Glucagon-Like Peptide-1 Receptor Agonists in Osteoarthritis: From Clinical Promise to Preclinical Evidence

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THIS YEAR, at the American College of Rheumatology (ACR) Convergence 2025, a dedicated session explored whether glucagon-like peptide-1 (GLP-1) receptor agonists could represent a new therapeutic frontier in osteoarthritis (OA). Tom Appleton, The University of Western Ontario and St. Joseph's Health Care in London, Ontario, Canada; and Francis Berenbaum, Sorbonne University, INSERM, AP-HP Saint-Antoine Hospital, Paris, France, provided an integrated view of how GLP-1 biology intersects with obesity, inflammation, pain, and joint tissue protection, highlighting the potential of this drug class as a novel therapeutic option for OA.

Appleton provided a comprehensive overview of the clinical application of GLP-1 agonists in knee osteoarthritis (KOA). He outlined their potential mechanisms, reviewed emerging evidence supporting their benefits, and summarized known side effects and contraindications. He concluded by highlighting the key unanswered questions and knowledge gaps that future research must address.

In the second part of the session, Berenbaum explained the pleiotropic effects of GLP-1 and its receptors on metabolic, inflammatory, and tissue-protective pathways relevant to OA. He reviewed pre-clinical data, including findings from his own research group, and discussed how these results support GLP-1 agonists as a potential new therapeutic class for OA.

BEYOND WEIGHT LOSS: UNCOVERING GLUCAGON-LIKE PEPTIDE-1's JOINT EFFECTS

GLP-1 agonists reduce the load on lower limb joints by treating obesity,[1] and protect against cardiovascular diseases. This is particularly relevant given that patients with KOA experience increased cardiovascular mortality, which is considered an independent risk factor.[2] Lastly, GLP-1 agonists modify both local (synovial joint) and systemic inflammation.

Groundbreaking Studies Demonstrate Benefits in Knee Osteoarthritis

Multiple studies have explored the effects of GLP-1 agonists on KOA. The first published study in 2021 showed that liraglutide induced weight loss but yielded only minimal pain improvement.[3]

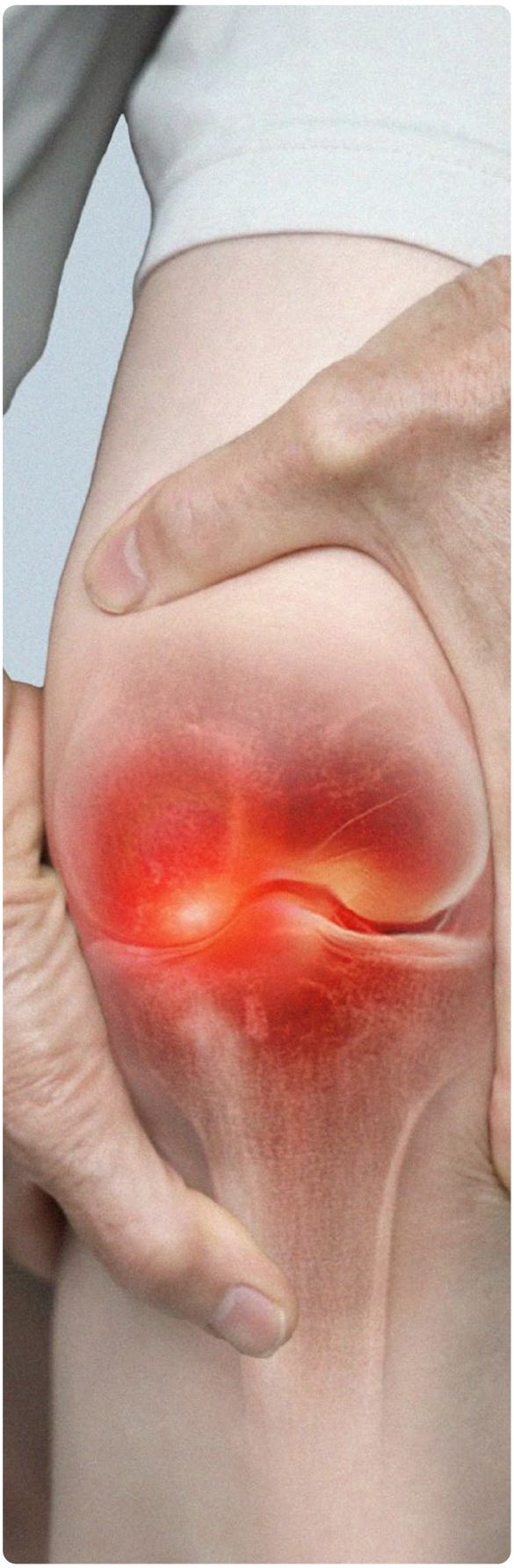
In 2023, Zhu et al.[4] reported observational data from Shanghai Sixth People's Hospital, China, showing that, with adequate treatment duration, GLP-1 agonists may have disease-modifying effects in patients with KOA

with comorbid Type 2 diabetes, potentially mediated by weight loss.

