Two birds with one stone — Semaglutide's impacts on obesity and knee osteoarthritis: From weight loss to pain relief

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Obesity and osteoarthritis (OA) are two intertwined conditions that exert tremendous socioeconomic burdens on individuals and healthcare systems worldwide.[1,2] Obesity, affecting over 650 million adults globally, is a leading cause of preventable diseases, contributing to metabolic disorders (e.g., non-alcoholic fatty liver disease and type 2 diabetes) and cardiovascular complications (e.g., coronary artery disease and hypertension).[2] Concurrently, OA is the most prevalent joint disorder, affecting over 500 million people globally and leading to chronic pain and reduced mobility. Obesity impacts OA by

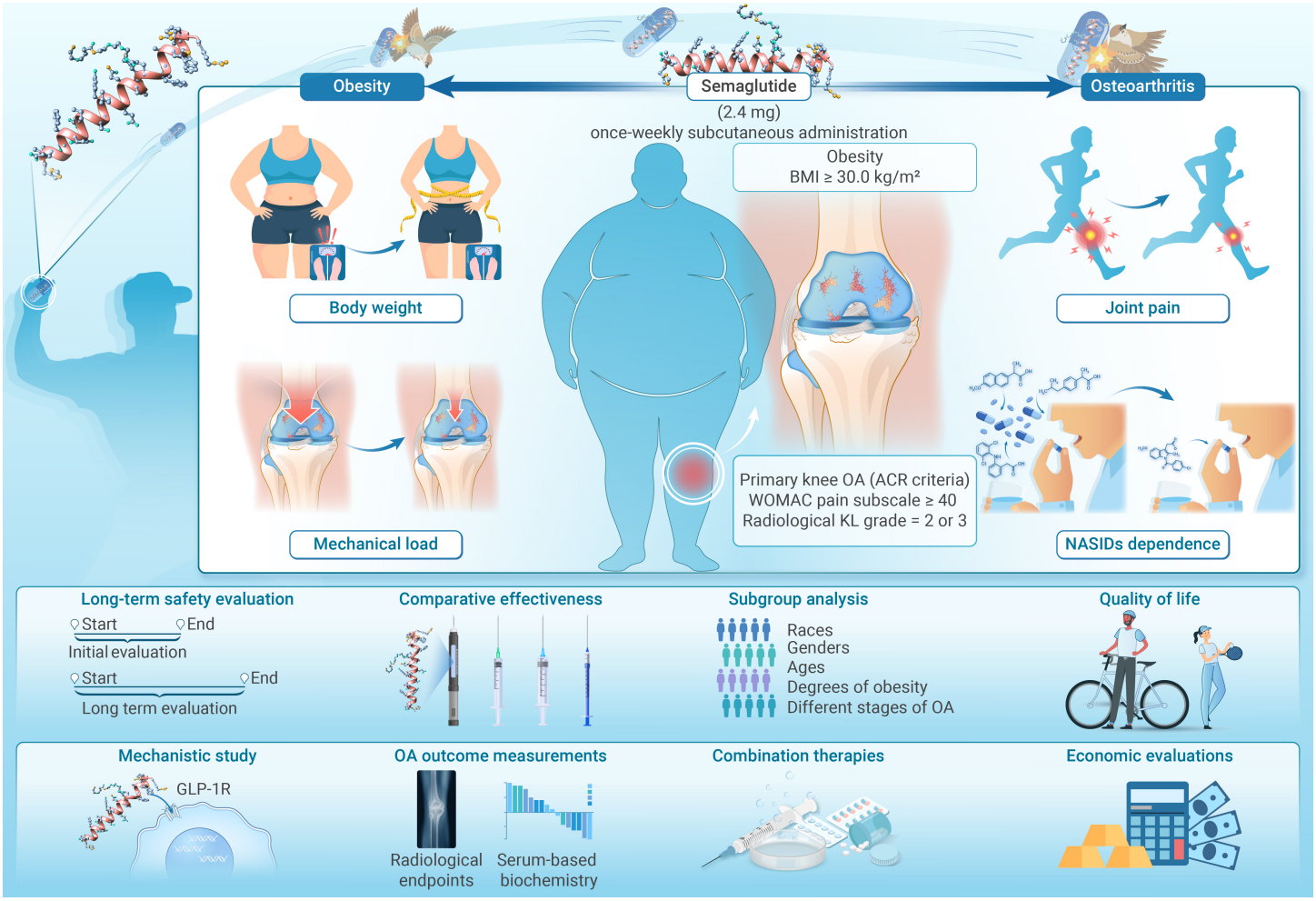

Figure 1. Two birds with one stone—the dual benefits of Semaglutide in addressing obesity and OA simultaneously and future possible follow-up research.

