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# Potential benefits of GLP-1 analogues and metformin in patients with osteoarthritis

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## ABSTRACT

### Introduction and purpose

Osteoarthritis (OA) is the most prevalent chronic joint disorder. It is the primary cause of chronic pain. Known risk factors for OA include obesity and type 2 diabetes mellitus (T2DM). One of the challenges in managing OA is the absence of disease-modifying treatments. Since obesity is an independent risk factor of OA, the use of medications like GLP-1 analogs and metformin may benefit patients with OA. The purpose of our article was to provide an overview of the findings from studies on the use of the mentioned drugs in OA patients.

### Materials and methods

To write this article, databases such as PubMed and Google Scholar were searched using the following terms: osteoarthritis, glucagon-like peptide-1 (GLP-1), obesity, anti-obesity medications.

### Description of the state of knowledge

Research on the effects of GLP-1 analogs in OA patients has yielded inconclusive results. Some studies showed that semaglutide provided benefits in reducing knee osteoarthritis symptoms in obese, nondiabetic patients. For those with knee OA and T2DM, GLP-1 receptor agonists lowered body weight and pain intensity. Furthermore, patients treated with GLP-1 receptor agonists have a reduced risk of knee surgery and lower cartilage loss velocity. Patients receiving semaglutide who underwent arthroplasty procedures experienced lower risks of prosthetic infections and hospital readmissions. The use of metformin was associated with reduced rates of joint replacement surgery.

**Conclusions**

GLP-1-based therapies and metformin, due to their pleiotropic effects, may provide advantages by alleviating joint inflammation and facilitating weight loss in OA patients. Additional research is required to validate these outcomes and identify the most effective treatment approaches for managing OA.

**Keywords**

Osteoarthritis, Glucagon-like peptide-1 (GLP-1), Liraglutide, Semaglutide, Anti-obesity medications, Weight management, Total knee arthroplasty, Total hip arthroplasty

## 1. Introduction

Osteoarthritis (OA) is the most common chronic joint condition. Approximately 4.3% of adults experience symptomatic knee osteoarthritis, characterized by frequent knee pain occurring on most days. [1] Its prevalence rises with age, affecting the majority of individuals over 65. [2,3] It is defined by progressive cartilage degradation, subchondral bone remodeling, and synovial inflammation. [4]

Articular cartilage can be impaired by everyday wear and tear or pathological factors like abnormal mechanical stress or injury. In the early stages of OA, inflammation of the synovium can occur, while the cartilage surface remains intact. [3,5]

In healthy joints, chondrocytes possess limited regenerative ability and exhibit low metabolic activity. However, in OA transient proliferative response and increased matrix synthesis occur in order to ensure repair processes. This leads to the formation of more catabolic factors and the destruction of proteoglycans and, subsequently, the collagen network. As a result, cartilage integrity is disrupted. The complete loss of cartilage, leading to decreased joint space, causes bone friction, resulting in pain and restricted joint movement. Other signs of OA, including subchondral sclerosis as well as muscle and tendon weakness and loosening will also emerge. [3,6] OA impacts joints such as the knees, hips, hands, and spine, and is the primary cause of chronic pain, reduced mobility, and functional impairment in older adults, particularly women. [3,7,8]

Although etiopathogenesis is not completely understood, the risk factors affecting OA are known, such as genetic predisposition, aging, obesity, and joint malalignment. The existence of a strong link between knee OA and obesity has been proven in scientific studies. In addition, weight loss can slow the progression of the disease. [7,9] Therefore, obesity is considered an independent risk factor for the development of osteoarthritis. [10]

One of the difficulties in treating patients with OA is the lack of disease-modifying treatments that can slow down the progression of OA or postpone the permanent breakdown of cartilage, aside from total joint replacement surgery. [2,3,5] While anticytokine therapies have proven highly effective in managing rheumatoid arthritis, they have not demonstrated similar success as treatments for osteoarthritis. [11] Current approaches focus on reducing pain, alleviating stiffness, preserving functional abilities, and enhancing overall quality of life. Available treatments include low-impact aerobic exercise, weight reduction, and surgical interventions. [3] Due to the association of OA with obesity, American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) advise obese patients with knee OA weight loss and engage in physical activity. [12,13]

