation rather than independent consequences of chronic inflammation [15-17,26].

Collectively, these findings support a fundamental reinterpretation of rheumatic diseases. Rather than being viewed exclusively as disorders of aberrant immunity, they increasingly emerge as systemic conditions arising from the collapse of coordinated immunometabolic resilience. This conceptual framework provides the biological rationale for therapeutic strategies aimed not only at suppressing inflammation but also at restoring metabolic homeostasis across multiple organ systems.

3.3. Molecular determinants of failed immunometabolic adaptation

The emerging field of immunometabolism has fundamentally reshaped contemporary concepts of rheumatic disease by demonstrating that chronic inflammation cannot be understood solely through the lens of cytokine dysregulation and aberrant immune activation. Instead, inflammatory

responses arise from the dynamic interplay between nutrient sensing, mitochondrial homeostasis, cellular stress responses, and environmental adaptation. The transition from physiological immunity to chronic disease therefore reflects not the dysfunction of isolated molecular pathways, but the progressive collapse of interconnected regulatory systems responsible for maintaining immunometabolic resilience [1-4,13].

Under physiological conditions, immune and stromal cells continuously adapt to fluctuations in energy availability, oxygen tension, and biosynthetic demands through tightly coordinated signaling networks. These mechanisms ensure the preservation of tissue homeostasis while enabling effective immune surveillance and repair. In rheumatic diseases, however, prolonged exposure to inflammatory and metabolic stress disrupts this adaptive capacity, transforming protective responses into self-perpetuating pathological programs [1,2,6].

3.3.1. Nutrient sensing and the erosion of metabolic flexibility

The ability of immune cells to maintain homeostasis critically depends on their capacity to sense energetic stress and dynamically adjust metabolic activity according to environmental demands. This process is orchestrated by an intricate balance between catabolic and anabolic pathways, primarily coordinated through AMP-activated protein kinase (AMPK) and the mammalian target of rapamycin (mTOR) [6,18,19].

As the principal sensor of cellular energy deficiency, AMPK is activated in response to ATP depletion, oxidative stress, and nutrient scarcity. Activation of AMPK promotes mitochondrial biogenesis, autophagy, fatty-acid oxidation, and redox homeostasis, thereby preserving cellular integrity under conditions of metabolic stress. Beyond its role in energy regulation, AMPK exerts broad immunomodulatory effects by restraining inflammatory signaling, limiting cytokine production, and supporting mechanisms of immune tolerance [1,6,18,23].

Conversely, mTOR integrates signals derived from glucose, amino acids, growth factors, and inflammatory mediators to stimulate glycolysis, protein synthesis, and cellular proliferation. Sustained mTOR activation promotes the differentiation of pro-inflammatory immune populations, enhances the pathogenic behavior of stromal cells, and contributes to persistent synovial inflammation [4,18-20].

Importantly, chronic inflammatory diseases do not arise from abnormalities in either pathway alone. Rather, increasing evidence suggests that rheumatic diseases are characterized by a

progressive loss of metabolic flexibility, whereby immune cells become unable to appropriately alternate between anabolic and catabolic states. This erosion of adaptive capacity compromises immune resilience and promotes the establishment of chronic inflammatory responses [1-4,25].

3.3.2. Hypoxia and the transition from adaptation to pathology

The inflamed synovium constitutes one of the most metabolically demanding microenvironments in human disease. Rapid cellular proliferation, increased biosynthetic activity, and inadequate vascular supply generate a state of persistent hypoxia that profoundly influences immune and stromal-cell behavior [8-10].

Central to this adaptive response is hypoxia-inducible factor-1 α (HIF-1 α), which coordinates transcriptional programs involved in glycolysis, angiogenesis, leukocyte recruitment, and inflammatory signaling. Although initially designed to preserve tissue viability during transient oxygen deprivation, sustained HIF-1 α activation promotes synovial hyperplasia, vascular remodeling, and the maintenance of inflammatory infiltrates [8,9,25].

Importantly, hypoxia is no longer regarded as a passive consequence of synovitis. Signals arising from mitochondrial dysfunction, oxidative stress, metabolite accumulation, and nutrient-sensing pathways converge on HIF-1 α , integrating oxygen availability with cellular metabolism. Consequently, hypoxia acts not merely as an environmental stressor but as an active driver of disease evolution [8,9,13].

This reinterpretation positions the inflamed synovium as a highly specialized metabolic niche in which physiological mechanisms of adaptation gradually become maladaptive and perpetuate chronic inflammation.

3.3.3. Mitochondria at the interface between inflammation and ageing

Mitochondria have emerged as central regulators of immune competence, extending far beyond their classical role as sources of cellular energy. In addition to ATP generation, mitochondria coordinate oxidative stress responses, apoptosis, calcium signaling, intermediary metabolism, and epigenetic regulation, thereby influencing virtually every aspect of immune-cell function [1,6,8].

Disruption of mitochondrial homeostasis has been increasingly recognized as a hallmark of rheumatic diseases. Impaired oxidative phosphorylation, defective mitochondrial quality control, dysregulated nucleotide metabolism, and altered redox balance collectively compromise the

capacity of immune cells to respond appropriately to environmental stress. These alterations promote persistent inflammatory activation while simultaneously impairing tissue repair and immune tolerance [4,8,9,25].

The consequences of mitochondrial dysfunction extend beyond the local inflammatory milieu. Accelerated biological ageing, cardiovascular disease, frailty, sarcopenia, and multimorbidity increasingly appear to arise from shared disturbances in mitochondrial fitness, providing a mechanistic explanation for the systemic manifestations of chronic rheumatic diseases [5,15–17]. From this perspective, rheumatic disorders can no longer be viewed exclusively as diseases of the joints; rather, they represent systemic conditions characterized by the progressive breakdown of cellular resilience and adaptive capacity.

