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Semaglutide in obesity-related knee osteoarthritis: Interpreting STEP 9 and implications for practice

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Obesity is a major driver of knee osteoarthritis (KOA) via joint overload and chronic inflammation; therefore, weight reduction is central to KOA management. Non-steroidal anti-inflammatory drugs (NSAIDs) and physical therapy could relieve KOA symptoms, but they do not address obesity, a key KOA factor. Glucagon-like peptide-1 receptor agonists (GLP-1RAs), initially designed for treating type 2 diabetes (T2DM), now show promise for KOA in individuals with obesity.

Bliddal et al. randomized a multicenter study of 407 patients with obesity and KOA 2:1 to once-weekly semaglutide 2.4 mg or placebo.[1] After 68 weeks, semaglutide significantly reduced weight compared to placebo (13.7% vs. 3.2%) and produced greater pain and performance improvements (WOMAC pain and SF-36 physical function score). For baseline WOMAC > 51.5, the minimal clinically important difference is 20.4 (both semaglutide and placebo exceeded this difference). In responder analyses, more semaglutide than placebo patients achieved >30% and >50% improvement in WOMAC scores (responder rate differences of 19.8% and 29.9%). Collectively, these findings show that semaglutide led to a clinically significant reduction in pain compared with placebo.

Notably, this is not the first study to examine the effects of GLP-1 receptor agonists in obese patients with KOA. The 2023 SHOACS study indicated that these agonists might decelerate cartilage degeneration and reduce the need for knee surgery in patients with KOA and T2DM; nonetheless, the study's design and eligibility criteria limited its applicability to only diabetic patients.[2] The STEP 9 study reduced potential confounding factors related to blood glucose control by excluding patients with T2DM, and provided clearer evidence for treating obesity-related KOA. On this basis, the STEP 9 study showed that semaglutide could improve the WOMAC pain score by approximately 14 points versus controls, and its efficacy matched that of NSAIDs, glucocorticoid injections, and physical therapy.[1] In addition to relieving symptoms, semaglutide may also reduce joint load through sustained weight loss and may exert anti-inflammatory effects. However, its efficacy emerges slowly, usually requiring long-term use, and may weaken after drug withdrawal. In contrast, NSAIDs and intra-articular corticosteroid injections take effect more quickly but mainly provide short-term symptom relief. Despite the high cost, semaglutide may be particularly useful for patients with a high BMI, severe pain, and a preference for drug treatment options that may offer long-term benefits. Further research should clarify the optimal treatment duration, the persistence of efficacy after drug withdrawal, and potential benefits in different diseases.

Nevertheless, the associated risks must be considered. It is thought that roughly 25% to 40% of the weight reduction associated with semaglutide treatment is attributable to loss of lean body mass, and older adults and women are particularly vulnerable to this. Given that quadriceps weakness accelerates the progression of KOA, muscle loss may compromise knee joint stability and increase the risk of falls; consequently, for patients considered to be at high risk, resistance training should be incorporated into treatment, and adequate protein intake should be ensured. Weight loss can also reduce bone mineral density, which is particularly important for patients who may need future joint replacement surgery. Therefore, bone health checks and calcium/vitamin D supplementation are advisable. Gastrointestinal adverse reactions are also relatively common and may affect patient adherence. In clinical practice, semaglutide should be considered a potentially effective treatment option, but patients should be carefully selected and receive concurrent nutritional support and exercise interventions.

Although STEP 9 results are positive, several limitations remain. Inflammatory or metabolic markers were not measured in the study, nor were imaging studies included; therefore, the effects of semaglutide on the pathophysiology and structural outcomes of KOA remain unclear. It is not possible to assess the durability of efficacy or rebound effects after discontinuation with only 7 weeks of follow-up. Moreover, most participants were women with severe obesity and severe baseline pain, so results may differ in less obese patients or those with milder symptoms. The use of semaglutide as a routine treatment for all patients with KOA is not supported by current evidence.

In STEP 9, the placebo was used without an active weight-loss comparator. Thus, it remains unclear whether the observed improvements were due solely to weight loss, to GLP-1 receptor agonism, or to both. Future studies should compare semaglutide with non-GLP-1 weight-loss therapies that achieve similar weight reduction, so that the specific contributions of metabolic, anti-inflammatory, and cartilage-related mechanisms can be better defined.