**Co-morbidity of obesity, type 2 diabetes mellitus and Osteoarthritis**

The global prevalence of obesity and type 2 diabetes mellitus (T2DM) has been consistently rising. Both conditions are influenced by notable genetic and environmental factors in their progression. Obesity amplifies the effect of genetic susceptibility and environmental factors on diabetes mellitus. Disturbed metabolic balance due to excess of adipose tissue and metabolite accumulation, results in insulin resistance and abnormalities in the functioning of the microbiome-gut-brain axis. In turn, these disorders result in low-grade systemic inflammation, which disrupts homeostasis, exacerbates the loss of functional β-cells, and chronic hyperglycemia. [14] Moreover, inflammation created by increased adipose tissue causes direct pathological effects on the musculoskeletal system through oxidative stress and endothelial cell dysfunction. In particular, proinflammatory cytokines secreted by adipose tissue interact with various components of the musculoskeletal system, including cartilage, bone, meniscal tissue, and synovial cells, leading to degradation of bone and subchondral structures, along with inflammation in the surrounding soft tissues. [6,10]

T2DM and OA are common chronic diseases with shared pathophysiological pathways, including inflammation and metabolic dysregulation. Moreover, T2DM is a risk factor for OA

progression. [4,6] The well-known link between osteoarthritis (OA) and T2DM is partially explained by hyperglycemia, which leads to cellular and tissue damage within joint tissues. [2] The prevalence of OA in the general population is 27%, whereas among patients with T2DM is up to 52%. [15] Therefore, since individuals with diabetes are at an increased risk of bone degradation, the use of antidiabetic drugs may have a protective effect on the condition of the skeletal system. [4]

## 2. Objective of the work

Conventional weight-loss approaches, such as lifestyle changes involving diet and exercise, are often associated with poor patient adherence, resulting in less effective outcomes than anticipated. for this reason, incorporating antidiabetic drugs can enhance the positive results of treatment. [10] The aim of the study was to investigate the possible benefits of antidiabetic drugs in patients with OA.

## 3. Materials and methods

For this review article, databases such as PubMed and Google Scholar were searched. The following terms were used to search for relevant scientific articles: osteoarthritis, glucagon-like peptide-1 (GLP-1), obesity, anti-obesity medications, semaglutide, liraglutide. Ultimately, 31 research articles were cited.

## 4. Description of the state of knowledge

### Mechanism of GLP-1 action

Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are the key incretin hormones responsible for glucose-dependent insulin release from pancreatic β cells. Due to the rapid degradation of native human forms, GLP-1 analogues are used for the treatment (*e.g.,* liraglutide, semaglutide). They play a crucial role in the treatment of T2DM. Research suggests that they have beneficial pleiotropic effects, including immunomodulation,

anti-inflammatory activity, and neuroprotection. [4,16,17] These characteristics could make them advantageous for patients with osteoarthritis (OA). [4]

Studies have proven that the use of GLP-1 analogs, due to their strong anti-inflammatory properties, provides therapeutic benefits in managing neurological, cardiovascular, and pulmonary diseases. [2,18] In addition, they may be beneficial in treating patients with atherosclerosis nonalcoholic steatohepatitis, diabetic nephropathy, and psoriasis. [16,19] GLP-1 analogues could also act locally at the joint level [5] as a result of the expression of the glucagon-like peptide-1 receptor (GLP-1R) in joint tissues [2], as well as in the central nervous system, where the activation of neuronal GLP-1 receptors suppresses toll-like receptor activity, leading to a reduction in the production of inflammatory cytokines. [20]

Considering the shared risk factors between OA and T2DM, along with the proven anti-inflammatory effects of GLP-1 in various tissues, GLP-1 analogs could be promising therapeutic options for treating OA. [2]

**GLP-1 in vitro and in vivo experiments**

The presence of GLP-1R has been proven in both synovial cell types: macrophages and fibroblast-like synoviocytes, as well as bone marrow stem cells, osteoblasts, osteocytes, and osteoclasts. [2] Research conducted using in vitro and in vivo experiments showed that intra-articular injection of liraglutide helped reduce pain associated with OA. This effect was probably caused by the GLP-1R-mediated anti-inflammatory activity of the drug. [2] A study in rats showed that liraglutide diminishes swelling and paw temperature by reducing acute peripheral inflammation. [21]

Additionally, liraglutide treatment notably decreases the expression of inflammatory genes in vitro in chondrocytes and macrophages, as well as the secretion of IL-6, PGE2, and nitric oxide. [2, 5] In vitro, it also reduced the activity of enzymes responsible for cartilage degradation such as metalloproteinases and aggrecanases. Moreover, liraglutide caused an increase in the anti-inflammatory M2 phenotype of macrophages, instead of the pro-inflammatory M1 phenotype [5].

