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THE POTENTIAL OF GLP-1 IN THE TREATMENT OF AUTOIMMUNE DISEASES: A REVIEW OF MECHANISMS AND CLINICAL DATA

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ABSTRACT

Introduction: Autoimmune diseases are a heterogeneous group of disorders characterized by dysregulated immune responses against self-antigens, leading to chronic inflammation and progressive organ damage. Despite advances in immunosuppressive and biologic therapies improving outcomes in conditions like systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and multiple sclerosis (MS), a subset of patients exhibit suboptimal responses or experience significant adverse effects. Additionally, access to certain biologic treatments may be limited by strict eligibility criteria. Metabolic comorbidities such as obesity, insulin resistance, and type 2 diabetes are prevalent in patients with autoimmune diseases and can exacerbate inflammation, accelerate organ damage, and diminish therapeutic efficacy. Glucagon-like peptide-1 receptor agonists (GLP-1RA), a class of drugs originally developed for type 2 diabetes and obesity, have demonstrated pleiotropic effects extending beyond glycemic control, including modulation of immune cell function, suppression of pro-inflammatory cytokine release, and improvement of endothelial function. These immunometabolic properties suggest that GLP-1RA could serve as promising adjunctive agents in managing autoimmune diseases, particularly in patients with coexisting metabolic disturbances.

Materials and Methods: The article was written based on scientific papers available on PubMed and Google Scholar

Key findings: Evidence gathered indicates that GLP-1 receptor agonists exert significant immunomodulatory and metabolic effects that may translate into clinical benefits across multiple autoimmune diseases. In psoriasis and psoriatic arthritis, where chronic Th1/Th17-driven inflammation often coexists with obesity and insulin resistance, GLP-1RA therapy has been associated with improvements in inflammatory markers and disease severity indices (such as PASI for skin lesions and DAPSA for joint disease), alongside substantial weight reduction and better glycemic control. Multiple sclerosis models and preliminary clinical observations suggest that GLP-1RA can attenuate neuroinflammation and promote neuroprotection: these agents reduce pathogenic Th1/Th17 cell activity, inhibit microglial activation, and may enhance remyelination processes, thereby potentially decreasing relapse rates and neurological damage. In systemic lupus erythematosus, a small retrospective analysis indicated that adjunctive GLP-1RA use led to significant weight loss and improved metabolic profiles without provoking new organ involvement or severe flares; notably, no acceleration of lupus disease activity was seen over short-term follow-up, aligning with GLP-1RA's known cardiovascular and renal protective effects. (An isolated case of GLP-1RA–induced lupus has been reported, underscoring the need for vigilance.) In rheumatoid arthritis, in vitro studies on fibroblast-like synoviocytes demonstrated that GLP-1RA (e.g., lixisenatide, dulaglutide) can suppress the production of pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) and matrix-degrading enzymes (MMP-1, -3, -13) by inhibiting NF-κB and MAPK signaling pathways, thereby potentially protecting joint cartilage and bone. Early clinical studies and case series in RA patients (especially those with coexisting type 2 diabetes or obesity) reported reduced disease activity scores (DAS28), lower C-reactive protein and erythrocyte sedimentation rate levels, fewer swollen joints, and diminished morning stiffness during GLP-1RA treatment, along with the expected weight reduction and improved insulin sensitivity. In type 1 diabetes mellitus, which involves autoimmune β-cell destruction, adjunctive therapy with GLP-1RA (such as exenatide, liraglutide, or semaglutide) has shown promise in patients with residual β-cell function. These agents consistently reduced exogenous insulin requirements and facilitated modest improvements in glycemic control (including lower HbA1c and increased time-in-range on continuous glucose monitoring) while promoting weight loss. In honeymoon-phase or early type 1 diabetes mellitus GLP-1RA addition even enabled temporary insulin independence in a few cases. However, across these studies, gastrointestinal side effects were common, and a few instances of euglycemic ketosis were noted, indicating that careful patient selection and monitoring are necessary. Overall, the integration of GLP-1RA into the treatment of autoimmune diseases has yielded partial improvements in disease control and significant benefits in managing metabolic comorbidities, though these benefits are often contingent on disease severity and the presence of a metabolic-inflammatory phenotype. No evidence to date suggests that GLP-1RA can replace standard immunotherapies; rather, they function as complementary agents that address an often overlooked metabolic component of autoimmunity.

