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Review article

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Glucagon-like peptide-1 receptor agonists in arthritis: current insights and future directions

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Abstract

Obesity affects nearly one in six adults worldwide. Excess adiposity is a pro-inflammatory state associated with increased risk of several types of arthritis, increased arthritis disease activity and/or severity, and poorer response to certain treatments. Obesity is a major risk factor for cardiovascular disease, the leading cause of death in people with common arthritides such as osteoarthritis (OA), gout, rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are a promising therapeutic option for people with arthritis and obesity or type 2 diabetes mellitus owing to their pleiotropic effects, including weight loss, improved survival and reduced risk of major cardiovascular and renal events. In vitro and preclinical in vivo experiments in arthritis have uncovered weight-loss-independent anti-inflammatory and chondroprotective properties of GLP-1RAs. In knee OA, clinical data suggest that GLP-1RAs improve pain and function and reduce the risk of surgical intervention; however, their effects on OA incidence remain incompletely understood. Evidence suggests that GLP-1RAs do not directly prevent gout attacks, but are effective in managing cardiometabolic conditions commonly associated with gout and other arthritides. More research is needed to clarify the effects of GLP-1RAs on incidence, disease activity, and progression of rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis.

Sections

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Key points

- Obesity is a risk factor for developing osteoarthritis (OA), gout, rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA), and is associated with higher disease activity and/or severity, and worse response to common treatments.
- Glucagon-like peptide-1 receptor agonists (GLP-1RAs) improve glycaemic control, facilitate clinically meaningful weight loss, improve survival, and reduce the risk of renal failure and major adverse cardiovascular events.
- In vitro and in vivo experiments in OA, RA and psoriasis models have demonstrated weight-loss-independent anti-inflammatory and chondroprotective effects of GLP-1RAs, commonly through inhibition of the NF-κB pathway.
- Evidence from randomized controlled trials suggests that OA-related knee pain and function improve with semaglutide but not with liraglutide treatment, and observational studies suggest that GLP-1RA use reduces the risk of surgery for knee OA.
- More data are needed to clarify the effects of GLP-1RAs on the incidence of OA, RA, PsA and axSpA, as well as on disease activity and progression in these conditions.
- Muscle loss with GLP-1RAs is probably proportional to the extent of weight loss, and resistance exercise with adequate protein intake is recommended to preserve muscle mass and function.

Introduction

Globally, nearly one in six adults lives with obesity, a state of excess adiposity commonly defined as BMI ≥30 kg/m^2 (ref. 1). Excess adipose tissue is pro-inflammatory and relevant across common arthritides[2] (Table 1). In rheumatoid arthritis (RA) and psoriatic arthritis (PsA), for example, systematic reviews have shown that obesity is associated with increased disease activity[3] as well as poorer response to biologic DMARDs, particularly TNF inhibitors[4]. Among people with RA or PsA, the odds of achieving remission or minimal disease activity are ~40–50% lower for those with obesity[5–7]. Moreover, excess body weight can cause biomechanical stress, entheseal microtrauma and deep koebnerization at weight-bearing sites, provoking local inflammation in PsA[8]. In axial spondyloarthritis (axSpA), systematic reviews have revealed that higher weight is associated with both higher disease activity and radiographic progression[3,9]. Persistent pain and functional impairments are probably major reasons why people with obesity and RA, PsA or axSpA experience more difficult-to-manage disease[3,5–7,10].

People with osteoarthritis (OA) and obesity also experience higher levels of pain than those without obesity[3]. Excess and dysfunctional adipose tissue amplifies OA-related pain through various mechanisms that extend beyond increased mechanical loading (for example, increased production of adipokines and/or pro-inflammatory cytokines leading to enhanced nociceptive pain and peripheral and central sensitization)[11]. Furthermore, Mendelian randomization studies have shown causal relationships between elevated BMI and the development of OA[12,13] and gout[13,14], the two most common forms of arthritis worldwide[15,16]. A rise in BMI by one standard deviation leads to 1.5-fold and 1.7-fold increases in the incidence of OA and gout, respectively[13], and it has been estimated that nearly one-third of incident gout cases among American men could be prevented if none was overweight (that is, had a BMI of <25 kg/m^2)[17].

Additionally, excess adiposity significantly increases cardiometabolic risk[18]. Every five-unit increase in BMI above 25 kg/m^2 is associated with a 40% increase in cardiovascular mortality in the general population[19], and cardiovascular disease (CVD) is the leading cause of death for people with OA, gout, RA, PsA and axSpA[20–22]. The greater burden of CVD in people with arthritis is attributable, in part, to inflammation from arthritis accelerating atherogenesis, to the use of medications (such as glucocorticoids and NSAIDs) that can increase cardiovascular risk, and to the increased prevalence of cardiometabolic conditions[23]. Across common arthritides, reducing cardiovascular risk through the management of cardiometabolic conditions such as obesity is therefore a priority for care providers[24–27]. In this regard, glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs), which have weight loss, antidiabetic, and cardioprotective and nephroprotective properties, have emerged as promising therapeutic drugs.

In this Review, we summarize the physiology of GLP-1 and the multisystem effects of activating the GLP-1 receptor, discuss the established pleiotropic benefits of this increasingly popular drug class, and appraise the data on GLP-1RAs in OA, gout, RA, PsA and axSpA (rheumatic diseases for which the influences of excess adiposity are best studied). We conclude with a discussion of practical points clinicians should consider when prescribing a GLP-1RA to a patient with arthritis. In this Review, we include tirzepatide (a glucose-dependent insulinotropic polypeptide (GIP)–GLP-1 receptor co-agonist) when referring to GLP-1RAs.

The GLP-1 pathway and its activation

GLP-1 is produced by L cells (enteroendocrine cells predominantly located in the ileum and colon) and secreted at low levels in the fasted state[28]. Following a meal, secretion of GLP-1 and GIP rise, facilitating glucose-dependent insulin secretion by the pancreas, which lowers blood sugar levels. Interestingly, the GLP-1 response following a glucose load is reduced in individuals with obesity[29]. Activation of GLP-1 receptors in the gut, brain, kidney and cardiovascular and immune systems by native GLP-1 or GLP-1RAs leads to various extrapancreatic effects, as discussed below[28].

The evolving landscape of GLP-1RAs

Since 2005, when the first GLP-1RA (twice-daily subcutaneous exenatide) was approved for use in type 2 diabetes mellitus (T2DM), advances have led to the development of daily GLP-1RAs (for example, liraglutide and lixisenatide) and then weekly subcutaneous GLP-1RAs (dulaglutide, semaglutide), followed by daily oral GLP-1RAs (semaglutide) and weekly GIP–GLP-1 receptor co-agonists (tirzepatide)[30]. Promising results of phase II trials of novel agents including orforglipron (small-molecule oral GLP-1RA)[31], retatrutide (GIP–glucagon–GLP-1 receptor triple agonist)[32], and combination amylin analogue–GLP-1RA therapy with cagrilintide and semaglutide[33] illustrate the ongoing progress in expanding the drug class.