**The use of GLP-1 in patients with osteoarthritis**

Studies examining the effects of GLP-1 analogs in individuals with OA have yielded inconclusive results. The observed benefits of these medications may result from their weight-loss properties rather than direct anti-inflammatory or pain-relieving actions. [22,23]

In a randomized controlled trial involving patients with knee osteoarthritis, participants were randomly assigned to receive either liraglutide 3 mg/d or a placebo. [23] After 52 weeks, weight loss, as well as pain severity were assessed using the Knee Injury and Osteoarthritis Outcome Score measurement scale. Significantly greater weight loss was observed in the liraglutide group compared to placebo, but pain intensity was comparable in both groups.

On the other hand, a double-blind, multicenter, placebo-controlled trial showed a beneficial effect of semaglutide in alleviating knee osteoarthritis symptoms in nondiabetic patients with obesity. [24] The study compared a group of patients using once-weekly injectable semaglutide for 68 weeks to a control group who were recommended exercise and a caloric deficit diet. Among patients in the study group, there was greater weight loss, as well as a reduction in pain severity measured by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and improvements in function and quality of life as assessed by 36-Item Short Form Health Survey version-2.0 (SF-36v2). In addition, these individuals covered more distance in the 6-minute walk test.

The prospective, observational, multicenter study conducted on patients with knee osteoarthritis and T2DM found that participants taking GLP-R agonists had significant weight loss and lower pain intensity in WOMAC pain subscale scores than the control group. [25] Furthermore, individuals treated with GLP-1R agonists had a lower risk of knee surgery, which was mediated by weight reduction They were also observed to have a lower cartilage loss velocity and fewer intra-articular injections of steroids.

Arthroplasty benefits OA patients with and without obesity. In recent years, the prevalence of obesity among patients undergoing hip or knee arthroplasty has been increasing. [26] Unfortunately, the procedure in people with excess adipose tissue is associated with an increased risk of infection, reoperation, and revision of surgical procedures. Furthermore, these patients tend to undergo total joint arthroplasty at an earlier age. Since preoperative weight can influence the complication rate in orthopedic surgery, achieving optimal weight before arthroplasty may be crucial. Anti-obesity medications such as GLP-1 analogues can be helpful in this regard. [10]

The retrospective study evaluated the effect of semaglutide use on decreasing complications in patients with diabetes undergoing total knee arthroplasty (TKA) for osteoarthritis shows the benefits of treatment. 90-day postoperative medical complications, 2-year implant-related complications, 90-day readmissions, in-hospital lengths of stay, and costs were assessed. [27] Semaglutide cohorts had lower odds of sepsis, prosthetic joint infections, and readmission. Unfortunately, it has also been shown that semaglutide use increases the risk of myocardial infarction, acute kidney injury, pneumonia, and hypoglycemic events.

Fewer 90-day readmissions and 2-year prosthetic joint infections were observed among diabetic patients treated with semaglutide undergoing total hip arthroplasty (THA). [28] Nevertheless, there were no notable differences observed in medical complication rates, duration of hospital stays, same-day surgery expenses, or 90-day episode costs.

**The use of metformin in patients with osteoarthritis**

Metformin is a popular first-line oral anti-hyperglycemic drug in the obese and T2DM patient population. Its pleiotropic effects are due to its beneficial effects on the endothelium along with its antioxidant and anti-inflammatory properties. [29] Metformin acts by enhancing peripheral glucose uptake, inhibiting hepatic gluconeogenesis, and increasing insulin sensitivity. [4] Its positive effects encompass reducing insulin resistance, promoting weight loss, and lowering the occurrence of cardiovascular events and mortality. [4,29] Additionally, its anti-inflammatory action through AMPK activation holds the potential for slowing OA progression by maintaining cartilage integrity and lowering levels of inflammatory markers. [4,30] A study conducted on a population of people with OA and T2DM showed lower joint replacement surgery rates in those using a combination of COX-2 inhibitor and metformin therapy, compared to a group using COX-2 inhibitor alone. [31]

| Used drug | Summary of positive effects | Study |
|---|---|---|
| Liraglutide | • **Significantly greater weight loss observed in the liraglutide group compared to placebo,**<br>• **Pain intensity was comparable in both groups** | [23] |
| Semaglutide | • **Significantly greater weight loss** | [24] |

| | | |
|---|---|---|
| | • **Reduction in pain severity measured by WOMAC**<br>• **Improvements in function and quality of life as assessed by SF-36v2.**<br>• **Longer distance in the 6-minute walk test** | |
| Semaglutide | • **Lower odds of sepsis, prosthetic joint infections, and readmission.**<br>• **Increased risk of myocardial infarction, acute kidney injury, pneumonia, and hypoglycemic events.** | [27] |
| Semaglutide | • **Fewer 90-day readmissions and 2-year prosthetic joint infections among diabetic patients treated with semaglutide THA** | [28] |
| GLP-1 analogs | • **Significant weight loss**<br>• **Lower pain intensity in WOMAC pain subscale**<br>• **Lower risk of knee surgery**<br>• **Lower cartilage loss velocity and fewer intra-articular injections of steroids.** | [25] |
| Metformin | • **Lower joint replacement surgery rates** | [31] |

Tabel 1. Overview of the beneficial outcomes of drug applications in the referenced studies.