Conclusions: Autoimmune diseases remain a therapeutic challenge, as many patients achieve only incomplete remission and continue to endure disease-related damage and comorbidities under current treatment paradigms. Glucagon-like peptide-1 receptor agonists offer a novel, multidimensional approach that simultaneously targets metabolic dysregulation and immune aberrations. The current body of evidence indicates that GLP-1RA can confer additional clinical benefits – such as reducing systemic inflammation, improving disease activity metrics, aiding weight loss, and lowering cardiovascular risk – especially in patients whose autoimmune disease is compounded by obesity or insulin resistance. These agents represent a promising adjunct to existing therapies, potentially bridging a gap between metabolic syndrome management and immunomodulation in autoimmune care. However, their therapeutic impact appears to be partial and disease-specific, often providing symptomatic relief or slowing disease activity rather than inducing full remission. Limitations such as high relapse rates upon GLP-1RA discontinuation (noted in conditions like hidradenitis suppurativa and suggested by analogy in other diseases), the risk of side effects (gastrointestinal intolerance, rare immune reactions), and the absence of long-term safety data in autoimmune populations underscore that GLP-1RA are not a standalone solution. The complex interplay of immune and metabolic pathways in autoimmunity highlighted by these findings reinforces the need for further research. Well-designed, large-scale clinical trials are urgently needed to confirm the efficacy and safety of GLP-1RA across different autoimmune diseases, to determine optimal patient selection criteria, and to elucidate the mechanisms by which metabolic modulation can alter immune-driven disease courses. Such studies will pave the way for the development of more targeted and personalized treatment strategies, potentially solidifying the role of GLP-1RA as part of a multidimensional therapeutic approach to autoimmune disorders.

KEYWORDS

Psoriasis, Psoriatic Arthritis, Rheumatoid Arthritis, Systemic Lupus Erythematosus, Multiple Sclerosis, Type 1 Diabetes, GLP-1 Receptor Agonists, Immunomodulation, Metabolic Comorbidities, Autoimmune Diseases

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Introduction

Autoimmune diseases are a group of disorders in which the immune system, due to dysregulated immunological control, recognizes the body's own cells and tissues as foreign, leading to their damage. These diseases can affect virtually any organ, and their course is often associated with chronic inflammation and progressive deterioration of organ function.

Currently, a variety of therapeutic options are available for the treatment of autoimmune diseases, including immunosuppressive agents and targeted therapies in the form of biologic treatments. The effectiveness of therapies for autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis has improved in recent years[1,2,3]. However, in certain cases, the response to treatment remains limited, or adverse effects occur, necessitating the search for alternative, available therapeutic options. It is also worth noting that in Poland, access to biologic therapy is limited by the criteria defined in drug program guidelines. To receive such treatment, patients must meet specific requirements related to disease severity and the failure of other available treatment options[4]. Therefore, the identification of additional therapeutic strategies—both pharmacological and non-pharmacological, including lifestyle modifications—becomes particularly important in alleviating symptoms, improving quality of life, and achieving disease control. Coexisting metabolic disorders such as obesity, insulin resistance, and type 2 diabetes are frequently observed in the population of patients with autoimmune diseases and may influence both the clinical course of the underlying disease and the response to treatment[5,6]. Excess body weight is an independent risk factor for cardiovascular complications[7], the incidence of which is already elevated due to the chronic inflammatory process characteristic of autoimmune diseases[8]. Additionally, obesity may negatively affect the pharmacokinetics and pharmacodynamics of immunosuppressive drugs, leading to the need for higher therapeutic doses, reduced drug concentrations in target tissues, and diminished clinical efficacy[9]. Moreover, observational studies have shown that excess body weight is associated with a poorer response to biologic treatment[10,11]. In this context, growing interest is directed toward the role of the incretin system, particularly GLP-1RAs, whose applications to date have been primarily limited to the treatment of type 2 diabetes and obesity. Increasing numbers of preclinical reports and clinical observations indicate that these agents, beyond their metabolic effects, also exhibit significant immunomodulatory properties. These mechanisms include, among others, the modulation of monocyte and macrophage function, suppression of pro-inflammatory cytokine expression (e.g., TNF-α, IL-6, IL-17), as well as the influence on T cell differentiation and the expansion of regulatory T cells (Tregs)[12]. GLP-1RAs have also been shown to exert beneficial effects on endothelial function, oxidative stress, and microcirculation, which may be relevant in the context of systemic inflammation accompanying autoimmune diseases[13]. Due to their pleiotropic effects—encompassing metabolic, immunological, and vascular mechanisms—GLP-1RAs represent a potential class of adjunctive agents in the treatment of selected autoimmune diseases, particularly in patients with metabolic symptoms and increased cardiovascular risk. The aim of this paper is to provide a synthetic overview of the current knowledge on the effects of GLP-1 receptor agonists and their potential utility in the treatment of selected autoimmune diseases.

