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Glucagon-like-peptide 1 (GLP-1) Receptor Agonists in Rheumatologic Disease

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Obesity

Obesity is a complex chronic disease that increases the risk of long-term medical complications and reduces lifespan due to excess body fat or adiposopathy. As of 2016, obesity affects 8.3 million (26.4%) of the Canadian population. Severe obesity, defined as a body mass index (BMI) >35 kg/m^2, affects an estimated 1.9 million Canadians. The financial burden of obesity, including both direct and indirect costs, was estimated to be $7.1 billion in 2010.[1] The pathophysiology of obesity is complex and involves a combination of genetic, metabolic, behavioural, and environmental factors. The hypothalamus regulates appetite and energy expenditure, while the mesolimbic area controls the emotional, pleasurable, and rewarding aspects of eating. The frontal lobe is responsible for overriding the hedonic drive of the mesolimbic system. Adipose tissue itself contributes to its regulation through the release of leptin in proportion to fat mass. Leptin binds to receptors in the hypothalamus to reduce appetite and increase energy expenditure. Similarly, insulin binds to receptors in the arcuate nucleus of the hypothalamus also reducing appetite and increasing energy expenditure.[1]

Prevalence of Obesity in Rheumatologic Disease

The prevalence of obesity in rheumatoid arthritis (RA) has been examined in multiple studies. One cross-sectional cohort study of patients conducted at three Brazilian teaching hospitals has shown that 26.9% of patients had BMI-defined obesity, which was associated with age, hypertension, and dyslipidemia.[2] Another cross-sectional analysis found that obesity was prevalent in 33.4% of patients with RA compared to 31.6% of control patients.[3] This suggests that obesity seems to be as prevalent in patients with RA, if not more so. Several studies have shown higher rates of obesity in psoriatic arthritis,[4] with obesity being more prevalent in those with psoriatic arthritis than in patients with RA or psoriasis.

Treatment of Obesity

Glucagon-like-peptide 1 (GLP-1) is an endogenous incretin hormone secreted by intestinal L-cells in response to food intake. Glucagon-like peptide receptor agonists (GLP-1RAs) are a class of medications which historically have been used for diabetes and weight management, given their ability to modulate glucose levels, insulin secretion, and appetite control.[5] Currently, GLP-1RAs are indicated for treating both type 2 diabetes and obesity. This pharmacologic category of medications continues to evolve, with the recent addition of tirzepatide to the market. Tirzepatide is a single molecule that acts as an antagonist to both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), an incretin synthesized in the K-cells of the duodenum and jejunum. GIP has also been shown to impact both insulin secretion and appetite, and dual agonism with GLP-1 results in greater impacts on glucose control and weight management. Currently, tirzepatide is indicated for treating type 2 diabetes. The future of this therapy continues to evolve, with multiple studies looking at co-agonism with amylin analogues and glucagon analogues.[5] The currently available incretin-based therapies are listed in **Table 1**.

However, the mechanisms of GLP-1RAs are complex, and thus their future therapeutic potential goes beyond their historical indications. Recent studies have been looking at a broad range of diseases which could be impacted by

Drug	Administration		Dose (*mg*)	Effect on A1c	Effect on Weight	Weight Loss Indication	CV Benefit
	Route	Frequency					
Exendin-based GLP-1 Receptor Agonists							
Exenatide	SC	BID	5–10	↓↓	↓↓	No	No
Lixisenatide	SC	Daily	10–20	↓↓	↓	No	No
Human GLP-1-based GLP-1 Receptor Agonists							
Liraglutide	SC	Daily	0.6–1.8*	↓↓	↓↓↓	Yes	Yes
Dulaglutide	SC	Weekly	0.75–1.5	↓↓	↓↓	No	Yes
Semaglutide	SC	Weekly	0.25–2*	↓↓↓	↓↓↓	Yes	Yes
	Oral	Daily	3–14	↓↓↓	↓↓↓	No	Yes
Dual GLP-1/G1P Receptor Agonists							
Tirzepatide	SC	Weekly	2.5–15	↓↓↓↓	↓↓↓↓	No	Pending

Table 1. Comparison among incretin-based therapies; *used with permission from Druce, I. (2025). GLP-1 Receptor Agonist Use in Pregnancy. Canadian Diabetes & Endocrinology Today, 3(1), 31–37. https://doi.org/10.58931/cdet.2025.3139.*

*Doses indicated for weight loss are higher than those listed, all listed dosages are for the indication of glycemic management.