3.3.4. Metabolites as regulators of immune-cell behaviour

One of the most important conceptual advances in immunometabolism has been the recognition that intermediary metabolites actively participate in immune regulation. Traditionally regarded as passive by-products of cellular metabolism, metabolites are now understood to function as signaling molecules capable of shaping inflammatory responses, tissue remodeling, and cellular differentiation [1,2,6].

Within chronically inflamed tissues, metabolites such as succinate, lactate, citrate, and reactive oxygen species regulate cytokine production, angiogenesis, epigenetic remodeling, and immune-cell migration. Succinate amplifies inflammatory signaling through stabilization of HIF-1 α , whereas lactate accumulation contributes to the establishment of inflammatory niches and promotes the aggressive phenotype of stromal cells. Disturbances in glutamine and lipid metabolism further influence immune-cell polarization and stromal activation [7-10,13].

The recognition that metabolites acquire cytokine-like properties has fundamentally expanded traditional concepts of rheumatic disease pathogenesis. Cellular metabolism is therefore increasingly understood not simply as a source of energy, but as an additional layer of communication coordinating immune responses within the inflamed microenvironment [1-3].

3.3.5. Self-sustaining inflammation and the emergence of immunometabolic memory

A defining feature of rheumatic diseases is the persistence of inflammation despite the elimination of the initial trigger. Increasing evidence suggests that this transition from acute

immune activation to chronic pathology reflects the establishment of self-reinforcing immunometabolic circuits that maintain inflammatory signaling independently of the initiating insult [14,25].

The NLRP3 inflammasome occupies a central position within these networks, functioning as a sensor of mitochondrial stress, oxidative injury, nutrient excess, and disturbances in glucose and lipid metabolism. Activation of this molecular platform promotes the maturation of interleukin-1 β and interleukin-18, thereby amplifying inflammatory responses and contributing to progressive tissue destruction [14,21,27].

However, inflammasome activation represents only one component of a broader network of feed-forward interactions involving nutrient-sensing pathways, hypoxic adaptation, mitochondrial dysfunction, and metabolite accumulation. Through these reciprocal mechanisms, inflammatory signaling becomes progressively uncoupled from its original stimulus and evolves into a self-sustaining pathological state [8,14,25].

This process gives rise to a form of immunometabolic memory in which prior metabolic stress reshapes subsequent immune responses, reinforcing chronic inflammation and impairing tissue recovery [14].

3.3.6. Re-establishing immunometabolic homeostasis as a therapeutic paradigm

Collectively, these observations support a fundamental reinterpretation of rheumatic diseases as disorders arising from the failure of interconnected molecular systems responsible for maintaining immunometabolic adaptation. Chronic inflammation emerges when nutrient sensing, mitochondrial homeostasis, hypoxic responses, and inflammatory signaling lose their physiological coordination and become locked in maladaptive feedback loops [1-4,14].

This systems-level perspective carries profound therapeutic implications. Conventional disease-modifying therapies primarily target downstream inflammatory mediators, whereas interventions directed at immunometabolic checkpoints may offer the possibility of restoring immune homeostasis at a more fundamental level [3,15-17].

Within this context, glucagon-like peptide-1 receptor agonists have attracted increasing interest because their biological effects extend across multiple components of the immunometabolic network, including mitochondrial function, oxidative stress, nutrient sensing, and inflammasome activation. Rather than acting solely as metabolic agents, these therapies may represent one of the

first clinically available strategies capable of simultaneously targeting chronic inflammation, metabolic dysfunction, cardiovascular risk, and accelerated ageing in rheumatic diseases [15,17,21–23,27,28].

3.4. GLP-1 signaling as a strategy for restoring immunometabolic resilience

The growing recognition that rheumatic diseases arise from the failure of coordinated immunometabolic adaptation has profound therapeutic implications. Although biologic agents and targeted synthetic disease-modifying drugs have revolutionized the management of chronic inflammatory diseases, substantial unmet needs remain. Many patients continue to experience persistent disease activity, progressive structural damage, cardiovascular complications, metabolic dysfunction, fatigue, and features of accelerated biological ageing despite effective suppression of canonical inflammatory pathways. These observations suggest that inflammation alone cannot fully explain the complexity of rheumatic disease and highlight the need for therapeutic strategies capable of restoring the broader networks that maintain immunometabolic homeostasis.

Against this background, glucagon-like peptide-1 receptor agonists (GLP-1RAs) have emerged as particularly intriguing therapeutic candidates. Initially introduced as treatments for obesity and type 2 diabetes mellitus, these agents have demonstrated beneficial effects extending far beyond glycaemic control, including improvements in body composition, endothelial function, cardiovascular outcomes, and systemic metabolism [18-20,26]. More importantly, GLP-1 signaling intersects with multiple pathways implicated in the maintenance of immunometabolic resilience, positioning GLP-1 receptor agonists at the interface between metabolism, inflammation, and ageing [15-23].

Rather than representing merely another class of anti-inflammatory agents, GLP-1 receptor agonists may offer the opportunity to address one of the central features of rheumatic diseases - the progressive loss of the adaptive mechanisms that coordinate immune and metabolic homeostasis.

3.4.1. From immunosuppression to immunometabolic intervention

For decades, therapeutic progress in rheumatology has been driven primarily by the selective inhibition of cytokines and intracellular signaling pathways. The introduction of tumor necrosis

factor inhibitors, interleukin antagonists, and Janus kinase inhibitors has substantially improved clinical outcomes and transformed the prognosis of many inflammatory disorders. Nevertheless, these therapies exert only limited effects on several major determinants of long-term morbidity, including obesity, insulin resistance, sarcopenia, frailty, and cardiovascular disease.