Psoriasis and Psoriatic Arthritis

Psoriasis (PsO) and psoriatic arthritis (PsA) are chronic autoimmune inflammatory diseases characterized by pathological activation of Th1 and Th17 lymphocytes and overproduction of pro-inflammatory cytokines such as IL-17, IL-23, TNF-α, and IL-6 [14,15]. These diseases are marked by considerable heterogeneity in clinical presentation and disease severity. Both PsO and PsA show a strong association with metabolic disorders, including obesity, insulin resistance, and type 2 diabetes mellitus (T2DM) [16,17]. In the PsA population, obesity is observed in approximately 27.6% of patients, while type 2 diabetes occurs in 12% [16]. Insulin resistance, assessed by the HOMA-IR index, affects up to 31% of patients and shows a significant correlation with disease activity as measured by the Disease Activity Index for Psoriatic Arthritis (DAPSA), with a strong positive association ($r = 0.768$; $p < 0.001$) [17]. DAPSA is a composite tool that incorporates the number of tender and swollen joints, the patient's global assessment of disease activity, pain level, and C-reactive protein (CRP) concentration, which is a key acute-phase inflammatory marker [18]. In patients with PsO, meta-analyses have shown that the risk of obesity is higher than in the general population [19]. An analysis of NHANES data demonstrated a significant association between PsO and an increased risk of developing type 2 diabetes (OR = 1.48; 95% CI: 1.16–1.90). The authors noted that obesity may partially mediate this relationship, acting as an intermediary factor in the mechanism of elevated metabolic risk [20]. Considering the coexistence of inflammatory and metabolic components, GLP-1RA appears to be a particularly promising therapeutic class. In addition to their documented effects on weight reduction and improvement in insulin sensitivity, they also exhibit immunomodulatory activity. Preclinical studies have shown that GLP-1RA inhibit activation of Th1 and Th17 lymphocytes, reduce expression of cytokines such as IL-6, TNF-α, and IL-17, and enhance the activity of regulatory T cells (Treg). These effects result in the suppression of both local and systemic inflammation [21].

Individual clinical observations suggest the potential for GLP-1RA to reduce skin and joint symptoms in patients with PsO and PsA treated for obesity or diabetes [22,23]. However, there is a lack of large, randomized clinical trials that definitively confirm the efficacy of GLP-1RA as immunomodulatory agents in these disease entities. Nevertheless, the data collected to date indicate that in patients with PsO and/or PsA—particularly those with a metabolic-inflammatory phenotype and resistance to standard therapies—the addition of GLP-1RA may offer therapeutic benefits. Improvements in inflammatory markers (CRP, DAPSA, PASI), glycemic control, body weight, and vascular protection suggest that this drug class may represent an attractive option for selected patients requiring an integrated treatment approach.

The Impact of GLP-1 Receptor Agonists on Multiple Sclerosis

Multiple sclerosis is a chronic, progressive autoimmune disease affecting the central nervous system (CNS). Autoantibodies target the myelin sheath, leading to inflammation, demyelination, and subsequent axonal damage [24]. Myelin injury disrupts neural conduction, resulting in a variety of neurological symptoms such as paresthesias, visual disturbances, sensory deficits, and paresis [25]. The progressive nature of the disease, its high prevalence, and substantial economic burden underscore the urgent need to develop more effective therapeutic strategies. Current treatments primarily aim to control relapses, reduce disease activity, and delay progression. The mainstay therapy for acute relapses involves corticosteroids, which alleviate inflammation by suppressing immune system activity. These agents help mitigate symptoms and accelerate recovery following acute episodes; however, they do not alter the long-term course of the disease nor reduce the risk of future relapses. Disease-modifying therapies (DMTs) represent a broad class of medications used for the long-term management of MS. Examples of DMTs include interferons, glatiramer acetate, and monoclonal antibodies. These agents target specific components of the immunopathogenesis of MS, with a focus on suppressing early disease activity that may otherwise result in long-term disability [26]. A key challenge associated with DMTs lies in their variable efficacy, tolerability, and safety profiles, which depend not only on the specific pharmacological agent but also on individual patient characteristics. Moreover, the financial burden of DMTs is substantial, with annual treatment costs often reaching tens of thousands of US dollars [27]. There is evidence that GLP-1 receptor agonists can modulate the inflammatory response by influencing immune cells such as macrophages, monocytes, and lymphocytes [28]. GLP-1 agonists have also been shown to exert anti-inflammatory and neuroprotective effects. Although the exact mechanisms underlying these actions are not yet fully elucidated, it is known that GLP-1 agonists reduce the activity of nuclear factor kappa B (NF-κB) and enhance the activation of the AMP-activated protein kinase pathway, thereby contributing to the suppression of inflammation [29]. Both Schwann cells and oligodendrocytes