Cardiometabolic and renal effects of GLP-1 receptor agonism

Although initially a drug class for the treatment of T2DM, the pleiotropic effects of GLP-1RAs have been translated into meaningful clinical benefits in large-scale randomized controlled trials (RCTs)[34–46] (Table 2). Placebo-subtracted weight loss, for example, ranged from

approximately 3% with liraglutide administered at the standard dose for diabetes in people with T2DM[34] to 18% with tirzepatide administered at the (higher) dose for obesity in people with obesity without T2DM[40]. GLP-1RAs facilitate weight loss by increasing satiety and reducing appetite through the stimulation of the anorexigenic POMC–CART pathway, inhibition of the orexigenic NPY–AgRP pathway[47] and slowing of gastric emptying and small-bowel motility[28]. Of note, among people with obesity, those with T2DM experience less weight loss than those without T2DM, even with equivalent GLP-1RA dosing (Table 2).

From a cardiorenal perspective, a 2025 meta-analysis of 11 RCTs involving 85,373 participants showed 16% reduction in risk of renal failure, 14% reduction in risk of major adverse cardiovascular events (MACE), and 13% reduction in risk of all-cause mortality with the use of GLP-1RAs compared with placebo[41]. Pharmacologically activating GLP-1 receptors throughout the cardiovascular system reduces blood pressure (if hypertensive) and cardiac ischaemic injury, possibly decreases vascular inflammation and atherosclerosis (currently being investigated), and increases heart rate[28]. The mechanisms through which GLP-1RAs affect kidney health remain uncertain. Beneficial effects of GLP-1RAs on metabolic dysfunction-associated steatohepatitis have also been observed in phase II trials[48–50]. Because hepatocytes do not express GLP-1 receptors, these benefits might relate to anti-inflammatory mechanisms that are both dependent on and independent of weight loss[51].

Immunomodulatory effects of GLP-1 receptor agonism

Independent of their effect on adiposity, synthetic human GLP-1 and GLP-1RAs have anti-inflammatory effects in humans, suppressing key pro-inflammatory cytokines such as IL-6, TNF and IL-1β[52,53]. Such findings have ignited interest in exploring the effects of GLP-1 receptor agonism in arthritis. In vitro and preclinical in vivo experiments in OA, RA and psoriasis models have consistently demonstrated beneficial immunomodulatory effects of GLP-1RAs[54,55]. Across studies, significant, often dose-dependent, reductions in pro-inflammatory cytokines (TNF, IL-6, IL-1β) and cartilage-degradative enzyme expression and/or activity have been observed[55–62]. Human chondrocytes express the GLP-1 receptor[55]. Activating this receptor has been shown to be chondroprotective in OA. People with OA have lower serum GLP-1 levels[63], and intra-articular liraglutide injection alleviates pain[55] and attenuates cartilage degradation in OA mouse models[63]. GLP-1RAs reduce MMP3-related and MMP13-related degradation of type II collagen and ADAMTS4-related and ADAMTS5-related degradation of aggrecan[56–58,61,62], two fundamental components of articular cartilage. Novel discoveries related to a gut–joint axis explaining the connection between the gut microbiota, GLP-1 and OA progression illustrate a potential disease-modifying role of native GLP-1 and GLP-1RAs in OA[63] (Fig. 1).

Whereas various mechanisms seem to contribute to the observed immunomodulatory properties of GLP-1RAs, inhibition of a common signalling pathway has been reported across OA, RA, and psoriasis models: the NF-κB pathway[57–59,61,62,64–67] (Fig. 2). In OA and RA, GLP-1RAs have been shown to inhibit this pathway by preventing phosphorylation of IκBα[58,65,66], a key inhibitory protein that, in its unphosphorylated form, prevents nuclear translocation of NF-κB transcription factors[68]. GLP-1RAs also inhibit phosphorylation of p38, thus preventing nuclear translocation of RelA[61,65], and reduce TNF production and thereby TNF-induced activation of NF-κB signalling[62] (Fig. 2). In psoriasis, phosphorylation of AMP-activated protein kinase (AMPK) leads to activation of an enzyme (sirtuin 1 deacetylase) that deacetylates RelA, preventing its entry into the nucleus[69]. The net effect of all these mechanisms is reduced downstream production of pro-inflammatory cytokines. The clinical implications of the weight-loss-independent anti-inflammatory effects of GLP-1RAs in arthritis, which can occur alongside weight-loss-dependent anti-inflammatory effects resulting from the reduction of pro-inflammatory adipose tissue, merit further study.

Table 1 | Associations between excess weight and risk, activity and/or severity, and progression of common arthritides

	Incidence (risk)	Disease activity or severity	Radiographic progression	Response to treatment
OA	Increased[12,13]	Increased[3]	Greater radiographic progression seen with high BMI in 12 of 24 and 4 of 11 studies in systematic reviews[3,162]	Probably no clinically meaningful effect of preoperative weight on persistent post-TKA pain[163,164]
Gout	Increased[13,14]	Increased[a] (refs. 3,165–167)	Not studied	Decreased[b] (refs. 168–171)
RA	Increased[13,111]	Increased[3,5]	Lower radiographic progression with high BMI in 6 of 7 studies[3]	Reduced response to TNF inhibitors[4]
PsA	Increased[13,172]	Increased[3]	Not studied	Reduced response to TNF inhibitors[4]
axSpA	Increased[13]	Increased[3]	Increased[9]	Reduced response to TNF inhibitors[4]

The table is based on systematic reviews, meta-analyses and Mendelian randomization studies, unless otherwise specified. axSpA, axial spondyloarthritis; OA, osteoarthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; TKA, total knee arthroplasty. [a]Based on three large observational studies, two showing increased risk of recurrent gout flares in patients with obesity[166,167] and one showing that weight gain increases the risk of recurrent gout attacks while weight loss decreases the risk (suggesting a dose–response relationship)[165]. [b]Based on one cross-sectional study[171], one prospective cohort[168], pooled data from one observational cohort plus two randomized controlled trials[170], and a post hoc analysis of one randomized controlled trial[169].

Effects of GLP-1RAs in common forms of arthritis

Considering the prevalence and effects of obesity across common forms of arthritis, questions around whether GLP-1RAs can improve arthritis symptoms, protect against adverse cardiovascular events in high-risk patients, or prevent arthritis onset altogether are being actively explored.

Osteoarthritis

Association with disease incidence. Data related to the risk of OA following exposure to GLP-1RAs are emerging, although the relationship remains unclear. Since 2024, four retrospective cohort studies have been performed by two research groups, and conflicting results have been reported[70–73].

In two US studies using Medicare data from a closed claims database, individuals with obesity, without prior OA, prescribed GLP-1RAs were compared with randomly selected individuals with obesity without anti-obesity medication use within 1 to 2 years[70,71]. Both groups were followed for 6 to 24 months for OA incidence. Cox proportional

Table 2 | Multi-system effects of GLP-1RAs based on RCT data

Outcome	Magnitude of effect (compared with placebo)	Refs.
Glycaemic control	1–2% improvement in HbA_{1c}	35,38,39,44,46
Weight loss	T2DM with or without obesity: Liraglutide[a] 3–4% Semaglutide[b] 5–6% Tirzepatide[c] 7–12%	34,35,37–39,44
	Obesity without T2DM: Liraglutide[a] 5% Semaglutide[b] 12% Tirzepatide[c] 18%	36,40,43,45
Mortality	13% reduction in risk	41
MACE	14% reduction in risk	41,42
Hospitalization for heart failure	11% reduction in risk	42
Renal failure	16% reduction in risk	41