The increasing prevalence of metabolic comorbidities among patients with rheumatoid arthritis, psoriatic arthritis, and systemic autoimmune diseases challenges the traditional distinction between inflammatory and metabolic disorders. Chronic inflammation, altered body composition, endothelial dysfunction, and accelerated ageing increasingly appear to arise from overlapping biological mechanisms rather than from independent pathological processes [15-17,26].

Within this evolving framework, the growing interest in GLP-1 signaling reflects a broader conceptual shift in rheumatology - from the exclusive suppression of inflammatory mediators toward therapeutic strategies aimed at restoring immunometabolic adaptation across multiple organ systems. This transition represents a fundamental change in therapeutic priorities, moving beyond the control of inflammation alone toward the preservation of systemic resilience.

3.4.2. Restoring metabolic fitness and cellular adaptability

A defining feature of immunometabolic failure is the progressive loss of metabolic flexibility, whereby immune and stromal cells become unable to appropriately adapt to fluctuations in nutrient availability and energetic demands. Impaired mitochondrial function, dysregulated nutrient sensing, oxidative stress, and defective cellular repair mechanisms collectively contribute to persistent inflammation and tissue injury.

GLP-1 signaling influences multiple molecular systems responsible for maintaining metabolic fitness, including nutrient sensing, mitochondrial homeostasis, oxidative stress, and cellular adaptation to metabolic stress [18-23,29]. Activation of GLP-1 receptors enhances insulin sensitivity, improves lipid metabolism, stimulates autophagy, and promotes mitochondrial biogenesis, thereby supporting cellular resilience under conditions of chronic inflammatory stress [18-20,22,23].

In parallel, GLP-1 receptor agonists modulate key nutrient-sensing pathways, including AMP-activated protein kinase (AMPK) and the mammalian target of rapamycin (mTOR), which collectively regulate cellular energetics, biosynthetic activity, and adaptive responses to environmental stress [21-23,28,30]. By influencing these pathways, GLP-1 signaling may

partially restore the metabolic flexibility that is progressively lost during chronic inflammatory disease.

Importantly, these effects extend far beyond glucose regulation. By preserving mitochondrial integrity and improving cellular adaptability, GLP-1 receptor agonists may target mechanisms that lie upstream of cytokine production and tissue destruction.

3.4.3. Mitochondrial homeostasis and the biology of immune ageing

Accelerated biological ageing has emerged as a defining feature of chronic rheumatic diseases. Patients with inflammatory arthritis exhibit disproportionately high rates of cardiovascular disease, frailty, sarcopenia, and multimorbidity, suggesting that persistent inflammation is closely linked to disturbances in the mechanisms governing cellular resilience and tissue maintenance [15-17,26].

Mitochondria occupy a central position within these processes. Beyond ATP production, they regulate oxidative stress, apoptosis, intermediary metabolism, and innate immune activation, thereby shaping immune competence and tissue adaptation. Progressive mitochondrial dysfunction contributes not only to persistent inflammatory signaling but also to immunosenescence and impaired tissue repair.

GLP-1 receptor agonists exert beneficial effects on mitochondrial homeostasis by reducing oxidative stress, improving mitochondrial efficiency, and promoting adaptive responses to cellular injury [22,23,28,29]. In parallel, GLP-1 signaling reduces reactive oxygen species production, improves mitochondrial quality control, and attenuates inflammatory signaling pathways that contribute to cellular ageing [21-23,28,30].

Consequently, the therapeutic potential of GLP-1 receptor agonists may extend beyond the control of inflammation to include the modulation of broader biological processes associated with immune ageing and systemic metabolic decline.

3.4.4. Reshaping the immunometabolic microenvironment

The persistence of inflammation in rheumatic diseases depends not only on immune-cell activation but also on complex interactions among fibroblasts, macrophages, adipocytes, endothelial cells, and infiltrating lymphocytes within metabolically specialized tissue niches.

Hypoxia, nutrient competition, oxidative stress, and metabolite accumulation create an immunometabolic ecosystem that actively sustains disease progression.

GLP-1 signaling influences multiple components of this microenvironment, including macrophages, endothelial cells, adipose tissue, and stromal compartments [21-23,27,29,31,32]. GLP-1 receptor agonists modulate macrophage polarization, improve endothelial function, reduce oxidative stress, and attenuate adipose-tissue inflammation, thereby influencing several of the mechanisms that perpetuate chronic inflammatory disease [22,23,27,31,32].

Emerging evidence further indicates that GLP-1 signaling extends beyond innate immunity and directly affects adaptive immune responses. Regulatory T cells have been shown to express functional GLP-1 receptors, whereas GLP-1-dependent pathways influence lymphocyte proliferation, immune tolerance, and T-cell activation. These observations support the concept that incretin biology contributes not only to metabolic regulation but also to the maintenance of immune homeostasis [33-35].

Particular attention has focused on the interaction between GLP-1 signaling and the NLRP3 inflammasome, which integrates signals derived from mitochondrial dysfunction, reactive oxygen species, and nutrient excess [21,27,28]. Excessive activation of this pathway contributes to the maintenance of chronic inflammation and tissue damage across a broad spectrum of inflammatory and metabolic disorders.

By influencing the cellular networks that connect metabolism with inflammation, GLP-1 receptor agonists may reshape the immunometabolic ecosystem sustaining rheumatic disease rather than merely suppress downstream inflammatory mediators.