express the GLP-1 receptor [29]. Activation of the GLP-1 receptor triggers the phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) signaling pathway, which plays a critical role in initiating myelination in Schwann cells [30]. Moreover, GLP-1 receptor agonists have demonstrated the ability to stimulate oligodendrogenesis in murine models [31]. The potential impact of GLP-1RA on MS is gaining increasing attention due to their neuroprotective and immunomodulatory properties. MS is a chronic autoimmune disorder characterized by demyelination and neuroinflammation, which provides a strong rationale for investigating the potential therapeutic benefits of GLP-1RA in the management of this condition. One of the primary mechanisms through which GLP-1RA may exert beneficial effects on the course of MS is the modulation of inflammatory responses within the CNS. Chiou et al. demonstrated that dulaglutide – a GLP-1RA – can influence the development of encephalitogenic T lymphocytes, particularly the Th1 and Th17 subsets, which play a pivotal role in the pathogenesis of MS-related neuroinflammation [32]. These findings suggest that GLP-1RA may reduce the pathogenicity of these cells and attenuate inflammatory attacks on neural tissues. Moreover, studies have shown that GLP-1RA, such as exenatide, may support recovery from peripheral neuropathy and promote nerve regeneration. Fujita et al. demonstrated that exenatide significantly enhances recovery from oxaliplatin-induced peripheral neuropathy in animal models, supporting its neuroprotective potential [33]. These effects may also extend to the CNS, potentially facilitating reparative processes in MS, where damage to the myelin sheath is a hallmark feature. The neuroprotective role of GLP-1RA is associated with their ability to inhibit microglial activation and support neuronal survival. Sango et al. emphasize that GLP-1 receptors are expressed not only in pancreatic tissues but also in the central and peripheral nervous systems, where their activation may exert anti-demyelinating effects and promote remyelination [34]. This suggests that GLP-1RA may play a role not only in modulating inflammatory processes but also in enhancing regenerative mechanisms that are critical in the course of MS. In animal models of MS-like conditions, GLP-1RA have been shown to reduce the severity of clinical symptoms, improve motor function, and decrease relapse rates in experimental autoimmune encephalomyelitis (EAE)—a widely accepted model that closely mimics human MS [35]. These findings highlight the potential utility of GLP-1RA in modifying the course of the disease. Hölscher points out that dual agonists—acting simultaneously on GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors—may exhibit even stronger effects due to their efficient ability to cross the blood–brain barrier and exert neuroprotective actions [36]. This could represent an expansion of therapeutic options for patients in whom conventional treatments have failed to yield satisfactory outcomes. Increasing attention is also being paid to the beneficial effects of GLP-1RA on the cardiovascular system, which is often impaired in patients with MS. Hardoňová et al. report that GLP-1 agonists may improve endothelial function and reduce cardiovascular risk, potentially offering additional clinical benefits for this patient population [37]. In summary, available evidence suggests that GLP-1 receptor agonists possess significant potential in modifying the course of MS through their anti-inflammatory and neuroprotective actions. Their pleiotropic effects—including immunomodulation, support of neuronal survival, and improvement of vascular function—offer promising therapeutic avenues in MS management. However, further clinical studies are warranted to confirm the efficacy and safety of these agents in routine clinical practice.

Systemic Lupus Erythematosus

SLE is an autoimmune disease characterized by heterogeneous clinical manifestations and the potential to affect nearly any organ system in the body [38]. Profound immune dysregulation observed in the course of SLE is associated with metabolic dysfunction and adverse cardiovascular outcomes. For example, individuals with SLE are more likely to develop premature subclinical coronary artery disease and vasculitis, with the risk of myocardial infarction reported to be up to 50 times higher than in the general population [39–41]. This risk may be further exacerbated by the use of glucocorticoids, which remain a mainstay of SLE therapy [42]. Therefore, management of traditional cardiovascular risk factors is a critical component of care in patients with SLE. It remains unclear whether GLP-1RA could serve as beneficial adjunctive agents in mitigating the metabolic dysfunction associated with corticosteroid use and the pathogenesis of SLE. Moreover, the safety profile of GLP-1RA in individuals with SLE has not yet been established. A recent case report of drug-induced lupus, characterized by the presence of anti-dsDNA and anti-histone antibodies following GLP-1RA administration, underscores these uncertainties and may prompt some clinicians to exercise caution when considering their use in SLE patients [43]. The marked weight loss associated with GLP-1RA therapy has recently contributed to their growing popularity for this indication, further emphasizing the need for a better understanding of their impact on the course of SLE [44]. An analysis of data from the NYU Lupus Cohort, which included 1,211 patients with SLE, identified only 24 individuals who had received a GLP-1RA. Of these,

18 patients (94% female; median age 50 years) were included in the analysis due to the availability of complete medical records. All patients were prescribed GLP-1RA for weight reduction, and only one had a diagnosis of type 2 diabetes. At the time of study inclusion, 14 patients were in DORIS remission, and none exhibited active lupus nephritis.