The lack of an active comparator arm in the study design likely undermines blinding. This concern is supported by a meta-analysis of 198 placebo-controlled osteoarthritis trials, which showed that the placebo had a significant effect on pain, stiffness, and function compared with no treatment.[3] Therefore, maintaining blinding is critical in randomized controlled trials of osteoarthritis. In the context of semaglutide, its common gastrointestinal side effects-often mild to moderate-can also compromise blinding. Notably, STEP 9 did not report gastrointestinal side-effect rates; however, the STEP 1 trial found nausea and vomiting in 44.2% and 24.8% of semaglutide-treated patients, versus 17.4% and 6.6% with placebo.[4] By applying Bayes' theorem to these rates (and considering the 2:1 randomization in STEP 9), if a patient experiences nausea or vomiting, the probability that they received semaglutide rises to approximately 84% and 88%, indicating a high risk of unblinding. Once subjects know their treatment is effective, bias may affect adherence and reporting of subjective outcomes (e.g., WOMAC Pain Score and SF-36 Functional Score), while the significant weight loss attributable to semaglutide has the potential to result in functional unblinding. For example, STEP 4 found a mean weight loss of 10.6% at 20 weeks with semaglutide. In contrast, in STEP 9, the placebo group lost only about 1.73% body weight by week 20, which is much less than the effects seen with semaglutide. This disparity indicates that placebo participants who experienced little weight loss by week 20 may have become aware they were not receiving active treatment, thereby defeating blinding and resulting in higher WOMAC pain scores and lower SF-36 scores. Adding a non-GLP-1 weight-loss drug can reduce bias from side effects and weight loss, improve study quality, and allow a fair comparison. Investigators must prioritize a double-blind design, including placebo and weight-loss drug arms, to ensure robust, reliable findings in the evaluation of osteoarthritis interventions.

In summary, the cartilage-protective effects of GLP-1RAs on KOA indicate that these agents may have therapeutic effects not only on the KOA itself but