3.4.5. Cardiometabolic health as a therapeutic target in rheumatology

The emergence of GLP-1-based therapies has reinforced the concept that cardiovascular disease and chronic inflammation represent interconnected manifestations of a shared pathogenic process. GLP-1 receptor agonists reduce body weight, improve glycaemic control, and confer substantial cardiovascular benefits, effects that may partially reflect the restoration of systemic immunometabolic homeostasis [18-20,26,36].

These observations are particularly relevant in rheumatology, where cardiovascular complications remain a major cause of morbidity and premature mortality despite significant advances in anti-inflammatory therapy. Obesity, insulin resistance, endothelial dysfunction, and

skeletal-muscle loss increasingly appear to reflect disturbances in common immunometabolic pathways linking systemic inflammation to metabolic disease [15-17,24,26].

Accordingly, the cardiovascular benefits associated with GLP-1 receptor agonists may not simply represent secondary consequences of weight reduction. Instead, they may reflect broader improvements in the mechanisms governing metabolic adaptation, tissue resilience, and immune homeostasis across multiple organ systems.

3.4.6. Toward an immunometabolic paradigm in rheumatology

The expanding understanding of immunometabolism suggests that the future of rheumatology may depend not only on controlling inflammation but also on restoring the adaptive mechanisms that maintain systemic homeostasis. Within this framework, GLP-1 receptor agonists represent more than antidiabetic agents; they illustrate how modulation of metabolic pathways can influence immunity, tissue integrity, cardiovascular health, and biological ageing.

Furthermore, emerging evidence suggests that interactions among incretin signaling, intestinal microbiota, and the immune system may constitute an additional regulatory layer shaping immunometabolic resilience. Experimental studies have demonstrated that specific gut microorganisms, including *Akkermansia muciniphila*, can stimulate endogenous GLP-1 production and improve systemic metabolic homeostasis, highlighting the existence of a complex gut–metabolism–immunity axis [37].

Although current evidence remains insufficient to establish GLP-1 receptor agonists as disease-modifying therapies in rheumatic diseases, their pleiotropic actions on mitochondria, nutrient sensing, oxidative stress, and inflammatory pathways position them as one of the first examples of a broader class of immunometabolic therapeutics capable of targeting the mechanisms that link chronic inflammation with metabolic dysfunction and accelerated ageing [15-17,21-23,28].

3.5. Clinical evidence for GLP-1 receptor agonists in rheumatic diseases

The translation of glucagon-like peptide-1 receptor agonists (GLP-1RAs) into rheumatology remains at an early but rapidly evolving stage. Although these agents have demonstrated substantial benefits in obesity, type 2 diabetes mellitus, and cardiovascular disease, their role in rheumatic diseases is considerably less established. Importantly, the strength of evidence varies markedly across different conditions. The most robust clinical data currently derive from

randomized controlled trials in obesity-associated osteoarthritis, whereas evidence in rheumatoid arthritis (RA), psoriatic arthritis (PsA), and systemic lupus erythematosus (SLE) is derived predominantly from observational studies, retrospective cohorts, and real-world analyses [26,38-45].

This distinction is particularly important because obesity, insulin resistance, dyslipidemia, and cardiovascular disease are increasingly recognized not simply as comorbidities but as active contributors to chronic inflammation, disease severity, treatment response, and long-term outcomes in rheumatic disorders. Consequently, the beneficial effects of GLP-1 receptor agonists may arise from several interconnected mechanisms, including weight reduction, improvement in metabolic fitness, attenuation of adipose-tissue inflammation, and, potentially, direct immunomodulatory actions. However, current evidence does not allow these mechanisms to be clearly disentangled [15-17,24,26,43].

Therefore, the available literature should be interpreted cautiously, distinguishing between established clinical benefits, preliminary therapeutic signals, and mechanistic hypotheses that remain to be validated in disease-specific trials.

3.5.1. Rheumatoid arthritis

Clinical evidence supporting GLP-1 receptor agonists in rheumatoid arthritis remains limited and largely observational. Recent reviews, retrospective studies, and real-world analyses suggest that treatment with GLP-1RAs in patients with rheumatoid arthritis and concomitant obesity or type 2 diabetes mellitus is associated with substantial reductions in body weight and improvements in metabolic and cardiovascular risk profiles. Several reports have additionally described reductions in pain, inflammatory markers, glucocorticoid use, and composite disease activity scores. Nevertheless, these findings should be interpreted with caution because prospective randomized studies specifically evaluating inflammatory outcomes in rheumatoid arthritis are currently lacking [26,41-44,46].

The interpretation of disease activity in rheumatoid arthritis presents additional challenges. Composite indices incorporate subjective components such as pain, fatigue, and patient-reported outcomes, which may improve following weight loss independently of changes in synovial inflammation. Thus, the currently available data do not establish whether improvements in

clinical measures reflect direct immunomodulatory effects of GLP-1 receptor agonists or secondary consequences of improved metabolic health [26,43,44].

Nonetheless, the close relationship between obesity and rheumatoid arthritis outcomes provides a strong rationale for further investigation. Excess adiposity has been associated with higher disease activity, poorer physical function, reduced likelihood of remission, and diminished response to selected disease-modifying therapies. Moreover, recent population-based studies suggest that GLP-1 receptor agonists may reduce thromboembolic and cardiovascular complications in patients with rheumatoid arthritis and diabetes, highlighting the importance of cardiometabolic pathways in determining long-term prognosis [16,17,26,41-44,46].

From an immunometabolic perspective, rheumatoid arthritis represents a particularly relevant model for evaluating the therapeutic potential of GLP-1 receptor agonists. The coexistence of chronic inflammation, metabolic dysfunction, accelerated immune ageing, and increased cardiovascular burden suggests that interventions targeting the interface between metabolism and immunity may complement conventional disease-modifying therapies and improve long-term outcomes in selected patient populations [16,17,46].