During the observation period:

- within 1–4 months, one patient developed recurrent leukopenia, while no disease activity progression was observed in the remaining individuals;
- between 6–10 months, one case of mild to moderate disease flare was reported according to SELENA-SLEDAI criteria, which required only adjustment of mycophenolate mofetil dosage;
- three patients (27%) developed reduced complement levels and/or anti-dsDNA antibodies, and two (18%) experienced a recurrence of alopecia areata; all of these manifestations were relapsing in nature and did not necessitate changes in the therapeutic regimen.

Throughout the observation period, no new SLE classification criteria or organ-related complications were reported. However, a statistically significant reduction in body weight was observed—median BMI decreased by 3% at 1–4 months ($p = 0.002$) and by 13% at 6–10 months ($p = 0.001$) compared to baseline values [45]. To date, there is a lack of systematic studies assessing the impact of GLP-1RA on cardiovascular risk in autoimmune inflammatory diseases. A systematic review conducted by Karacabeyli and Lacaille identified only limited data on the use of these agents in RA, PsA, and gout, with no studies identified in the context of SLE [46]. The absence of safety data regarding GLP-1RA in patients with autoimmune conditions is particularly relevant in light of a reported case of drug-induced lupus triggered by semaglutide, which was associated with the presence of anti-dsDNA, anti-histone, and other autoantibodies [43]. GLP-1RA demonstrates cardioprotective and nephroprotective effects, as well as significant efficacy in promoting weight loss [47]. In SLE, cardiovascular risk is elevated due to chronic systemic inflammation and the use of glucocorticoids [39,41], while obesity has been associated with reduced quality of life and, in some studies, increased disease activity [46]. In the analyzed cohort, a significant reduction in median BMI was observed (3% at 1–4 months and 13% at 6–10 months), suggesting the potential utility of GLP-1RA in modifying cardiovascular risk factors in SLE. Moreover, these agents have been shown to reduce albuminuria in diabetic kidney disease [45], indicating the need for future research into their potential role in lupus nephritis, which affects approximately 60% of patients with SLE and may progress to end-stage renal disease [48]. A limitation of the study was its retrospective design, the small sample size, and the lack of standardized follow-up duration and drug dosing. In summary, despite the study's limitations, GLP-1RA were not found to induce new clinical manifestations of SLE and were associated with a significant reduction in BMI. These findings support the need for prospective studies to evaluate the potential benefits and safety of GLP-1RA in patients with systemic lupus erythematosus [45].

The Therapeutic Potential of GLP-1 Receptor Agonists in Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune disease in which T lymphocytes (mainly Th1 and Th17), B cells, and macrophages induce inflammation of the synovial membrane, leading to synoviocyte proliferation, overproduction of pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) and matrix metalloproteinases (MMP-3, MMP-13), thereby contributing to cartilage and bone destruction. Multiple studies have suggested that GLP-1RA possess immunomodulatory properties—by inhibiting the activation of NF-κB and p38 MAPK, reducing the secretion of pro-inflammatory cytokines and oxidative stress, and promoting macrophage polarization toward the anti-inflammatory M2 phenotype. In addition, GLP-1RA reduces body weight and leptin levels, thereby decreasing systemic inflammation in patients with RA [49].

In Vitro Studies

The effects of GLP-1RA on fibroblast-like synoviocytes derived from patients with rheumatoid arthritis (RA-FLS) have been evaluated in several in vitro studies. Du et al. demonstrated that lixisenatide at a concentration of 20 nM almost completely abolished the induction of pro-inflammatory cytokines TNF-α, IL-6, and IL-8, and significantly inhibited the expression of matrix metalloproteinases MMP-1, MMP-3, and MMP-13, suggesting a protective effect on cartilage. Lixisenatide also reduced oxidative stress, stabilized mitochondrial membrane potential, limited LDH release, and protected cells from apoptosis. Additionally, it inhibited the phosphorylation of JNK and c-Jun, AP-1 activity, and nuclear translocation of the p65 subunit of

NF-κB, effectively suppressing key inflammatory signaling pathways [50]. A study by Zheng et al. (2019) investigated the effects of dulaglutide. It was shown that dulaglutide restored normal mitochondrial function and inhibited the JNK/NF-κB pathway. Moreover, it significantly decreased the levels of IL-1β, IL-6, and MMP-13, indicating that its protective effects include both the regulation of inflammatory cytokines and the inhibition of cartilage degradation [51]. Similar findings were reported by Tao et al., who studied the effects of exenatide. This study also demonstrated reduced cytokine production, inhibition of the p38 MAPK and NF-κB pathways, and decreased LDH release [52]. Collectively, these studies indicate that selected GLP-1RAs can, under in vitro conditions, effectively reverse the pro-inflammatory phenotype of RA-FLS, making them promising candidates for disease-modifying therapy in RA.