Abbreviations: BID: twice daily, **CV:** cardiovascular, **GIP:** glucose-dependent insulinotropic polypeptide, **GLP-1:** glucagon-like peptide 1, **SC:** subcutaneous

GLP-1 therapy including cardiovascular disease, non-alcoholic fatty liver disease, chronic kidney disease, degenerative neurologic diseases, as well as musculoskeletal and inflammatory diseases.[6]

Possible Mechanisms of GLP-1RA in Arthritis

There are multiple potential mechanisms through which GLP-1RAs could affect rheumatologic diseases. First, visceral adipose tissue releases inflammatory mediators such as tumour necrosis factor (TNF)-α, interleukin (IL)-6, and leptin, which can drive multiple inflammatory pathways.[7] Therefore, it is unsurprising that obesity can affect clinical outcomes in various subtypes of inflammatory arthritis. In the context of RA, obesity is a risk factor for poor response to treatment in early RA and reduces the odds of achieving remission in established RA.[8-11] Similarly, in psoriatic arthritis, obese patients experience worse outcomes in terms of remission, and an elevated BMI is a risk factor for developing the condition.[12,13] In ankylosing spondylitis, obesity is associated with worse clinical outcome measures including the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Axial Spondyloarthritis Disease Activity Score (ASDAS).[14] Conversely, studies in both RA and psoriatic arthritis that looked at the effect of weight loss on clinical outcomes have shown positive effects.[15-17] However, similar data supporting weight loss to improve outcomes in ankylosing spondylitis is currently lacking.

While GLP-1RAs can produce significant weight loss, which in turn may affect outcomes in inflammatory arthritis patients, this is not the only mechanism by which these medications are postulated to exert their effects. GLP-1R expression is present in chondrocytes in osteoarthritis (OA), macrophages and fibroblast-like synoviocytes in RA, as well as in osteoblasts, osteocytes, and osteoclasts.[6] Therefore, GLP-1RAs potentially operate through various mechanisms to affect inflammation and suppress cytokine release, including inhibiting the

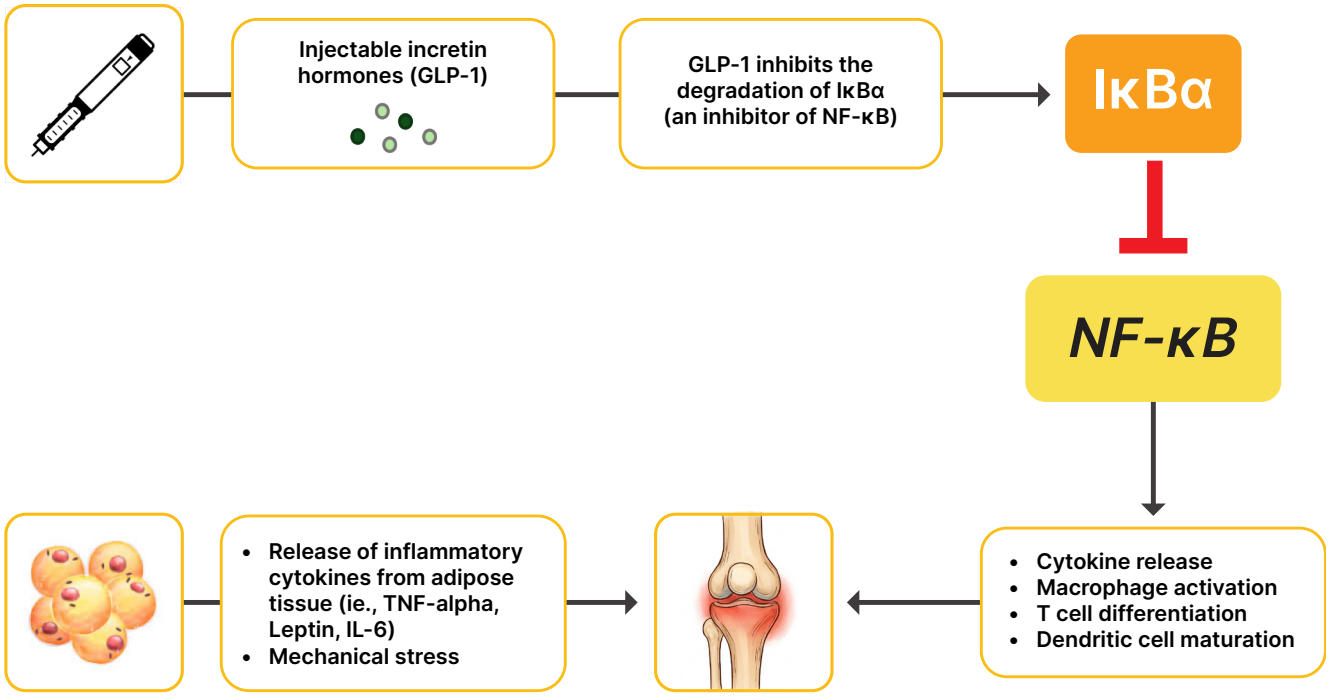

Figure 1. A proposed mechanism of GLP1 mechanisms in rheumatoid arthritis: **1)** Immune: IκBα inhibits nuclear translocation of NF-κB, and thus the downstream inflammatory effects of the NF-κB pathways. GLP1 receptor agonists inhibit phosphorylation and degradation of IκBα, therefore, allowing IκBα to maintain its inhibition on NF-κB pathway and decreasing its downstream inflammatory effects. **2)** Adipose tissue releases inflammatory adipokines which can also contribute to inflammation. **3)** Mechanical stress from adipose tissue; *adpated from Karacabeyli D, Lacaille D. Glucagon-like peptide 1 receptor agonists in patients with inflammatory arthritis or psoriasis: a scoping review J Clin Rheumatol. 2024;30(1):26-31. doi:10.1097/RHU.0000000000001949.*