GLP-1RA, glucagon-like peptide 1 receptor agonist; HbA_{1c}, serum haemoglobin A_{1c}; MACE, major adverse cardiovascular events; RCT, randomized controlled trial; T2DM, type 2 diabetes mellitus. [a]For T2DM without obesity, 1.8 mg per day (subcutaneous); for obesity with or without T2DM, 3 mg per day. [b]For T2DM without obesity, 1 mg per week (subcutaneous); for obesity with or without T2DM, 2.4 mg per week. [c]For T2DM without obesity, 5 mg per week (subcutaneous); for obesity with or without T2DM, 15 mg per week.

hazards models (with adjustment for age, sex, socioeconomic status and selected comorbidities unbalanced at baseline) revealed a 16% lower risk of incident OA with semaglutide use than without[70], and a 27% lower risk with liraglutide, semaglutide or tirzepatide relative to no anti-obesity medications[71]. However, misclassification was possible as diagnosis was based on a single International Classification of Diseases, Tenth Revision (ICD-10) code for OA, and a 1-year look-back might have been too short to confidently exclude prevalent cases. The 21% incidence of OA after 1 year of follow-up in one of the studies could reflect these issues[70]. Furthermore, in one of two studies, the methods specify that only formulations of liraglutide, semaglutide and tirzepatide FDA-approved for weight loss were considered, suggesting that off-label use of formulations approved for T2DM were not captured[71].

By contrast, GLP-1RA exposure was associated with an increased risk of OA in two US studies that used data from TriNetX, a global network of electronic health records (EHR) data[72,73]. Individuals with obesity, without prior OA, prescribed GLP-1RAs were compared with propensity score-matched individuals without a GLP-1RA prescription. Propensity scores were calculated using age, sex, race, BMI, T2DM and, in those with T2DM, serum haemoglobin A_{1c} (HbA_{1c}) level. OA incidence, defined as one ICD-10 code for knee or hip OA, was determined using follow-up periods of 1 year[73] or ≥5 years[72]. Both studies found an increased incidence of hip and knee OA in the groups with a GLP-1RA prescription, with the risk being ~30–40% higher after 1 year and ~50–60% higher after 5 years. Baseline BMI after propensity score matching was not balanced between the groups exposed and unexposed to GLP-1RAs. Residual confounding by indication (that is, participants with high BMI being more likely to receive GLP-1RAs and to develop OA) might have remained. The groups might also have differed with respect to other unmeasured characteristics that influence the likelihood of OA diagnosis, such as access to clinical care or frequency of visits, causing ascertainment bias. Contamination (that is, prescription of a GLP-1RA to initially unexposed patients) during the follow-up period and low adherence were also concerns. At 2 years, only 38–62% of those initially prescribed a GLP-1RA were still being prescribed a GLP-1RA, and weight loss and improvements in HbA_{1c} levels were practically identical in all groups. Thus, the study had limited ability to capture true treatment effects.

All four studies acknowledged the limitations of using data from insurance claims and/or EHRs to evaluate the association between GLP-1RAs and OA incidence, including missing data on potential confounders, information on prescription dispensed rather than used, and the uncertainty of OA diagnosis based on ICD codes. Moreover, studies using EHR data from sources such as TriNetX could be limited in their ability to perform on-treatment or per-protocol analyses if the data are analysed within the platform (rather than being downloaded) and therefore treatment duration cannot be determined. As such, estimates of therapeutic effectiveness from analyses emulating an intention-to-treat approach could be clouded by contamination and early discontinuation. Nonetheless, studies to date have laid the foundation for future research. Moving forward, studies investigating the association between GLP-1RA use and OA incidence would benefit from extended look-back periods (to exclude prevalent cases of OA), several-year follow-up periods (given the slow development and progression of OA)[74], validated algorithms for diagnosing OA (to minimize misclassification)[75,76], analyses estimating on-treatment effects, and statistical methods to reduce risk of confounding.

Effect on OA disease outcomes. Excitement around GLP-1RAs as a therapeutic option for people with OA and excess adiposity has grown given the well-recognized benefits of weight loss in this population[77] as well as results from the STEP 9 trial[78]. This multicentre, international, double-blind RCT in 407 adults with obesity, moderate clinical and radiographic knee OA and no diabetes evaluated the effectiveness of semaglutide versus placebo as an adjunct to regular physical activity and dietary counselling over 68 weeks (Table 3).

Study participants who received semaglutide with lifestyle counselling lost 13.7% of their body weight, whereas those who received placebo with counselling lost 3.2% of their body weight, yielding a 10.5% absolute difference in weight reduction. Also, in the semaglutide group, 70% and 87% of people achieved ≥5 and ≥10% weight loss, respectively, a range in which several obesity-related complications improve[79]. Normalized Western Ontario and McMaster Universities OA index (WOMAC) pain score improved from baseline to week 68 by 42 points with semaglutide compared with 28 points with placebo. The 14-point greater improvement with semaglutide exceeds previously described minimal clinically important differences of ~10 points for knee OA interventions[80,81]. Similarly, significantly greater improvements in physical function, measured on WOMAC and SF-36 subscales, were observed with semaglutide relative to placebo. Rates of serious adverse events were similar between the groups and were consistent with the findings in prior trials of semaglutide[36,37,82]. Of the 87% of people who completed the treatment period with semaglutide, 90% were taking the full (2.4 mg) dose at the end, indicating good adherence and tolerance.

Although the generalizability of this trial's results to individuals with milder OA and/or less excess weight can be questioned, it demonstrated significantly greater, and clinically relevant, improvements in weight, pain and function with semaglutide compared with placebo, alongside lifestyle counselling.

Prior to the STEP 9 trial, one trial had evaluated the effects of GLP-1RAs on OA-related outcomes[83] (Table 3). This 52-week investigator-initiated single-centre triple-blind RCT was performed in 156 adults with mild-to-moderate symptomatic knee OA and elevated

BMI (≥27 kg/m^2). No difference in pain was observed with liraglutide relative to placebo[83]. However, prior to randomization, all participants underwent an 8-week diet intervention and only those achieving >5% weight loss (156 of 168) entered the trial and were randomly allocated to liraglutide treatment or placebo. The effects of this pre-randomization intervention were large: participants lost an average of 12.5 kg and pain decreased by 12 points on the Knee Injury and Osteoarthritis Outcome Score (KOOS) pain subscale, both clinically meaningful changes[79,84]. In contrast to the STEP 9 trial, participants had lower mean BMI (32 kg/m^2) and milder OA at baseline. Although changes in weight at 1 year were significantly different between groups (2.8 kg loss with liraglutide versus 1.2 kg gain with placebo), no differences in pain, function or quality of life were observed. The lack of improvement with liraglutide might have been partially attributable to a ceiling effect from the benefit of the pre-randomization intervention. After the initial improvement, mean KOOS pain score (0–100, with 100 representing no pain) at randomization was 78, leaving limited room for further improvement. Furthermore, liraglutide induces less weight loss than newer-generation GLP-1RAs (Table 2), and more weight loss (>7%) might be necessary to improve OA-related symptoms[77].