elevating mechanical stress on weight-bearing joints and driving systemic inflammation, accelerating cartilage matrix degradation and exacerbating OA progression.[1,3] Despite the well-documented benefits of weight reduction in alleviating OA symptoms, effective therapeutic interventions remain limited. The recent study published in *The New England Journal of Medicine*, titled "Once-Weekly Semaglutide in Persons with Obesity and Knee Osteoarthritis,"

addresses this gap by exploring the efficacy of Semaglutide, an anti-obesity drug functioning as a glucagon-like peptide-1 (GLP-1) receptor agonist, in promoting weight loss and ameliorating OA-related pain (Figure 1).[4] This 68-week, double-blind, randomized, placebo-controlled trial spanned 61 sites in 11 countries, enrolling 407 participants with obesity (BMI ≥ 30) and moderate knee OA with moderate to severe pain. Participants were randomized 2:1 to receive once-weekly subcutaneous Semaglutide (2.4 mg) or placebo, and both groups received counseling on physical activity and a calorie-restricted diet. The primary endpoints were the percentage change in body weight and the change in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score. Additionally, the study assessed the physical function score using the 36-Item Short Form Health Survey (SF-36). The trial results are compelling: participants treated with Semaglutide experienced a mean body weight reduction of 13.7%, significantly greater than the 3.2% reduction observed in the placebo group.[4] This prominent weight loss has important clinical implications. The mean change in the WOMAC pain score was -41.7 points with Semaglutide compared to -27.5 points with placebo, demonstrating a substantial reduction in OA-related pain.[4] Moreover, the SF-36 physical-function score improved more in the Semaglutide group (mean change of 12.0 points) than in the placebo group (change of 6.5 points).[4] After taking Semaglutide, the patient lost weight and became less dependent on NSAIDs. By decreasing mechanical load on knee joints and lowering systemic inflammation, Semaglutide helps alleviate pain and improve joint function. The enhancements in physical function and quality of life underscore the dual benefits of Semaglutide in addressing obesity and OA simultaneously.

The safety profile of Semaglutide observed in this study aligns with previous research on GLP-1 receptor agonists.[5] The incidence of serious adverse events was comparable between the Semaglutide and placebo groups.[4] However, the discontinuation rate due to adverse events was higher in the Semaglutide group (6.7% *vs.* 3.0%), with gastrointestinal disorders being the most common cause.[4] This finding highlights the need to monitor and manage gastrointestinal side effects in clinical practice. Semaglutide offers a novel therapeutic option that simultaneously addresses obesity and knee OA. The significant weight reduction not only alleviates OA symptoms but also reduces the risk of obesity-related comorbidities, including cardiovascular disease and type 2 diabetes. Conversely, improved physical function due to less debilitating pain enables patients to engage in more physical activities, further contributing to weight management and overall health.

Although this study presents robust evidence for using Semaglutide in obesity and knee OA, several questions remain, warranting further research in the following areas (Figure 1). First, long-term efficacy and safety evaluations were missing. Extending the observation period to assess the long-term impacts of Semaglutide on joint health and OA progression is essential. Monitoring any delayed adverse effects, including potential tumor-related risks, will be crucial to establishing a comprehensive safety profile. Besides, it is necessary to conduct mechanistic studies to investigate the signaling pathways through which Semaglutide alleviates pain and improves joint function in OA. Understanding these mechanisms underlying pain reduction as well as the relationship among Semaglutide, body weight, and OA could guide the development of more targeted therapies and optimized treatment protocols, maximizing the benefits of GLP-1 receptor agonists while minimizing adverse effects. Moreover, conducting comparative trials between Semaglutide and other weight loss interventions or OA treatments would help identify the most effective strategies for concurrently managing these two conditions. Future studies should also include more endpoint evaluations of OA (e.g., radiological imaging results and serum inflammatory markers after Semaglutide treatment) to identify if it has a disease-modifying or anti-inflammatory effect. Since OA-associated pain and limited mobility can have a negative impact on patients' mental health and the side effects of Semaglutide also include emotional disorders, we also recommend that future studies on the use of Semaglutide in obese patients with knee OA incorporate validated anxiety and depression scales (such as PHQ-9, GAD-7). This will help thoroughly in assessing the psychological impact of the treatment and ensuring that any negative emotional effects are identified and managed promptly. The original study primarily involved white women, highlighting the need for a gender-balanced and more inclusive approach. To develop personalized OA treatments, it will be beneficial to examine the efficacy and safety of Semaglutide across diverse patient subgroups, including those with different races, genders, ages, varying degrees of obesity, different stages of OA, or other comorbid conditions. Additionally, we expect follow-up studies exploring the potential enhancement of treatment outcomes by combining Semaglutide with other pharmacological or non-pharmacological interventions, such as physical therapy, exercise programs, psychological support or other complementary medications aimed at managing OA. Besides, the potential for drug interactions and side effects, such as gastrointestinal issues, should be carefully examined. A comprehensive assessment of the quality of life and functional outcomes is also desirable. Future studies should prioritize the impact of Semaglutide on patients' quality of life, functional capacity, and overall well-being, using patient-reported outcomes to gain a holistic understanding of treatment effects. Finally, conducting cost-effectiveness analyses of Semaglutide for obesity and OA treatment is essential to determine the economic impact of this treatment and inform healthcare decision-making and policy development.

This study on the STEP 9 trial marks a significant advancement in managing obesity and knee OA, highlighting the transformative potential of Semaglutide in addressing both conditions. The dual benefits of weight loss and pain relief position Semaglutide as a promising therapeutic option for patients with obesity and knee OA, providing a multifunctional approach to treatment that has been elusive in clinical practice. This groundbreaking clinical research paves the way for better outcomes and improved quality of life for millions of individuals suffering from these chronic, debilitating conditions.

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AUTHOR CONTRIBUTIONS

All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.