Clinical Studies

As early as 2013, C. Sullivan et al. conducted a 24-week observational study involving 11 patients with RA and type 2 diabetes. Administration of liraglutide at a dose of 1.2 mg/day, with concurrent DMARD therapy left unchanged, led to a reduction in mean DAS28 scores from approximately 4.3 to 2.8. According to EULAR criteria, 64% of patients achieved a good or moderate clinical response. Among responders, the number of swollen joints decreased from 3.2 to 1.1, whereas no significant changes were observed in non-responders. A correlation was noted between weight loss and improvement in disease activity ($p < 0.05$), suggesting that the anti-inflammatory effects of liraglutide may be partly mediated through its beneficial metabolic actions [53]. Similarly, in a prospective study by Gavazova et al., involving 30 patients with RA, type 2 diabetes, and obesity, treatment with a GLP-1 receptor agonist—administered without concurrent use of DMARDs, glucocorticoids, or biologic agents—resulted after six months in a mean weight reduction of 10%, shortening of morning stiffness, and a decrease in joint swelling and finger pain. Significant reductions in CRP and ESR levels were also observed [54]. The largest of the studies reviewed—a population-based cohort study—compared RA patients treated with GLP-1 receptor agonists ($n = 1,367$) to those receiving DPP-4 inhibitors ($n = 2,913$). This analysis revealed a 45% reduction in all-cause mortality in the GLP-1RA group, without a significant difference in the incidence of major cardiovascular events [55]. Taken together, these findings suggest that GLP-1RAs may exert therapeutic effects in RA through their immunomodulatory properties. They inhibit the production of pro-inflammatory cytokines, suppress the NF-κB, MAPK, and JNK signaling pathways, reduce oxidative stress, and promote macrophage polarization toward an anti-inflammatory phenotype. Additionally, their favorable metabolic effects—such as weight loss and decreased leptin levels—may further contribute to reductions in systemic inflammation and cardiovascular risk. Preliminary data indicate potential improvements in disease activity, but further clinical trials are needed to confirm these observations.

The Therapeutic Potential of GLP-1 Receptor Agonists in Type 1 Diabetes

Hyperglycemia in type 1 diabetes mellitus (T1DM) results from autoimmune destruction of pancreatic beta cells and dysfunction of alpha cells. At the time of diagnosis, only 10–20% of beta-cell reserve typically remains, while concomitant hyperglucagonemia exacerbates glucose dysregulation by enhancing gluconeogenesis. Current therapy relies almost exclusively on exogenous insulin which, although effective, is associated with several limitations, including the risk of hypoglycemia, weight gain, and a lack of impact on alpha-cell dysfunction. Despite advances in insulin therapy, most patients experience symptomatic hypoglycemia, and nearly half meet criteria for obesity. This highlights the need for novel therapeutic strategies. GLP-1RA, through inhibition of glucagon secretion and an insulinotropic effect (in patients with preserved residual beta-cell function), represent a promising adjunctive treatment option. Additionally, they contribute to weight loss and reduce insulin requirements, improving overall treatment tolerability [56]. The most extensively studied GLP-1RAs in T1DM are exenatide, liraglutide, and semaglutide.

Exenatide

Exenatide is available in two formulations: an immediate-release version (5–10 μg subcutaneously twice daily) and an extended-release formulation (2 mg subcutaneously once weekly). Both forms have demonstrated significant efficacy in lowering HbA1c levels and reducing body weight in patients with type 2 diabetes, with a minimal risk of hypoglycemia. In recent years, efforts have been made to evaluate its efficacy as an adjunctive therapy in T1DM as well [56]. In a study conducted by Raman et al., the effects of immediate-release exenatide on postprandial glycemia were assessed in adolescents with T1DM. Administration of 1.25–2.5 μg of the drug