Observational studies have also provided important evidence highlighting that improvements in OA outcomes can be seen with varying degrees of excess weight and with different GLP-1RAs[73,85,86]. In the Shanghai Osteoarthritis Cohort, for example, the risk of undergoing knee surgery for OA was significantly lower with GLP-1RA exposure than without (1.7% versus 5.9%) after adjustment for age, sex, BMI, OA severity (Kellgren–Lawrence grade) and WOMAC total score[85] (Table 3). Furthermore, 32% of this effect was mediated through weight loss. The cohort comprised adults with specialist-diagnosed OA, T2DM, and ≥5 years of follow-up data, 233 of whom had ≥2 years of GLP-1RA exposure and 1,574 had no GLP-1RA exposure. Mean BMI at baseline (~25 kg/m^2) was lower than in the RCTs by Bliddal et al.[78] (STEP 9) and Gudbergsen et al.[83], and people receiving GLP-1RAs lost 4.6 kg over the follow-up period whereas unexposed people gained 2.7 kg (ref. 85). In the group receiving GLP-1RAs, WOMAC pain score improved by 3.4 more points, the number of intra-articular injections per year was ~0.1 lower, and there was 0.02 mm less cartilage loss per year. However, although statistically significant, these differences probably fall below thresholds for clinical relevance[80,81]. That said, pain at baseline was mild (~18/100 on the normalized WOMAC pain subscale, with 0 representing no pain), limiting room for improvement. Furthermore, significantly more people achieved a minimal clinically important change in pain score of 9 points with GLP-1RAs (35%) than without (28%). Certain potentially confounding factors were not accounted for (for example, socioeconomic status or comorbidities such as CVD that might increase GLP-1RA prescription and decrease the probability of undergoing surgery due to perioperative risk), and excluding those with <2 years of exposure to GLP-1RAs (17 people) could have introduced selection bias. Nonetheless, the results were consistent with those of three subsequently published observational studies[63,73,86] (Table 3).

Appraising experimental and observational evidence to date, GLP-1RAs are a promising therapy for the management of OA in people with excess adiposity. Ongoing trials evaluating retatrutide (NCT05931367) and tirzepatide (NCT06191848) in knee OA are estimated to conclude as early as December 2025 and May 2027, respectively (Supplementary Table 1).

Management of comorbidities. People with OA are at increased risk of various cardiometabolic and renal comorbidities and complications relative to those without OA[87–89], and GLP-1RAs have established

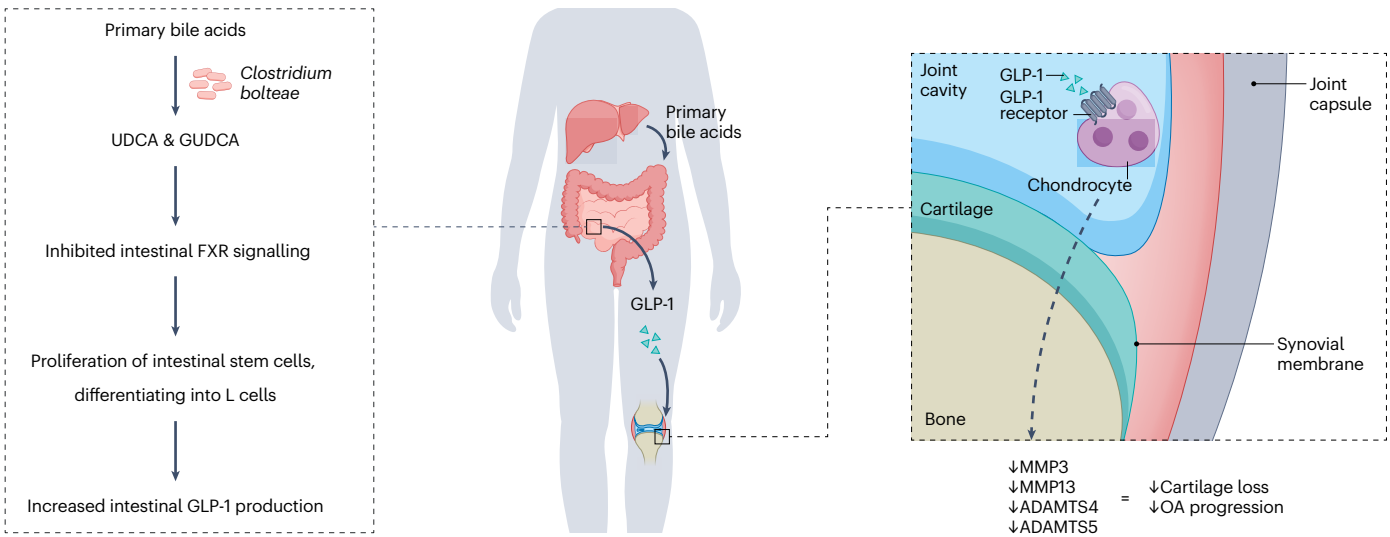

Fig. 1 | The GLP-1-mediated gut–joint axis in osteoarthritis. Evidence demonstrates a pathway linking the gut microbiota, glucagon-like peptide-1 (GLP-1) and joint health[63]. The gut microorganism *Clostridium bolteae* facilitates the conversion of primary bile acids, which are synthesized in the liver, to ursodeoxycholic acid (UDCA). UDCA is a precursor of glycoursodeoxycholic acid (GUDCA), a secondary bile acid that inhibits intestinal farnesoid X receptor (FXR) signalling. Both *C. bolteae* and GUDCA are less abundant in people with osteoarthritis (OA) than in those without OA, resulting in upregulated intestinal FXR signalling (which is pathogenic in OA)[63]. When FXR is inhibited by GUDCA, there is increased proliferation of intestinal stem cells that differentiate into L cells, the cell type responsible for producing GLP-1. Intestinal GLP-1 then travels to joints, where it binds to GLP-1 receptors on chondrocytes. Here, activation of GLP-1 receptors results in reduced expression of key catabolic enzymes including MMP3, MMP13, ADAMTS4 and ADAMTS5 (refs. 56–58,61,62), attenuating cartilage breakdown and OA progression[63]. This gut–joint axis could explain why serum levels of GLP-1 are decreased in people with OA and illustrates the disease-modifying potential of targeting GLP-1 receptors expressed in synovial joints[63].