At present, GLP-1 receptor agonists cannot be considered disease-modifying therapies in rheumatoid arthritis. Their most plausible role lies in the management of obesity and cardiometabolic risk in carefully selected patients while dedicated randomized trials evaluate their potential anti-inflammatory effects.

3.5.2. Psoriatic arthritis and psoriasis

Psoriatic disease represents a particularly attractive setting for immunometabolic interventions because obesity, metabolic syndrome, insulin resistance, and cardiovascular disease are closely linked to both cutaneous and musculoskeletal manifestations. Excess adiposity is associated with greater disease severity, lower rates of minimal disease activity, and poorer response to conventional and biologic therapies [40,43,47].

Clinical evidence regarding GLP-1 receptor agonists is currently more extensive in psoriasis than in psoriatic arthritis. Systematic reviews and observational studies have demonstrated substantial reductions in body weight and improvements in metabolic parameters, while selected cohorts have reported improvements in psoriasis severity and patient-reported outcomes. However, the

available findings remain heterogeneous, and randomized trials have yielded inconsistent results regarding direct anti-inflammatory effects independent of metabolic improvement [40,43,47].

Evidence specifically addressing psoriatic arthritis remains sparse. Existing reports suggest improvements in pain, systemic inflammation, and cardiometabolic health, but these benefits frequently correlate with the degree of weight reduction. Consequently, current evidence supports the hypothesis that metabolic optimization constitutes an important mediator of clinical benefit, whereas direct disease-modifying effects remain unproven [41,43,47].

The multidimensional nature of psoriatic arthritis further complicates interpretation. Peripheral arthritis, enthesitis, dactylitis, axial disease, skin involvement, fatigue, and cardiovascular complications may respond differently to metabolic interventions. Future studies should therefore incorporate domain-specific outcomes and stratify patients according to obesity, metabolic profile, and background antirheumatic therapy.

3.5.3. Osteoarthritis

Among rheumatic diseases, osteoarthritis currently provides the strongest clinical evidence supporting the therapeutic potential of GLP-1 receptor agonists. In patients with obesity and symptomatic knee osteoarthritis, treatment with once-weekly semaglutide resulted in significantly greater weight loss and clinically meaningful improvements in pain and physical function compared with placebo. These findings established pharmacological weight reduction as an effective strategy for improving outcomes in obesity-associated osteoarthritis [38,39].

Importantly, the implications of these results extend beyond mechanical unloading. Osteoarthritis is increasingly recognized as a heterogeneous disorder involving adipose-tissue dysfunction, insulin resistance, altered adipokine signaling, mitochondrial abnormalities, and chronic low-grade inflammation. Experimental and translational studies indicate that disturbances in chondrocyte energetics, mitochondrial homeostasis, and lipid metabolism contribute substantially to cartilage degeneration and disease progression. Consequently, GLP-1 receptor agonists may influence osteoarthritis through both biomechanical and immunometabolic mechanisms [11,15-17,48].

Accumulating evidence suggests that metabolically driven osteoarthritis may represent a distinct disease phenotype characterized by obesity, metabolic syndrome, and systemic inflammation. In this context, alterations in cellular metabolism extend beyond cartilage degradation and involve

complex interactions among adipose tissue, inflammatory mediators, and stromal cells within the joint microenvironment. These observations further support the concept that osteoarthritis should not be regarded solely as a consequence of mechanical wear but also as a disorder of impaired metabolic adaptation [11,48].

Nevertheless, current evidence primarily supports symptomatic and functional benefits rather than definitive disease modification. It remains unclear whether GLP-1 receptor agonists directly affect cartilage integrity, synovial inflammation, subchondral bone remodeling, or structural progression. Long-term studies incorporating imaging outcomes and joint replacement rates will therefore be necessary to establish whether these agents possess true disease-modifying properties [38,39].

Moreover, the available evidence relates predominantly to obesity-associated knee osteoarthritis and cannot automatically be generalized to other osteoarthritis phenotypes. Patients characterized by obesity, metabolic syndrome, and systemic low-grade inflammation are likely to derive the greatest benefit from these therapies [11,48].

3.5.4. Systemic lupus erythematosus

Compared with inflammatory arthritis and osteoarthritis, evidence regarding GLP-1 receptor agonists in systemic lupus erythematosus remains extremely limited. At present, there is insufficient evidence to support a direct therapeutic role for GLP-1RAs in controlling lupus activity, preventing disease flares, or modifying organ damage [45].

Interest in GLP-1 signaling in SLE derives primarily from the intersection between immunometabolism, obesity, glucocorticoid exposure, insulin resistance, and accelerated cardiovascular disease. Systemic lupus erythematosus is characterized by profound metabolic abnormalities, mitochondrial dysfunction, and disturbances in immune-cell energetics that contribute to both immune dysregulation and long-term complications [12,45].

Preliminary observational data indicate that GLP-1 receptor agonists can produce substantial reductions in body weight without an apparent increase in lupus flare rates. However, these findings originate from limited cohorts and should not be interpreted as evidence of disease-modifying efficacy. At present, the principal rationale for GLP-1RA use in SLE lies in the management of obesity, diabetes, glucocorticoid-associated metabolic complications, and cardiovascular risk rather than in direct immunosuppression [45].

Future studies should evaluate not only disease activity but also renal outcomes, glucocorticoid exposure, body composition, fatigue, physical function, and cardiovascular morbidity in this high-risk population. Until such data become available, any conclusions regarding the therapeutic role of GLP-1 receptor agonists in SLE must remain cautious.