A large retrospective analysis of 237,043 patients with hip or knee OA, including 23,000 individuals exposed to GLP-1 agonists for at least 1 year, found that arthroplasty risk at 1 year was reduced by approximately 40% for hip replacement and 25% for knee replacement.[5]

The STEP-9 trial, a 68-week, double-blind, randomized study conducted across 61 sites in 11 countries, evaluated semaglutide in people with obesity (mean BMI: 40 kg/m²) and KOA with at least moderate pain.[6] Semaglutide produced significantly greater weight loss (an 11–12 kg difference versus placebo) and larger improvements in pain (Western Ontario and McMaster Universities Arthritis Index [WOMAC] score: −41.7 versus −27.5). No serious adverse effects were reported. However, potential limitations included possible unblinding due to noticeable weight loss and the absence of assessments of joint structure or other pathological endpoints.

The STEP-5 trial examined the 2-year effects of semaglutide on body weight in adults who were obese or overweight with comorbidities.[7] Semaglutide led to an average weight loss of 15.2% versus 2.6% with placebo. More participants on semaglutide achieved ≥5% weight loss at Week 104 (77.1% versus 34.4%). Mild-to-moderate gastrointestinal adverse events were more frequent with semaglutide (82.2% versus 53.9%). Although partial weight regain was observed after withdrawal, overall long-term efficacy remained clear.



Adverse Effects and Contraindications

Safety data from meta-analyses of semaglutide trials show that the most common adverse events are gastrointestinal, including nausea, vomiting, and constipation.[8] Contraindications include medullary thyroid carcinoma, multiple endocrine neoplasia Type 2,

and pregnancy. Lean muscle mass loss occurs proportionally with weight loss, highlighting the importance of resistance exercise and adequate protein intake to preserve muscle and bone health. Cardiovascular and renal benefits have been consistently demonstrated, with lower rates of cardiovascular events observed in semaglutide-treated patients compared with placebo.[8]

Remaining Questions and Knowledge Gaps

There is strong evidence that synovitis drives worse outcomes in osteoarthritis, contributing to more severe and persistent pain, heightened pain sensitization, faster structural deterioration, and an increased need for joint replacement.[9-13] A key unanswered question is whether GLP-1 agonists, beyond promoting weight loss, can directly target chronic synovial inflammation. Understanding their potential disease-modifying effects on the inflamed synovium is essential to determine whether these therapies could alter the trajectory of OA rather than solely improve symptoms.

Appleton highlighted several important remaining gaps in the understanding of GLP-1-based therapies for OA. It is uncertain whether their effects are similar in non-obese or less-obese populations, or whether benefits extend to other disease subtypes such as hand OA. It also remains unclear whether improvements are driven purely by biomechanical changes from weight loss or whether cardiometabolic mechanisms contribute independently, potentially offering disease-modifying effects or benefits through intra-articular delivery. Additional questions include how to mitigate lean muscle mass loss, which is important for joint stability, and whether adding glucose-dependent insulinotropic polypeptide or glucagon receptor activation could offer advantages over GLP-1 agonists on their own.

GLUCAGON-LIKE PEPTIDE-1 IN OSTEOARTHRITIS: WHAT PRECLINICAL STUDIES REVEAL

A recent groundbreaking study described a gut–joint pathway that may help explain the development of OA.[14] In healthy people, the gut bacterium *Clostridium bolteae* converts primary bile acids into ursodeoxycholic acid, which is then conjugated into glycoursodeoxycholic acid (GUDCA). These bile acids suppress the farnesoid X receptor (FXR) in the intestine. When FXR is inhibited, intestinal stem cells generate more L-cells, which produce GLP-1. This endogenous GLP-1 enters the bloodstream, reaches the joint, binds to GLP-1 receptors in joint tissue, and protects cartilage.

In patients with OA, levels of *C. bolteae* are reduced. Because of this, less GUDCA is produced, FXR remains activated, fewer L-cells are formed, and GLP-1 production falls. The study showed that restoring *C. bolteae* or giving GUDCA directly protects cartilage in a mouse OA model. Importantly, when researchers blocked the GLP-1 receptor by injecting its inhibitor into the joint, the protective effects disappeared. This indicates that the benefit depends on GLP-1 signaling itself, rather than on unrelated metabolic changes.