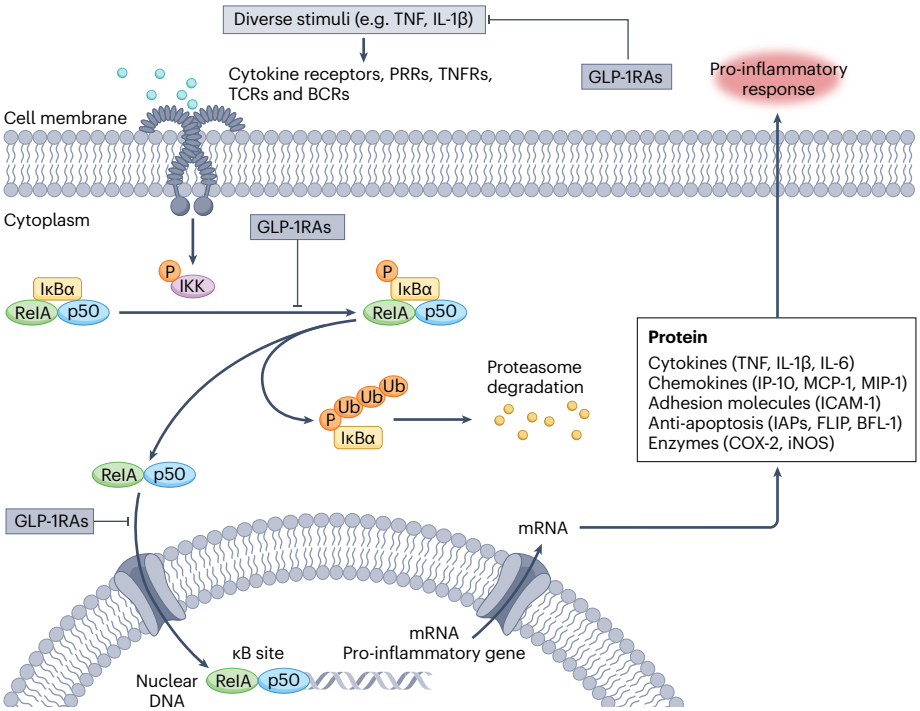

Fig. 2 | Inhibition of the NF-κB pathway through GLP-1 receptor agonists. The NF-κB pathway consists of a group of inducible transcription factors which, when activated, leads to the expression of various genes that encode important pro-inflammatory cytokines and chemokines. These transcription factors are normally sequestered in the cytoplasm by inhibitory proteins, the most important being IκBα. The NF-κB pathway is activated when IκBα is phosphorylated. Phosphorylation of IκBα (via the IKK complex) is normally triggered by stimuli such as cytokines (for example, TNF and IL-1β), growth factors, mitogens, microbial components or stress agents, and leads to degradation of IκBα. Phosphorylation of IκBα enables nuclear translocation of NF-κB transcription factors and subsequent expression of pro-inflammatory genes that encode cytokines (IL-1, IL-6, IL-12, IL-23, TNF) pertinent in osteoarthritis, rheumatoid arthritis and/or psoriatic disease. Glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs) reduce levels of cytokines that activate the NF-κB pathway. GLP-1RAs also preventing phosphorylation of IκBα and nuclear translocation of RelA (one of five NF-κB family members). Through these effects, GLP-1RAs reduce downstream pro-inflammatory cytokine and chemokine production and resultant inflammation. BCR, B cell receptor; PRR, pattern recognition receptor; TCR, T cell receptor; TNFR, TNF receptor. Adapted from ref. 68, Springer Nature.

benefit in preventing or treating these conditions[34–46] (Table 2). Of note, walking difficulty and/or disability is a major driver of the elevated cardiovascular risk observed in people with OA[90,91], and exercise, even just once weekly, might attenuate the excess risk of cardiovascular events in people with knee OA[87]. In the STEP 9 trial, along with improvements in patient-reported physical function, 6-min walk distance improved by 43 m more with semaglutide than with placebo[78]. Hence, for people with OA and excess adiposity, GLP-1RAs might improve cardiometabolic health directly, through cardioprotective class effects, and indirectly, by increasing capacity for physical activity.

Gout

Effects on disease risk. Several studies, including a network meta-analysis of RCTs, have shown that GLP-1RA use is not associated with a decreased incidence of gout[92–94]. GLP-1RAs have also been frequently compared with sodium–glucose cotransporter 2 (SGLT2) inhibitors in observational cohort studies using large datasets to estimate the risk of developing gout[93,95–97]. SGLT2 inhibitors (for example, canagliflozin, empagliflozin and dapagliflozin) are another second-line T2DM drug class with cardioprotective and nephroprotective effects[98]. They too induce weight loss (~1.5–2 kg more than placebo), albeit to a lesser degree than GLP-1RAs[99]. Consistently, the risk of gout has been reported to be ~20–40% lower with SGLT2 inhibitor exposure than with GLP-1RA exposure. Considering all available evidence, SGLT2 inhibitors probably reduce the risk of developing gout when compared with GLP-1RAs, and GLP-1RAs probably do not reduce this risk relative to placebo. Mechanistically, SGLT2 inhibitors directly reduce serum urate concentrations in a clinically meaningful way[100], whereas GLP-1RAs do not[101,102]. Post-hoc analyses of four controlled clinical trials found no clinically relevant changes in serum urate concentrations following GLP-1RA exposure, neither immediately nor after several weeks of therapy[101]. Of note, only exenatide, lixisenatide and liraglutide were assessed, weight loss relative to placebo was only 1.4–1.9 kg after 8–12 weeks, and only 17–22% of participants across the four trials were hyperuricaemic at baseline (median serum urate concentration 321–377 μmol/l). A 2022 meta-analysis also found no significant urate-lowering effects of GLP-1RAs compared with placebo, but semaglutide was used in only one study[102]. Because GLP-1RAs have no direct uricosuric effect, any potential benefit in lowering serum urate levels would probably need to be mediated through weight loss (that is, indirectly)[103]. Since newer-generation GLP-1RAs such as semaglutide and tirzepatide facilitate greater weight loss than older GLP-1RAs, opportunities exist to explore whether these newer agents could indirectly lower serum urate concentrations long-term.

Effects on disease outcomes. GLP-1RAs have been studied as active comparators in two population-based studies evaluating SGLT2 inhibitors in people with pre-existing gout[104,105]. In both studies, the risk of recurrent flares (calculated after applying propensity score-based methods to account for baseline differences between groups) was approximately 30% lower with SGLT2 inhibitors than with GLP-1RAs.

Management of comorbidities. National estimates of comorbidity burden show that Americans with gout have 21% higher prevalence of obesity (53.3% versus 32.8%, adjusted OR 2.4), 18% higher prevalence of T2DM (25.7% versus 7.8%, adjusted OR 2.4), and 12% higher prevalence of myocardial infarction (14.4% versus 2.9%, adjusted OR 2.4) compared with people without gout[106]. Although available evidence does not suggest a role for GLP-1RAs in the primary or secondary prevention of gout flares, they do have a role in managing these cardiometabolic conditions[41,98,107].

Rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis

Effects on disease risk. Our literature review revealed no full-length articles on the risk of PsA or axSpA following GLP-1RA exposure. Data on the association between GLP-1RAs and the development of RA