3.5.5. Weight loss as a modifier of rheumatic disease outcomes

Weight reduction represents the most consistent and clinically established effect of GLP-1 receptor agonists and is likely to account for a substantial proportion of their therapeutic benefits in rheumatology. Adipose tissue actively contributes to chronic inflammation through adipokine imbalance, macrophage activation, insulin resistance, ectopic lipid accumulation, and alterations in immune-cell metabolism. Consequently, reductions in adiposity may influence disease activity, physical function, and cardiovascular risk across multiple rheumatic conditions [15-17,24,26].

However, weight loss should not be regarded exclusively as a reduction in total body mass. Patients with chronic inflammatory diseases frequently exhibit sarcopenia, frailty, and rheumatoid cachexia, emphasizing the importance of preserving skeletal muscle during pharmacological weight reduction. Future studies should therefore incorporate detailed assessments of body composition, muscle function, and physical performance rather than relying solely on conventional anthropometric measures [16,17,26].

An unresolved question concerns the relative contribution of metabolic improvement and direct immunomodulation to the observed clinical effects of GLP-1 receptor agonists. Clarifying this relationship will be essential for defining the future place of these agents in rheumatology.

3.5.6. Cardiovascular outcomes and implications for rheumatology

Cardiovascular disease remains a leading cause of morbidity and premature mortality in rheumatoid arthritis, psoriatic arthritis, and systemic lupus erythematosus. Despite major advances in anti-inflammatory treatment, substantial residual cardiovascular risk persists, suggesting that suppression of inflammation alone is insufficient to restore vascular health [15-17,36].

Large cardiovascular outcome trials in obesity and metabolic disease have demonstrated that GLP-1 receptor agonists reduce major adverse cardiovascular events. In parallel, population-based studies involving patients with immune-mediated inflammatory diseases suggest favorable

cardiovascular outcomes following GLP-1RA initiation. These findings support the concept that chronic inflammation and cardiovascular disease share common immunometabolic determinants [26,36,43,44].

For patients with rheumatic diseases, the clinical significance of GLP-1 receptor agonists may therefore extend beyond musculoskeletal manifestations. Improvements in body composition, endothelial function, glycemic control, and vascular risk factors could address an important component of residual morbidity that is not fully eliminated by conventional immunosuppressive therapies. Nevertheless, dedicated cardiovascular studies in rheumatic populations remain necessary, as chronic inflammation, glucocorticoid exposure, renal disease, and disease-specific mechanisms may substantially modify treatment responses [15-17,26,36].

3.5.7. Current limitations and future directions

The available evidence supports a cautious yet promising interpretation of glucagon-like peptide-1 receptor agonists in rheumatology. At present, the strongest clinical data derive from randomized controlled trials in obesity-associated osteoarthritis, in which GLP-1RAs have demonstrated meaningful improvements in pain, physical function, and body weight. By contrast, evidence in rheumatoid arthritis and psoriatic arthritis remains largely observational, whereas clinical data in systemic lupus erythematosus are still insufficient to establish therapeutic efficacy or disease-modifying potential [26,36,38-45,47].

Taken together, current findings suggest that the most immediate clinical value of GLP-1 receptor agonists lies in the management of obesity, metabolic dysfunction, and cardiovascular risk among selected patients with rheumatic diseases. Nevertheless, it remains unclear to what extent the observed benefits result from direct immunomodulatory effects rather than from improvements in body composition, insulin sensitivity, and systemic metabolic health. Consequently, the relative contributions of metabolic optimization and immune regulation to therapeutic outcomes have yet to be fully elucidated [26,36,38,41-45].

Several important questions therefore remain unanswered. Future studies should determine whether GLP-1 receptor agonists can modify inflammatory pathways independently of weight reduction, identify the patient populations most likely to benefit from treatment, and establish the long-term safety of these agents in individuals receiving concomitant immunosuppressive

therapy. Particular attention should also be paid to the potential interactions between GLP-1 signaling, ageing, immunosenescence, and cardiometabolic comorbidity.

To address these challenges, future clinical trials should incorporate objective inflammatory biomarkers, imaging outcomes, detailed assessments of body composition and physical function, as well as long-term cardiovascular endpoints. Stratification according to obesity status, metabolic phenotype, background antirheumatic therapy, and disease subtype will be essential for accurately defining treatment effects. Ultimately, such studies will determine whether GLP-1 receptor agonists function primarily as metabolic adjuncts or whether they represent a novel class of immunometabolic therapeutics capable of reshaping the management of rheumatic diseases.

4. Discussion

4.1. Immunometabolism reshapes the conceptual framework of rheumatic diseases

The central message emerging from this review is that immunometabolism fundamentally reshapes the current understanding of rheumatic diseases. We propose that immunometabolic resilience constitutes a higher-order biological property integrating immune competence, metabolic flexibility, tissue adaptation, and systemic homeostasis across chronic inflammatory disorders. Viewed through this perspective, rheumatoid arthritis, psoriatic arthritis, osteoarthritis, and systemic lupus erythematosus no longer appear solely as diseases of dysregulated immunity but rather as complex systemic conditions arising from the progressive failure of coordinated metabolic adaptation across immune, stromal, and vascular compartments [1-5,13].

For decades, rheumatic diseases have been interpreted primarily within a cytokine-centered framework. This paradigm has profoundly influenced clinical practice and enabled the development of biologic and targeted synthetic therapies that have transformed patient outcomes. However, despite these advances, persistent inflammation, accelerated cardiovascular disease, metabolic dysfunction, frailty, sarcopenia, and marked interindividual variability in treatment response remain major unmet needs. These observations suggest that inflammatory pathways alone cannot fully explain disease initiation, progression, and long-term prognosis [4,5,15-17].