before meals resulted in a significant reduction in postprandial glucose levels and delayed gastric emptying. No significant changes were observed in glucagon or C-peptide concentrations. Adverse events were mild and included isolated cases of nausea and hypoglycemia [57]. In contrast, Rother and colleagues conducted a study involving adult patients with long-standing T1DM, most of whom still had detectable C-peptide levels. Administration of exenatide over a 6-month period resulted in a significant reduction in body weight (mean decrease of 4.1 kg) and daily insulin requirements. However, no improvement in glycemic control or endogenous insulin production was observed. The authors suggested that the absence of an insulinotropic effect may be attributed to the complete destruction of β-cells in these patients [58]. In a study involving adult patients with newly diagnosed T1DM and preserved β-cell function, the use of exenatide in combination with insulin led to a significant reduction in insulin requirements (by an average of 39 units), weight loss, and decreased HbA1c levels. In two participants, temporary discontinuation of insulin therapy was possible. These results suggest that exenatide may have therapeutic potential during the early phase of the disease (the so-called "honeymoon period") when residual β-cell function is still present [59]. Furthermore, in an observational study involving adults with T1DM treated with weekly exenatide for at least 3 months, improvements in HbA1c (mean reduction of 0.6%), BMI, and daily insulin dose (13% reduction) were reported. However, half of the patients discontinued therapy due to adverse events [60]. In a randomized trial published in 2020, extended-release exenatide (2 µg/week) improved glycemic control after 12 weeks, particularly in patients with preserved β-cell function, although this effect was not sustained at 24 weeks. Reductions in body weight and insulin requirements were also observed, without an increased risk of hypoglycemia. These findings suggest a short-term therapeutic benefit of exenatide in selected patients with T1DM [61].

Liraglutide

Liraglutide has been extensively investigated as an adjunctive therapy in T1DM, including in large-scale, 52-week clinical trials—ADJUNCT ONE and ADJUNCT TWO—which enrolled approximately 1,400 and 835 participants, respectively. The results consistently demonstrated reductions in body weight, daily insulin requirements, and, in many cases, improvements in glycemic control (HbA1c reduction of 0.23–0.8%), particularly in individuals with preserved β-cell function. However, increased rates of symptomatic hypoglycemia and, at the highest dose, a risk of hyperglycemia with ketosis were also reported [62,63]. Another important study was a randomized trial by Kuhadiya et al., in which 72 patients with T1DM were randomly assigned to receive either insulin alone or insulin combined with liraglutide at daily doses of 0.6 mg, 1.2 mg, or 1.8 mg over 12 weeks. Significant reductions in body weight and insulin requirements were observed at doses ≥1.2 mg, although the effect on HbA1c was inconsistent, and adverse effects such as nausea were more frequent [64]. In a study by Dejgaard et al., which included 100 overweight patients (approximately 20% with detectable C-peptide), liraglutide (0.6–1.8 mg/day) significantly reduced body weight, insulin dose, and hypoglycemia frequency, but did not significantly improve HbA1c compared to insulin monotherapy [65]. Similar outcomes were reported in other studies as well [66,67]. In a shorter, 4-week trial involving both C-peptide–positive and C-peptide–negative patients, liraglutide produced comparable effects; notably, two participants in this group were able to discontinue insulin entirely during the study period [68]. In the most recent trial published in 2024 (52-week duration, 68 patients with newly diagnosed T1DM and baseline C-peptide >0.2 nmol/L), liraglutide at 1.8 mg/day significantly slowed the decline in β-cell function and reduced insulin requirements (from 0.30 to 0.23 U/kg/day, compared to an increase in the placebo group; $p < 0.001$). Temporary discontinuation of insulin therapy was possible in 13 patients in the liraglutide group (average duration: 22 weeks), compared to only 2 in the placebo group [69].

Semaglutide

Semaglutide is another GLP-1 receptor agonist that has been investigated as an adjunctive therapy in T1DM. It was evaluated, among others, in a randomized crossover study as an add-on to automated insulin delivery (AID) therapy. In 24 patients, semaglutide significantly increased the time in target glucose range (3.9–10.0 mmol/L) by an average of 4.8 percentage points compared to placebo ($p = 0.006$), without increasing the time spent in hypoglycemia. No cases of severe hypoglycemia or diabetic ketoacidosis were reported, although two instances of euglycemic ketosis occurred [70]. In another 26-week study involving 72 adult patients with T1DM, once-weekly semaglutide added to an AID system significantly improved the likelihood of achieving a composite therapeutic target (36% vs. 0%; $p < 0.001$). Compared to placebo, semaglutide reduced HbA1c by 0.3 percentage points, increased time in target glucose range by 8.8 percentage points, and

led to an average weight loss of 8.8 kg. No cases of diabetic ketoacidosis were observed, and the frequency of severe hypoglycemia was comparable between the groups [71]. In summary, available data suggest that selected GLP-1 receptor agonists may serve as useful adjunctive agents in a subset of patients with T1DM—particularly those with residual β-cell function. While results indicate improvements in certain metabolic parameters and, in some cases, temporary discontinuation of insulin, data on long-term efficacy and safety remain limited. Further large-scale studies involving broader patient populations are needed to clearly define the role of GLP-1RA in the management of type 1 diabetes.