Furthermore, in a series of preclinical studies, GLP-1 analogues demonstrated protective effects on joint tissues across multiple OA models.[14-15] Liraglutide reduced cartilage degradation more effectively than intra-articular dexamethasone, which showed no structural benefit. In human cartilage pellet cultures, GLP-1 analogues restored proteoglycan markers suppressed by IL-1β. They also reduced catabolic enzyme activity and promoted anabolic matrix formation, consistent with the anti-catabolic and anabolic actions described in preclinical OA models.

Glucagon-Like Peptide-1 Analogues Reduce Pain and Fibrosis in Animal Models

Berenbaum discussed his own research in this area, where his team first demonstrated that multiple GLP-1 analogues markedly reduced pain in the monoiodoacetate mouse model. He then compared the effects of liraglutide and dexamethasone on synovitis in rat models, finding that, although inflammatory scores were similar between the two treatments, the density scores differed. In subsequent anterior cruciate ligament transection combined with medial meniscectomy rat studies, the team showed that liraglutide produced a strong antifibrotic effect, whereas dexamethasone had no measurable impact on fibrosis.

Macrophage–Fibroblast Crosstalk: A Potential New Paradigm

To begin dissecting potential cellular mechanisms within the synovium, Berenbaum's group examined how GLP-1 analogues influence innate immune and stromal cells. In synovial macrophages, liraglutide treatment shifted cells from a pro-inflammatory M1 phenotype toward an anti-inflammatory M2 state, a transition that correlated with an overall reduction in inflammatory activity. Complementing these findings, preliminary data from human synovial fibroblasts show that GLP-1 stimulation reduces cytokine production and alters inflammatory gene expression, suggesting broader immunomodulatory effects across key synovial cell populations.[16]

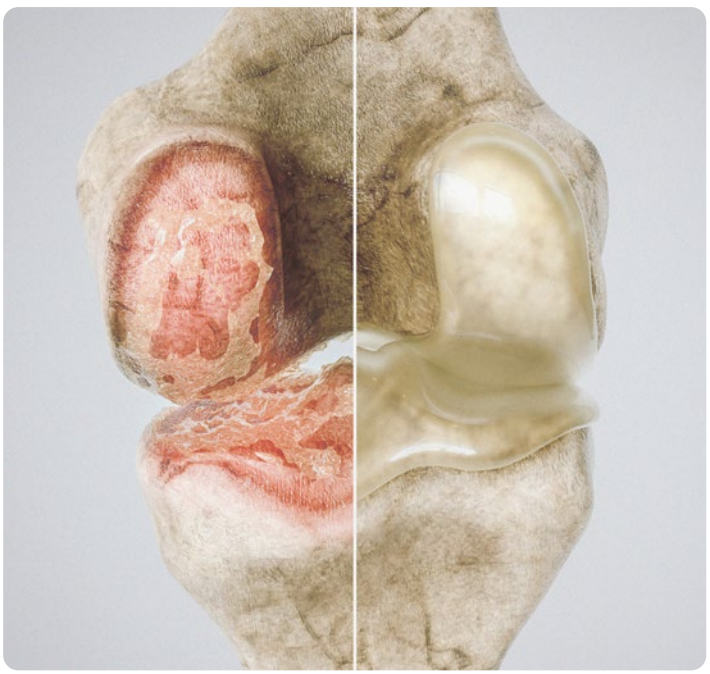
Berenbaum hypothesized that the therapeutic potential of GLP-1 in OA may arise from targeting the crosstalk between macrophages and fibroblasts, which are known to drive inflammation, fibrosis, and downstream cartilage damage. This dual effect could explain why GLP-1 analogues, unlike dexamethasone, improve both synovitis and fibrosis in preclinical models.

A Potential New Osteoarthritis Therapeutic Class

Together, these findings suggest that GLP-1 receptor modulation influences multiple joint-specific pathways: reducing inflammation, preventing cartilage catabolism, promoting matrix regeneration, and modifying synovial tissue responses. These pleiotropic actions, combined with robust analgesic and antifibrotic effects, support GLP-1 analogues as a promising new therapeutic class for OA. Ongoing mechanistic studies and upcoming clinical trials will determine how these preclinical benefits translate to human disease.

CONCLUSION

The clinical and preclinical data presented at the ACR Convergence 2025 show both the therapeutic potential and the scientific complexity of GLP-1 agonists in OA. While early findings suggest significant effects on weight, pain, inflammation, and joint tissues, main mechanisms and clinical implications remain unclear. As larger and longer-term trials start to report their results, we will gain a clearer picture of whether GLP-1 agonists can ultimately modify disease progression or serve as mainly symptomatic therapies.



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