Table 3 | Studies evaluating effects of GLP-1RAs on disease outcomes in OA

Study (year)	Design	Sample and baseline characteristics	Main results	Ref.
STEP 9 trial (2024)	68-week multicentre international double-blind RCT evaluating effectiveness and safety of semaglutide (up-titrated to 2.4 mg SC weekly) versus placebo, along with lifestyle counselling every 4–8 weeks, for weight loss, pain, and function in knee OA plus obesity	407 adults (mean age 56 years, 82% women, 61% white) with obesity (mean BMI 40 kg/m^2), moderate clinical and radiographic knee OA (mean normalized WOMAC pain 70.9/100; KL grade 2 or 3), and no diabetes[a]	10.5% absolute difference in weight loss with semaglutide compared with placebo (−13.7% versus −3.2%; $P<0.001$) 14.1-point greater improvement in WOMAC pain with semaglutide (−41.7 versus −27.5; $P<0.001$) 14.9-point greater improvement in WOMAC physical function with semaglutide (−41.5 versus 26.7; $P<0.001$) Similar incidence of serious AEs (10% versus 8.1%), but more permanent discontinuations with semaglutide (6.7% versus 3%)	78
Gudbergsen et al. (2021)	52-week investigator-initiated single-centre triple-blind RCT evaluating effectiveness and safety of liraglutide (up-titrated to 3 mg SC daily) versus placebo on weight loss, pain and function in OA plus high BMI; randomization was preceded by an 8-week diet intervention	156 adults (mean age 59 years, 65% female) with BMI ≥27 kg/m^2 (mean BMI 32 kg/m^2), mild-to-moderate knee OA (mean KOOS pain score 77.8/100; KL grade 1–3), and no diabetes[b]	3.9 kg absolute difference in weight loss with liraglutide compared with placebo (−2.8 kg versus +1.2 kg; $P=0.008$) No difference in KOOS pain score, function or serious AEs	83
Shanghai OA Cohort (2023)	Multicentre prospective cohort study assessing associations between GLP-1RA exposure (≥2 years versus none) and incidence of surgery for knee OA[c], use of pain medications and intra-articular injections, as well as changes in WOMAC scores and medial knee cartilage thickness	1,807 adults >45 years old (mean age 61 years; 73% female; mean BMI 25 kg/m^2) with specialist-diagnosed OA (mean WOMAC pain score 17.5) and T2DM who received ($n=233$) or did not receive ($n=1,574$) GLP-1RAs	Mean treatment duration 5 years Significantly lower incidence of knee surgery with ≥2 years of GLP-1RA use versus no use (1.7% versus 5.9%; $P=0.014$)[d], 32% mediated by weight loss −7.3 kg mean difference in weight change (4.6 kg loss with GLP-1RAs versus 2.7 kg gain without; $P<0.001$)[d]	85
Yang et al. (2025)	Retrospective cohort study in adults with diabetes mellitus and knee OA that used IMRD EHR data to assess risk of knee replacement in GLP-1RA new users versus non-users matched for age, sex, BMI and calendar year	3,816 adults with diabetes mellitus and knee OA (mean age 64 years; 58% women; mean BMI 37 km/m^2), including 915 GLP-1RA new users and 2,901 matched individuals	Lower risk of knee replacement with GLP-1RA use over a 4-year mean follow-up (RD −5.4 (95% CI −10.0 to −0.8) per 1,000 person-years; adjusted HR 0.73 (95% CI 0.54–0.99)[e])	63
Porto et al. (2025)	Retrospective cohort study using TriNetX EHR data to assess rates of THA, TKA and major joint injections within 1 year for patients with OA plus obesity prescribed GLP-1RAs versus PS-matched individuals without GLP-1RA prescriptions[f]	45,676 participants total; 22,838 people with obesity and knee or hip OA prescribed GLP-1RAs PS-matched in a 1:1 ratio to individuals without GLP-1RA prescriptions (mean BMI 37 kg/m^2, mean age 63–64 years)	Lower incidence of THA (1.1% versus 2.2%; HR 0.6 (0.45–0.79)) and TKA (1.4% versus 2.1%; HR 0.75 (0.63–0.89)) within 1 year of GLP-1RA prescription, but no difference in weight loss or major joint injections	73
Samajdar et al. (2024)	Uncontrolled retrospective cohort study describing changes in outcomes 6 months after starting dulaglutide for the treatment of T2DM in older adults with OA	98 patients ≥60 years old (mean age 67 years; 59% male; mean BMI 31 kg/m^2) with T2DM and bilateral knee OA (mean VAS pain 6.9/10)	10.2% weight loss plus 3.8-unit improvement in mean VAS pain 6 months after starting treatment with dulaglutide (unadjusted $P<0.001$ for both)	86

AE, adverse event; EHR, electronic health record; GLP-1RA, glucagon-like peptide-1 receptor agonist; IMRD, IQVIA Medical Research Database; KL, Kellgren–Lawrence; KOOS, knee injury and osteoarthritis outcome score; OA, osteoarthritis; PS, propensity score; RCT, randomized controlled trial; RD, rate difference; SC, subcutaneous; T2DM, type 2 diabetes mellitus; THA, total hip arthroplasty; TKA, total knee arthroplasty; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities osteoarthritis index. [a]Other relevant exclusions beyond relative and absolute contraindications to GLP-1RAs included joint replacement or other joint pathology in the target knee, symptomatic hip OA, chronic widespread pain, and history of major depressive disorder within 2 years of screening, severe psychiatric disorder, or prior suicide attempt. [b]Only participants achieving >5% weight loss with the pre-randomization diet intervention underwent randomization (156 of 168), and this intervention led to clinically meaningful weight loss (−12.5 kg) and reduction in pain (−11.1 points). [c]Total knee arthroplasty, unicompartmental knee arthroplasty, arthroscopic procedures and high tibial osteotomy. [d]Adjusted for age, sex, BMI, KL grade and WOMAC total score. [e]Adjusted for BMI, socioeconomic deprivation index, haemoglobin A_{1c}, T2DM and OA duration, smoking and alcohol use, comorbidities, medications and hospital utilization. [f]Study also separately assessed risk of developing knee or hip OA with versus without GLP-1RA exposure in patients without existing OA (described in the text but not in the relevant table).

(or an RA-like syndrome) are limited to two case reports and one large retrospective cohort study[108–110]. In both case reports, patients' arthritis symptoms improved after stopping treatment with GLP-1RAs. In one report in which arthritis developed 3 months after dulaglutide initiation, the patient was found to be dual seropositive for RA and began improving with DMARD therapy before dulaglutide was stopped[108]. Hence, the patient's arthritis might have been independent of dulaglutide exposure. The other report described a 42-year-old man who developed seronegative polyarthritis (resistant to treatment with glucocorticoids and NSAIDs) 6 months after starting liraglutide[109]. The arthritis fully resolved 1 week after stopping liraglutide.

The association between GLP-1RA exposure and risk of RA was further explored in a retrospective cohort study using EHR data from TriNetX[110]. Cohorts of adults with either T2DM (n = 854,197) or obesity (n = 230,782), treated with GLP-1RAs, were propensity score-matched 1:1 to individuals without GLP-1RA treatment. After 5 years of follow-up, a lower risk of incident RA was observed with GLP-1RA exposure in individuals with obesity without T2DM. Four excess cases of RA per 1,000 patients followed over 5 years were identified in the unexposed compared with the exposed cohort (19.5 versus 15.5 cases per 1,000 patients). No difference was observed in the groups with T2DM. The findings should, however, be interpreted with caution. Although propensity score matching was applied to balance baseline covariates, only age, sex and ethnicity were mentioned as being included in the propensity score. Analyses did not account for other potential confounders such as comorbidities or factors influencing access to care that could have created ascertainment bias. Furthermore, the duration of GLP-1RA exposure and the competing risk of death were not considered. Although obesity is a risk factor for developing RA[13,111], the observed incidence rates for RA (19–24 new cases per 1,000 individuals followed for 5 years) were roughly six to eight times higher than reported estimates for American and Northern European populations of similar ages[112,113]. The high incidence rates might have been attributable to the RA definition used, which required only a single ICD-10 code billing. Also, the look-back period to exclude prevalent cases was not specified. Nonetheless, this study provides preliminary evidence of a potential protective effect of GLP-1RAs on RA incidence in individuals with obesity. Further studies are needed to clarify the effect of GLP-1RAs on the risk of autoimmune inflammatory arthritides.