Conclusions

Available preclinical and clinical data suggest that glucagon-like peptide-1 receptor agonists represent a promising class of compounds with potential adjunctive applications in the treatment of selected autoimmune diseases, particularly in patients with coexisting metabolic disturbances. Autoimmune diseases represent a diverse group of chronic inflammatory disorders driven by dysregulated immune responses targeting self-antigens. Despite advancements in immunosuppressive and biologic therapies, treatment efficacy remains suboptimal in a substantial proportion of patients, often complicated by adverse effects or limited access. Moreover, metabolic comorbidities such as obesity, insulin resistance, and type 2 diabetes are prevalent in this population, exacerbating disease activity and negatively impacting therapeutic outcomes. Glucagon-like peptide-1 receptor agonists, initially developed for the treatment of metabolic disorders, have demonstrated notable immunomodulatory and anti-inflammatory effects. These include regulation of T cell activity, suppression of pro-inflammatory cytokines, promotion of anti-inflammatory macrophage polarization, inhibition of NF-κB/MAPK signaling pathways, and improvement of endothelial and metabolic function. Such pleiotropic actions support the hypothesis that GLP-1RA may serve as valuable adjunctive agents in selected autoimmune conditions, especially in patients exhibiting a metabolic-inflammatory phenotype. In psoriasis and psoriatic arthritis, diseases often coexisting with obesity and insulin resistance, GLP-1RA may contribute to symptom improvement by modulating Th1/Th17 pathways and reducing systemic inflammation. Preliminary clinical observations indicate potential benefits in skin and joint manifestations, although robust randomized trials are still lacking. In multiple sclerosis, GLP-1RA have shown promise in preclinical studies, exerting anti-inflammatory and neuroprotective effects, including the promotion of remyelination and modulation of T-cell responses. However, clinical data remain scarce, highlighting the need for further investigation to determine their role in MS management. In systemic lupus erythematosus, GLP-1RA use has been associated primarily with weight loss and metabolic improvements rather than direct immunologic modulation. Still, preliminary findings suggest stable disease activity with few and mild flares, and the associated weight reduction may be relevant in mitigating cardiovascular risk—a major concern in this population. In rheumatoid arthritis, GLP-1RA exerts direct anti-inflammatory effects by inhibiting cytokine production, oxidative stress, and inflammatory signaling cascades. These mechanisms help limit cartilage and bone destruction and restore synovial fibroblast homeostasis. Additionally, metabolic improvements may further aid in the control of systemic inflammation. In type 1 diabetes mellitus, selected GLP-1RA may be beneficial as adjunctive therapy, particularly in early-stage disease when residual β-cell function is preserved. Observed benefits include weight loss, reduced insulin requirements, and in some cases, temporary insulin independence. Nevertheless, current evidence is limited, and long-term safety and efficacy remain to be established. GLP-1 receptor agonists exhibit a range of anti-inflammatory and metabolic effects that support their potential as adjunctive therapies in autoimmune diseases. While preliminary findings are promising, especially in patients with overlapping metabolic disturbances, further high-quality clinical studies are essential to validate their therapeutic utility and define their place in the management of autoimmune disorders. GLP-1 receptor agonists exhibit a range of anti-inflammatory and metabolic effects that support their potential as adjunctive therapies in autoimmune diseases. While preliminary findings are promising, especially in patients with overlapping metabolic disturbances, further high-quality clinical studies are essential to validate their therapeutic utility and define their place in the management of autoimmune disorders. The authors believe that further well-designed studies are necessary to investigate the properties of GLP-1 receptor agonists in the context of autoimmune disease treatment, as current observations indicate their promising therapeutic potential.

Disclosure

Author's contribution: Małgorzata Stopyra; Conceptualisation: Małgorzata Stopyra, Krzysztof Feret; Methodology: Agata Andrzejczyk, Natalia Nafalska; Software: Aleksandra Tomaszewska, Joanna Gadzinowska; Check: Maciej Kokoszka, Michalina Chodór;

Formal: Gabriela Szpila, Angelika Lewandowska; Investigation: Krzysztof Feret, Agata Andrzejczyk, Michalina Chodór; Resources: Małgorzata Stopyra, Aleksandra Tomaszewska; Data curation: Joanna Gadzinowska, Gabriela Szpila; Writing – Rough Preparation: Natalia Nafalska, Angelika Lewandowska; Writing – Review and Editing: Małgorzata Stopyra, Krzysztof Feret, Agata Andrzejczyk; Visualisation: Michalina Chodór, Gabriela Szpila; Supervision: Aleksandra Tomaszewska, Krzysztof Feret; Project Administration: Joanna Gadzinowska, Angelika Lewandowska.

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