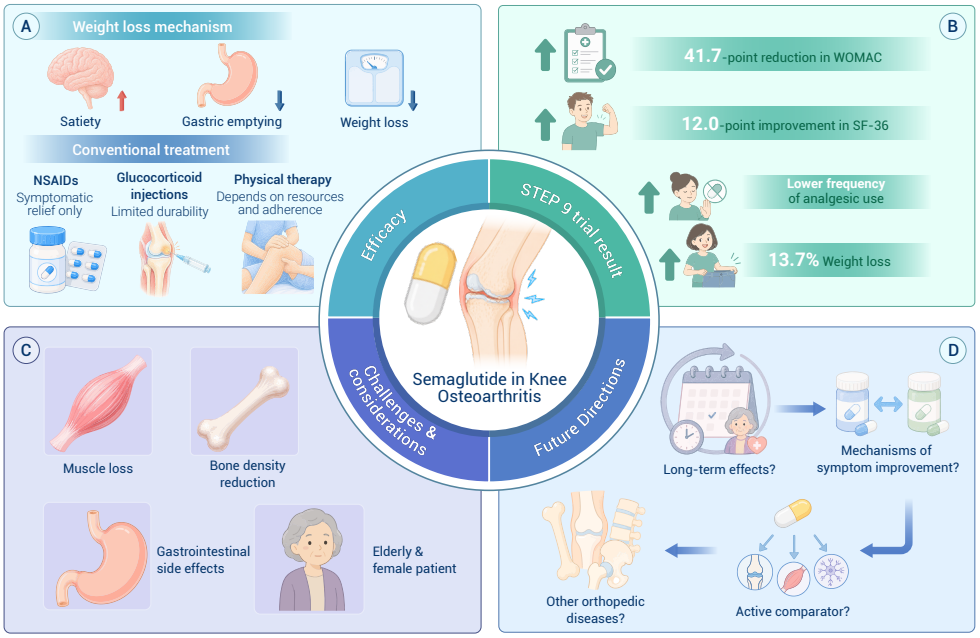

Figure 1. Overview of the potential role of semaglutide in obesity-related knee osteoarthritis (KOA) (A) Semaglutide may improve KOA symptoms mainly through weight loss, partly by increasing satiety and delaying gastric emptying, thereby reducing joint loading and improving physical function. This mechanism confers distinct advantages over conventional KOA treatments. (B) In STEP 9, semaglutide was associated with greater weight loss, larger reductions in WOMAC pain score, improved SF-36 physical function score, and less analgesic use than placebo. (C) The main issues are loss of muscle mass, decreased bone density, intestinal disturbances, and higher vulnerability of elderly patients and female patients. (D) Further research on the long-term persistence of effect, mechanisms of improvement, active control design, and the role of semaglutide in other obesity-related diseases is needed.

also on other comorbidities. Obesity-related orthopedic disorders, such as low back pain, occur at a high rate. However, there are no systemic treatments, and the underlying metabolic and inflammatory conditions related to obesity are the primary targets for medication. Thus, the application of GLP-1RAs could be expanded to other obesity-associated orthopedic diseases.

Obesity and T2DM are risk factors for low back pain (LBP) and intervertebral disc disease (IVDD). The odds of LBP are approximately 1.47- and 1.68-fold higher in individuals with obesity and T2DM patients, respectively, compared with controls. Given the substantial weight-loss and antidiabetic effects of GLP-1RAs, there is a strong rationale to further investigate their potential therapeutic role in LBP and IVDD. Supporting this, a retrospective study demonstrated GLP-1RA users had a significantly lower 5-year cumulative incidence of IVDD (14.6% vs. 18.7%; OR = 0.74).[5] Furthermore, the proportion of patients undergoing surgery for IVDD was also lower among GLP-1RAs users (0.5% vs. 0.6%, OR ≈ 0.86).[5] Although current results are still preliminary, the cartilage-protective effects reported for GLP-1RAs may suggest a new mechanism for treating degenerative disc disease. Future high-quality prospective trials will be needed to determine the true effectiveness and safety of semaglutide in IVDD.

However, many important questions must be answered in future studies: First, can the benefits of semaglutide persist after discontinuation, and how can weight maintenance after weight loss be optimized? Second, does semaglutide alleviate osteoarthritis symptoms independent of weight loss? Third, could the study's possible unblinding lead to an overestimation of semaglutide's efficacy? Finally, is it possible for semaglutide to treat other obesity-related orthopedic diseases, such as IVDD? It is worth noting that GLP-1RAs are not traditional analgesics or standard anti-inflammatory drugs. Their efficacy appears gradually and requires long-term use, so incorporating them into clinical orthopedic practice will face practical challenges (e.g., determining which patients should start this treatment and how to combine it with physical therapy and analgesic drugs). Nevertheless, the success of the STEP 9 trial has enabled exploration of metabolism-targeted therapies for orthopedic diseases. As a bridge between the metabolic and skeletal systems, GLP-1RAs prompt us to consider the broader impact of systemic diseases such as obesity on orthopedic diseases, thereby encouraging multidisciplinary research and innovation.

In conclusion, semaglutide and other GLP-1RAs may have broad applications in osteoarthritis and other orthopedic fields, suggesting that future medical practice may increasingly prevent and treat chronic orthopedic diseases through systemic metabolic regulation (Figure 1). High-quality research and long-term follow-up are crucial to translate this potential into practice, ultimately bringing extensive interdisciplinary health benefits to patients.

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L.M.R., Y.C.X., and X.M.L. contributed equally. Conceptualization and supervision: K.T.M., C.Z., and C.L.Z. Methodology and investigation: L.M.R., Y.C.X., X.M.L., and L.L. Literature search and evidence interpretation: L.M.R., Y.C.X., and X.M.L. Pharmacological and clinical interpretation: K.T.M., C.Z., and C.L.Z. Writing - original draft: L.M.R., Y.C.X., and X.M.L. Writing - review and editing: K.T.M., C.Z., and C.L.Z. Final approval of the manuscript: All authors. L.M.R., Y.C.X., and X.M.L. are listed as co-first authors because they made substantial contributions to the literature review, evidence interpretation, and writing of this manuscript. All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.