Effects on disease activity. Published data on the effects of GLP-1RAs on disease activity in RA and PsA are sparse, and, to our knowledge, absent in axSpA. Several basic science experiments using models of RA or psoriasis have demonstrated anti-inflammatory properties (for example, significant reductions in TNF, IL-6, IL-17 and IL-23 expression) with GLP-1RA treatment, but the clinical implications of these effects have yet to be fully elucidated[54]. A scoping review that we performed in 2022 (ref. 54) identified two conference abstracts: one case report of a patient with RA treated with liraglutide for T2DM, and one uncontrolled prospective cohort study in 15 patients with T2DM and a concomitant diagnosis of either RA (n = 11) or PsA (n = 4) treated with liraglutide for 24 weeks[114,115]. In the case report, the patient's 28-joint Disease Activity Score (DAS28) improved from 5.5 to 3 with 12 weeks of liraglutide treatment. In the cohort study, 9 of 15 patients were deemed DAS28 responders, with significant reductions in DAS28 (from 4.2 to 2.7) and swollen joint count (from 3 to 1) with liraglutide treatment. Mean weight loss and HbA_{1c} improvement in these nine patients were 3.4 kg and 1.4%, respectively. The other six patients did not experience improvements in DAS28, swollen joint count, weight or HbA_{1c} level despite having comparable baseline characteristics. We did not find reports of any additional studies investigating the effects of GLP-1RAs on RA disease activity but identified one case series of ten patients with PsA (mean disease duration 10 years) and obesity (mean BMI 40 mg/m^2) treated with liraglutide 3 mg daily[116]. At baseline, one patient had minimal disease activity; after 3 months of liraglutide treatment, eight of the ten patients achieved minimal disease activity. Mean scores on Dermatology Life Quality Index (DLQI) and Psoriasis Area and Severity Index (PASI) improved by 54% and 62%, respectively[116].

More data have been published on the effects of GLP-1RAs in people with psoriasis and T2DM and/or elevated BMI, including three small RCTs, but either people with PsA were excluded[117] or articular outcomes were not reported[118,119]. Nonetheless, two of the three RCTs identified significant improvements in PASI and DLQI with GLP-1RA treatment[118,119]. Limitations of these trials, however, included small sample sizes (20–31 participants each), predominantly male populations, lack of blinding or an injected control (in two of three trials), and short durations (8–12 weeks). Furthermore, in one of the trials[119], randomization was mentioned in the title and abstract but not in the methods, the control group was assigned to receive no therapy (as opposed to placebo or an active comparator), and between-group differences in PASI or DLQI at the end of the trial were not formally tested for significance.

Overall, although promising, the paucity of data in RA, PsA and axSpA highlights that more research is required to determine whether GLP-1RAs can improve disease activity. Findings from phase III RCTs, TOGETHER-PsO (NCT06588283) and TOGETHER-PsA (NCT06588296), will shed light on the potential disease-modifying effects of adjunctive tirzepatide in active psoriatic disease (Supplementary Table 1).

Management of comorbidities. Immunocompromised individuals were either not described in or excluded from RCTs demonstrating the effectiveness of GLP-1RAs for reducing risk of MACE and all-cause mortality in adults with T2DM or obesity[107,120–122]. To determine whether people with immune-mediated inflammatory diseases (IMIDs) would derive similar benefits from GLP-1RAs as these broader populations, we conducted a population-based cohort study using administrative health data from a Canadian province[121]. We identified nearly 11,000 adults with T2DM and IMIDs, including RA, psoriatic disease (encompassing both psoriasis and PsA), axSpA, inflammatory bowel disease and systemic autoimmune rheumatic diseases (systemic lupus erythematosus, systemic sclerosis, Sjögren disease, idiopathic inflammatory myopathies and systematic vasculitides), who were incident users of GLP-1RAs or dipeptidyl peptidase-4 (DPP4) inhibitors. Like GLP-1RAs, DPP4 inhibitors (for example, linagliptin, sitagliptin and saxagliptin) are second-line T2DM agents that increase GLP-1 receptor signalling[98,123]. They do so more modestly than GLP-1RAs by preventing breakdown of native GLP-1 rather than by directly stimulating the GLP-1 receptor, and, unlike GLP-1RAs, DPP4 inhibitors are weight-neutral and cardioneutral[98,120]. Propensity score overlap weighting was applied to achieve balance in baseline covariates (including sociodemographic variables, comorbidities, T2DM duration and complications, IMID duration, use of other relevant medications and health-care utilization) and Cox proportional hazards models were used to estimate the risks of all-cause mortality and MACE. Risks of all-cause mortality and MACE were 52% and 34% lower with GLP-1RA than with DPP4 inhibitor exposure, yielding numbers-needed-to-treat of 107 and 96 for preventing one death or one MACE, respectively. Analyses were repeated in age-matched and sex-matched adults with T2DM without

IMIDs to assess whether people with IMIDs derived greater benefit from GLP-1RAs given their higher baseline cardiovascular risk. This was not the case, as a similar reduction in risk was found in people with and without IMIDs. Observed reductions in relative risk were larger than findings from RCTs, potentially because of differences in sample selection and unmeasured confounding. Our population-based sample included individuals who might not have participated in RCTs, such as those with very high cardiovascular and mortality risk.

Practical considerations when prescribing GLP-1RAs

Weighing risks versus benefits is essential when prescribing GLP-1RAs. Contraindications include personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 (ref. 124). These contraindications are based on data from studies in rodents showing that GLP-1RAs act directly on thyroid C cells to cause C cell hyperplasia and tumours in a dose-dependent and duration-dependent manner[125]. The relevance of these findings to humans remains unknown. Clinicians should also review contraception in women of childbearing age. Weight loss can improve fertility, and it is currently recommended that women generally avoid GLP-1RAs during pregnancy owing to limited data and the potential for harm[126]. The most commonly reported adverse effects of GLP-1RAs are gastrointestinal (nausea, vomiting, diarrhoea and constipation), the majority of which are mild to moderate, occur with drug initiation and dose escalation, and improve over weeks[30,36,40]. Agents should be started at low doses and up-titrated slowly (for example, every 4 weeks for semaglutide and tirzepatide). If adverse effects lead to reduced oral intake, patients are at risk of acute kidney injury[127]. Gallbladder-related diseases have also been observed with greater frequency in patients treated with GLP-1RAs than in groups unexposed to these agents, attributable to direct effects (that is, acutely attenuated gallbladder emptying) and potentially indirect effects mediated by rapid weight loss[30,128]. Because of delayed gastric emptying, concerns regarding aspiration of residual gastric contents despite preoperative fasting have been raised; however, existing data do not support the view that increased residual gastric content from GLP-1RA use increases aspiration rates or aspiration-related complications[30,129].

Although findings from some cohort and pharmacovigilance studies have raised concerns related to GLP-1RA use and self-harm and/or suicidality[130–133], most studies have not identified elevated risk of self-harm, suicidal ideation or behaviours, or death from suicide among people using GLP-1RAs[134–139]. The FDA has stated that available data do not suggest a causal link between GLP-1RAs and suicidality[140]. Nevertheless, clinicians should be aware of these reports and patients should be informed of mental health supports as appropriate.

Another key consideration for people with arthritis taking GLP-1RAs is musculoskeletal health. Sarcopenia is prevalent in RA, PsA and axSpA[141,142]. Whereas weight loss interventions are intended to reduce adipose tissue, loss of lean mass (including muscle) is common[30], as are increased bone turnover and decreased bone mineral density (BMD). Observational and RCT data, however, suggest that GLP-1RA therapy does not increase the risk of fragility fractures[30,143] and might in fact decrease fracture risk in people with T2DM[144]. RCTs in adults without T2DM reveal reductions in BMD with GLP-1RAs, probably from weight loss lessening mechanical load[145,146]. In one study, regular exercise alongside liraglutide treatment permitted significant weight loss with preserved BMD[146]. Additional studies on bone health with long-term follow-up in adults with obesity and other high-risk features (including inflammatory arthritis) are warranted.