The emergence of immunometabolism has expanded this traditional model by demonstrating that cellular metabolism is not merely a passive consequence of immune activation but an active determinant of immune-cell function and tissue behavior. Nutrient sensing, mitochondrial

homeostasis, oxidative stress, intermediary metabolism, and stromal–immune interactions collectively shape immune-cell differentiation, inflammatory responses, and the capacity of tissues to adapt to chronic stress. Consequently, chronic inflammation increasingly appears not simply as the product of aberrant immunity but as the manifestation of disrupted biological programs that normally coordinate metabolism, tissue repair, and immune homeostasis [1,2,6,8,13].

Collectively, these observations support a transition from reductionist models focused on isolated inflammatory mediators toward a systems-level understanding of rheumatic diseases in which inflammation, metabolism, ageing, and tissue adaptation represent interconnected components of a shared pathogenic network.

4.2. Immunometabolic resilience as a unifying pathogenic principle

The concept of immunometabolic resilience provides a framework capable of integrating many of the seemingly disparate manifestations of rheumatic diseases into a common biological model. Under physiological conditions, immune and stromal cells continuously adapt their metabolic programs in response to changing energetic demands, nutrient availability, and environmental stressors. Mitochondrial function, redox balance, nutrient-sensing pathways, and tissue-specific metabolic networks cooperate to preserve cellular integrity and maintain systemic homeostasis [1,2,6,13].

Chronic inflammatory diseases progressively disrupt these adaptive mechanisms. Persistent immune activation alters mitochondrial function, impairs metabolic flexibility, promotes oxidative stress, and drives profound changes in tissue microenvironments. As these compensatory systems become exhausted, immune dysregulation and metabolic dysfunction reinforce one another, generating self-sustaining cycles of inflammation and tissue injury [4,5,8,14,25].

Within this framework, synovial inflammation, adipose-tissue dysfunction, endothelial injury, skeletal-muscle loss, and cardiovascular disease should not be regarded as isolated clinical phenomena. Rather, they may represent different manifestations of a common failure of adaptive capacity operating across cellular, tissue, and organismal levels. Disease progression can therefore be interpreted not merely as the accumulation of inflammatory damage but as the

gradual collapse of the mechanisms that ordinarily preserve resilience under conditions of prolonged inflammatory and metabolic stress [15-17,24,26].

Importantly, this perspective also helps explain why distinct rheumatic diseases exhibit substantial overlap despite differences in their immunological profiles. Rheumatoid arthritis, psoriatic arthritis, osteoarthritis, and systemic lupus erythematosus are characterized by varying combinations of mitochondrial dysfunction, metabolic imbalance, stromal-cell activation, and increased cardiovascular burden. The convergence of these features suggests that chronic inflammation and metabolic dysregulation are deeply intertwined processes linked by shared mechanisms of failed adaptation [11-13,15-17].

4.3. GLP-1 signaling and the emergence of immunometabolic therapeutics

The growing interest in glucagon-like peptide-1 receptor agonists reflects a broader transformation in therapeutic thinking within rheumatology. Originally developed for the treatment of obesity and type 2 diabetes mellitus, these agents have demonstrated pleiotropic effects extending beyond glucose regulation, including influences on nutrient sensing, mitochondrial homeostasis, oxidative stress, endothelial function, adipose-tissue biology, and inflammatory signaling [18-23,36].

Within the conceptual framework proposed in this review, GLP-1 receptor agonists are important not simply because of their individual pharmacological properties but because they illustrate a more fundamental shift in the therapeutic paradigm. Traditional treatment strategies have largely focused on suppressing specific inflammatory mediators. In contrast, incretin-based therapies raise the possibility that future interventions may target the metabolic infrastructure that sustains chronic inflammation, tissue remodeling, and systemic complications [15-23].

Nevertheless, the current evidence warrants caution. The established clinical benefits of GLP-1 receptor agonists relate primarily to weight reduction, improvements in metabolic health, and cardiovascular protection. Although experimental and translational studies suggest potential immunomodulatory properties, it remains unclear whether these effects are sufficient to alter the natural history of rheumatic diseases independently of metabolic improvement [21-23,26,28,36,38-45,47].

Accordingly, GLP-1 receptor agonists should not yet be regarded as disease-modifying therapies in rheumatology. Rather, they may represent the first clinically available example of a broader

class of interventions aimed at restoring immunometabolic resilience and improving systemic adaptation to chronic inflammatory stress.

Beyond their effects on body weight and glucose metabolism, GLP-1 receptor agonists exert pleiotropic actions across multiple organ systems, including the cardiovascular, renal, and vascular compartments. Experimental and clinical studies have demonstrated favorable effects on endothelial function, renal hemodynamics, oxidative stress, and systemic metabolic homeostasis, further supporting the concept that incretin signaling operates at the intersection of metabolic regulation and tissue adaptation. These broader biological effects may be particularly relevant in rheumatic diseases, in which chronic inflammation frequently coexists with renal impairment, endothelial dysfunction, and an increased burden of cardiometabolic comorbidity. Consequently, the therapeutic potential of GLP-1 receptor agonists may extend beyond immune modulation alone and encompass mechanisms that preserve systemic resilience in the setting of chronic inflammatory stress [49-54].

4.4. Clinical translation, limitations, and future directions

The integration of immunometabolism and incretin biology has important implications for both clinical practice and future research. First, it challenges the conventional distinction between inflammatory and metabolic diseases. Obesity, insulin resistance, endothelial dysfunction, and cardiovascular disease should no longer be viewed merely as comorbid conditions but as active participants in disease pathogenesis, therapeutic response, and long-term outcomes [15-17,24,26,36].