nuclear factor-kappa B (NF-kB) pathway.[6] In RA, one mechanism is via IκBα, an inhibitor protein that keeps NF-kB transcription factors inactive in the cytoplasm.[18] GLP-1RAs inhibit phosphorylation and degradation of IκBα, which in turn inhibits nuclear activation of the NF-kB pathway, thus blocking its downstream inflammatory effects.[18]

Current Evidence for GLP-1RAs in OA

Currently, the strongest evidence supporting the use of GLP-1RAs is found in OA. OA is the most common degenerative joint disease, and its incidence is higher in obese patients. Studies have shown that weight loss in these patients can both improve symptoms and reduce the risk of developing knee OA.[19] In a recent large randomized controlled trial comparing once weekly semaglutide to a placebo in obese patients with knee OA, those taking semaglutide experienced a significant reduction in pain scores and improved function compared to those taking a placebo.[20] Additionally, the semaglutide group showed a greater reduction in the use of non-steroidal anti-inflammatory drugs compared to the placebo group. Given that the patients in the treatment arm achieved significant weight loss during the trial, it is unclear whether the improved outcomes were soley due to the metabolic effect of GLP-1RAs, or if cellular level effects also played a role.

Current Evidence for GLP-1RAs in Inflammatory Arthritis

The current evidence supporting the use of GLP-1RAs in inflammatory arthritis is less robust compared to OA. There are no published randomized controlled trials for GLP-1RAs in RA, psoriatic arthritis, or ankylosing spondylitis. However, a retrospective cohort study of RA patients on GLP-1RAs reported improvements in the erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), and pain scores.[21] Additionally, in a study of 15 patients with

type 2 diabetes and active rheumatoid or psoriatic arthritis, nine patients treated with liraglutide achieved improvement in Disease Activity Score-28 (DAS-28) scores.[18] These patients also showed superior A1c and weight reduction.[22] Currently, there is no evidence for the use of GLP-1RAs in ankylosing spondylitis.

Cardiovascular Risk Reduction

Cardiovascular disease (CVD) is prominent in RA. One study showed that 39.6% of deaths among patients with RA were attributable to CVD.[23] In addition, RA has been associated with a 48% increased risk of cardiovascular events. Patients with RA also face a 50% higher risk of cardiovascular-related mortality compared to the general population.[24,25] The mechanism of increased risk of CVD in patients with RA appears to be related to risk factors including obesity, diabetes, smoking, and hypertension, as well as inflammatory mechanisms. It is suggested that pro-inflammatory cytokines, which contribute to the disease course of RA, may also contribute to the development of atherogenesis.[26] GLP-1RAs have shown a reduction in cardiovascular events in patients with diabetes and in those with obesity. For patients with type 2 diabetes, risk reduction was observed both in those with known cardiovascular disease and those at high risk.[27,28] For patients with obesity, semaglutide has been shown to reduce the risk of major adverse cardiovascular events in those with pre-existing cardiovascular disease.[29] Notably, this cardiovascular benefit was independent of weight loss.

While GLP-1RAs have not been directly studied in patients with RA and CVD, a population-based cohort study of patients in British Columbia assessed the risk of all-cause mortality and major adverse cardiovascular events (MACE) in patients with immune-mediated inflammatory diseases and type 2 diabetes newly initiating GLP-1RAs versus dipeptidyl peptidase-4 inhibitors (DPP-4is).[30] Rates of both mortality and MACE were lower in patients who initiated GLP1-RA therapy compared to those who initiated DPP-4i therapy. This study included patients with comorbid diabetes and therefore the effect in patients with immune-mediated inflammatory disease without diabetes is not yet known.

Conclusion/Future Directions

The potential benefits of GLP-1RAs in rheumatology extend beyond their historical use as weight loss medications, showing promising effects seen on inflammation, immune responses, and direct effects on tissue. While obesity has been shown to be a risk factor for worse outcomes, such as remission in inflammatory arthritis, the link between GLP-1RA medications and better outcomes has yet to be established. Further clinical research is required to demonstrate both the clinical efficacy and safety of GLP-1RAs in inflammatory arthritis patients. As the landscape of GLP-1RAs continues to evolve, more robust evidence is needed before they can be considered a viable treatment strategy for managing chronic inflammatory arthritis.

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