Box 1 | Do GLP-1RAs cause disproportionate loss of muscle tissue?

In the STEP 1 trial, a subgroup analysis of 95 participants who underwent dual energy X-ray absorptiometry (DEXA) scanning to assess changes in body composition following treatment with the glucagon-like peptide-1 receptor agonist (GLP-1RA) semaglutide or placebo revealed that loss of fat-free (lean) mass accounted for 39% of total weight loss in the group receiving semaglutide[36]. Of nearly 14 kg total weight loss, 5.3 kg was from losses in lean mass. This fraction was higher than that commonly estimated with diet alone (~25–30%)[147,148], raising concerns. Three factors, however, argue against disproportionate loss of muscle tissue with GLP-1RAs. First, the percentage of lean mass loss in the placebo arm of the STEP 1 trial was 57% (1.8 kg lean mass loss out of 3.2 kg total weight loss). Second, in the 255 participants in the SURMOUNT-1 trial who underwent DEXA scanning before and after treatment with tirzepatide or placebo, the ratio of fat loss to lean mass loss was similar in both groups (~3.1% fat loss per 1% lean mass loss)[40]. Third, muscle tissue is not synonymous with lean (that is, fat-free) mass and adipose tissue is not synonymous with fat mass[150]. Body composition assessments with DEXA measure lean and fat mass, not skeletal muscle tissue and adipose tissue[173]. Beyond skeletal muscle protein, lean mass includes water, other sources of protein (including the lean component of adipose tissue), glycogen stored within organs and muscle, non-fat lipids and minerals in soft tissues[173–175]. Interestingly, ~15% of adipose tissue (the greater part of its 'lean' component) is water[175,176], meaning that when a person loses 6 kg of adipose tissue, DEXA will record ~1 kg of lean mass loss. Furthermore, because ~73% of lean mass is water[174], only a minor part of lean-mass losses measured by DEXA represent true loss of skeletal muscle protein. More data are needed to understand the effect of GLP-1RAs on muscle mass and function[177].

Concerns about disproportionate muscle mass loss with GLP-1RAs were raised when a subgroup analysis of 95 participants from the STEP 1 trial revealed that fat-free (lean) mass loss, measured by dual energy X-ray absorptiometry, accounted for 39% of total weight loss in the group that received semaglutide[36]. This percentage was higher than that typically found with diet alone (that is, ~25–30%)[147,148]. However, a closer look at these findings along with results from the SURMOUNT-1 trial (in which a similar ratio of fat loss to lean mass loss was observed with tirzepatide and placebo)[40] cast doubt on whether muscle loss with GLP-1RAs is truly disproportionate (Box 1). Nonetheless, efforts to minimize muscle mass loss and preserve (or improve) function are critical for people with arthritis beginning any mode of weight-loss therapy. Two suggested strategies are resistance training (at least twice per week)[149,150] and prioritizing protein intake (1.2–1.6 g/kg daily)[150,151]. We recommend engaging allied health professionals where possible, such as kinesiologists and physiotherapists to recommend exercises tailored to a patient's functional capacity, and dietitians to facilitate implementation of sustainable healthy eating patterns. Another promising option is bimagrumab, a monoclonal antibody that blocks activin receptor II to preferentially reduce adipose tissue while sparing muscle[30]. Phase II trials assessing bimagrumab versus placebo in either individuals with T2DM and elevated BMI or in older adults with sarcopenia have shown significant fat loss and concurrent lean mass

Box 2 | Outstanding research questions

- How do glucagon-like peptide-1 receptor agonists (GLP-1RAs) affect the risk of developing osteoarthritis (OA), rheumatoid arthritis (RA), psoriatic disease or axial spondyloarthritis (axSpA)?
- By inducing greater weight loss, can newer-generation GLP-1RAs (such as semaglutide and tirzepatide) indirectly lower serum urate concentrations by a meaningful extent?
- Do GLP-1RAs, through anti-inflammatory mechanisms that are dependent on or independent of weight loss, improve disease activity in RA, PsA or axSpA?
- What are the effects of GLP-1RAs on musculoskeletal health, and what are the implications of these effects for patients with arthritis?
- Does the presence of diabetes modify potential weight-loss-independent benefits of GLP-1RAs in arthritis?
- Does bimagrumab, with or without GLP-1RAs, effectively reduce adiposity while preserving muscle mass in individuals with arthritis?

gain with bimagrumab[152,153]. Final results of phase II trials assessing this agent alone or in combination with semaglutide (NCT05616013) or tirzepatide (NCT06643728 and NCT06901349) in people with excess adiposity, with or without T2DM, are awaited (Supplementary Table 1). Whether bimagrumab can mitigate GLP-1RA-related lean mass loss in individuals with arthritis is one of several remaining questions (Box 2).

Clinicians should also consider the cost and risk of weight regain following discontinuation of GLP-1RAs. The STEP 4 and SURMOUNT-4 trials provide insights into expected weight regain after stopping GLP-1RAs[154,155]. Following a 20-week or 36-week open-label run-in, adults were randomized to continue semaglutide (STEP 4) or tirzepatide (SURMOUNT-4) or switch to placebo in a blinded manner. After 1 year, participants switching off GLP-1RAs regained roughly half to two-thirds of the weight they initially lost. Because participants in these trials were followed closely and continued to receive lifestyle counselling, weight regain might be greater in real-world settings. If full-dose GLP-1RA therapy is not feasible in the long term, strategies to minimize weight regain with GLP-1RA deprescribing need to be considered, although evidence supporting each approach is currently limited[156]. Options include tapering to a lower dose or less-frequent administration schedule[157], switching to less costly generic medications with weight-loss properties (for example, metformin, topiramate or bupropion)[158], or prescribing regular moderate-to-vigorous (supervised) exercise[159].

Lastly, the use of GLP-1RAs is lower in low-income and marginalized groups, independent of cardiovascular risk[160,161]. Barriers such as cost could widen existing health inequities, and advocacy efforts are needed to support patients in accessing a class of medications that has been shown to prolong survival, reduce leading causes of morbidity, and, in people with OA, improve pain and function.

Rheumatologists often establish longitudinal relationships with their patients and are therefore well-positioned to identify cardiometabolic comorbidities that could be treatable with GLP-1RAs. Because scope of practice is setting-dependent, we recommend that GLP-1RAs be prescribed and managed by providers who have comfort and experience with these agents. These providers could include family physicians, internists, endocrinologists, cardiologists, nephrologists or rheumatologists.

Conclusions

Exploring the effects of GLP-1RAs in arthritis presents an exciting and timely opportunity. At present, it is clear that this drug class is an effective option for managing T2DM and obesity, as well as for reducing the risk of mortality and major adverse cardiovascular and renal outcomes. Emerging data suggest they can help improve pain and function in OA, mediated only partly through weight loss. In vitro and in vivo evidence of immunomodulatory, chondroprotective and anti-inflammatory effects of GLP-1RAs in arthritis illustrate a potential weight-loss-independent disease-modifying effect worthy of further clinical research. As the use of GLP-1RAs increases, experience accumulates, and the class expands to include additional co-agonists, triple agonists and oral small molecules, many knowledge gaps can be filled. Much is left to learn, but the potential benefits of this medication class for rheumatological diseases are highly encouraging.

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