Second, this framework highlights the need to identify patient populations most likely to benefit from immunometabolic interventions. Individuals with obesity, metabolic syndrome, increased cardiovascular risk, or features of accelerated biological ageing may represent particularly relevant candidates for therapeutic strategies that simultaneously influence inflammatory and metabolic pathways [15-17,21-23,26].

Despite substantial progress in understanding the molecular basis of immunometabolic dysfunction, important limitations remain. Most mechanistic insights originate from experimental studies, whereas clinical evidence supporting immunometabolic interventions in rheumatic diseases is still limited. The strongest data regarding GLP-1 receptor agonists are currently available for obesity-associated osteoarthritis, while evidence in rheumatoid arthritis, psoriatic

arthritis, and systemic lupus erythematosus remains predominantly observational [21-23,26,28,36,38-45,47].

One of the most important unresolved questions concerns the relative contribution of weight reduction, metabolic improvement, and direct immunomodulatory effects to the observed clinical benefits of GLP-1 receptor agonists. Moreover, considerable heterogeneity exists across rheumatic diseases with respect to inflammatory pathways, metabolic phenotypes, therapeutic exposure, and comorbidity burden, making it difficult to determine whether immunometabolic interventions will exert comparable effects across different patient populations [15–17,26,36,38-45,47].

Future investigations should therefore integrate conventional clinical outcomes with advanced imaging, metabolic profiling, body-composition analyses, biomarkers of mitochondrial and immune function, and long-term cardiovascular endpoints. The development of robust biomarkers capable of quantifying immunometabolic resilience will be essential for patient stratification, treatment selection, and monitoring therapeutic responses [1-5,13,21-23].

Ultimately, the convergence of immunometabolism and incretin biology challenges the traditional view of rheumatic diseases as disorders driven solely by immune dysregulation. Viewed through the lens of immunometabolism, these conditions increasingly emerge as systemic failures of adaptation unfolding across interconnected cellular, tissue, and organismal networks. The future of rheumatology may therefore depend not only on the ability to suppress inflammation, but also on understanding how metabolic adaptation preserves tissue integrity, systemic homeostasis, and resilience in the face of chronic inflammatory stress.

5. Conclusions

Immunometabolism is redefining the conceptual foundations of rheumatology by challenging the traditional view that chronic inflammatory diseases arise solely from dysregulated immune responses. The evidence synthesized in this review indicates that immune-cell activation, stromal-cell behavior, tissue remodeling, and systemic complications are inseparably linked to metabolic adaptation, mitochondrial homeostasis, oxidative stress, and nutrient-sensing pathways.

We propose immunometabolic resilience as a unifying framework that integrates immune competence, metabolic flexibility, mitochondrial function, and tissue adaptation across rheumatic

diseases. Within this model, rheumatoid arthritis, psoriatic arthritis, osteoarthritis, and systemic lupus erythematosus emerge not as isolated inflammatory entities but as complex systemic disorders characterized by the progressive loss of adaptive capacity operating across immune, stromal, and vascular compartments.

This perspective provides a biological explanation for the coexistence of chronic inflammation, cardiovascular disease, metabolic dysfunction, frailty, and accelerated ageing, suggesting that these manifestations represent interconnected consequences of disrupted immunometabolic homeostasis rather than independent disease processes. Accordingly, the restoration of immunometabolic resilience may become an important therapeutic objective alongside the suppression of inflammation.

The growing interest in GLP-1 receptor agonists illustrates the therapeutic potential of targeting the interface between metabolism and immunity. Beyond their established effects on body weight, glucose metabolism, and cardiovascular risk, these agents influence multiple pathways involved in immunometabolic regulation, including mitochondrial function, oxidative stress, nutrient sensing, and inflammasome activity. However, despite compelling mechanistic and translational evidence, current clinical data remain insufficient to establish GLP-1 receptor agonists as disease-modifying therapies in rheumatology. Whether their potential benefits arise predominantly from improvements in metabolic health and reductions in adiposity or reflect direct immunomodulatory effects remains an important unresolved question.

Future studies integrating clinical outcomes with metabolic profiling, advanced imaging, biomarkers of mitochondrial and immune function, and long-term cardiovascular endpoints will be essential to determine whether therapies targeting immunometabolic pathways can alter disease trajectories and improve systemic resilience. Such approaches may ultimately facilitate the identification of patient populations most likely to benefit from immunometabolic interventions and help define the place of incretin-based therapies within modern rheumatology.

Ultimately, the convergence of immunometabolism and incretin biology suggests that the future of rheumatology may extend beyond the suppression of inflammatory pathways alone. Viewed through the lens of immunometabolism, rheumatic diseases increasingly emerge as disorders of failed adaptation, in which the restoration of metabolic resilience may become as important as the control of immune activation.

Disclosure Statement

The author confirms that this manuscript represents original work that has not been published previously and is not currently under consideration for publication elsewhere. The author assumes full responsibility for the content, interpretation, and conclusions presented in this review.

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No supplementary materials are associated with this article.

Author Contributions

Paulina Patrycja Turzyńska conceived and designed the study, developed the conceptual framework, conducted the literature review, interpreted the evidence, and wrote, reviewed, and revised the manuscript. The author has read and approved the final version of the manuscript.

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Declaration of Generative AI and AI-Assisted Technologies

During the preparation of this work, the author used ChatGPT-5.2 to improve grammar and language clarity. After using this tool, the author reviewed and edited the content as needed and takes full responsibility for the content of the publication.

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