## 5. Conclusion

OA is a common problem in daily medical practice due to its high prevalence, as well as the lack of disease-modifying treatments. Pain is the primary reason patients seek medical assistance. Often, patients have difficulty complying with recommendations that include lifestyle modification. Current symptomatic treatment fails to provide the expected improvement, leading to chronic pain, decreased mobility, and functional limitations. Due to the burden of co-morbidities, joint replacement surgeries, which are sometimes the only viable option, come with potential complications. GLP-1-based therapies and metformin, with

their pleiotropic effects, could offer benefits by reducing cytokine-driven joint inflammation, supporting cartilage repair, and promoting weight loss in patients with OA. Further investigation is needed to confirm these findings and determine the most effective treatment strategies for OA.

**Disclosure:**

**Authors' contribution:**

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**References**

1. Long H, Liu Q, Yin H, et al. Prevalence Trends of Site-Specific Osteoarthritis From 1990 to 2019: Findings From the Global Burden of Disease Study 2019. Arthritis Rheumatol. 2022;74(7):1172-1183. doi:10.1002/art.42089

2. Meurot C, Jacques C, Martin C, et al. Targeting the GLP-1/GLP-1R axis to treat osteoarthritis: A new opportunity?. *J Orthop Translat*. 2022;32:121-129. Published 2022 Feb 25. doi:10.1016/j.jot.2022.02.001

3. Xia B, Di Chen, Zhang J, Hu S, Jin H, Tong P. Osteoarthritis pathogenesis: a review of molecular mechanisms. *Calcif Tissue Int*. 2014;95(6):495-505. doi:10.1007/s00223-014-9917-9

4. Halabitska I, Babinets L, Oksenych V, Kamyshnyi O. Diabetes and Osteoarthritis: Exploring the Interactions and Therapeutic Implications of Insulin, Metformin, and GLP-1-Based Interventions. *Biomedicines*. 2024;12(8):1630. Published 2024 Jul 23. doi:10.3390/biomedicines12081630

5. Meurot C, Martin C, Sudre L, et al. Liraglutide, a glucagon-like peptide 1 receptor agonist, exerts analgesic, anti-inflammatory and anti-degradative actions in osteoarthritis. *Sci Rep*. 2022;12(1):1567. Published 2022 Jan 28. doi:10.1038/s41598-022-05323-7

6. Veronese N, Cooper C, Reginster JY, et al. Type 2 diabetes mellitus and osteoarthritis. *Semin Arthritis Rheum*. 2019;49(1):9-19. doi:10.1016/j.semarthrit.2019.01.005

7. Messier SP, Loeser RF, Miller GD, et al. Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis: the Arthritis, Diet, and Activity Promotion Trial. *Arthritis Rheum*. 2004;50(5):1501-1510. doi:10.1002/art.20256

8. Katz JN, Arant KR, Loeser RF. Diagnosis and Treatment of Hip and Knee Osteoarthritis: A Review. JAMA. 2021 Feb 9;325(6):568-578. doi: 10.1001/jama.2020.22171. PMID: 33560326; PMCID: PMC8225295.

9. Cicuttini FM, Proietto J, Lim YZ. Our biology working against us in obesity: A narrative review on implications for management of osteoarthritis. *Osteoarthr Cartil Open*. 2023;5(4):100407. Published 2023 Sep 9. doi:10.1016/j.ocarto.2023.100407

10. Amanatullah DF, Ohanisian L, Bailony R. Medications Available for Weight Reduction in Elective Total Joint Arthroplasty. *JBJS Rev*. 2020;8(6):e0123. doi:10.2106/JBJS.RVW.19.00123

11. Felson DT. Glucagon-Like Peptide-1 Receptor Agonists and Osteoarthritis. *N Engl J Med*. 2024;391(17):1643-1644. doi:10.1056/NEJMe2409972

12. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. *Arthritis Rheum*. 2000;43(9):1905-1915. doi:10.1002/1529-0131(200009)43:9<1905::AID-ANR1>3.0.CO;2-P

13. Pendleton A, Arden N, Dougados M, et al. EULAR recommendations for the management of knee osteoarthritis: report of a task force of the Standing Committee

for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Ann Rheum Dis*. 2000;59(12):936-944. doi:10.1136/ard.59.12.936

14. Ruze R, Liu T, Zou X, et al. Obesity and type 2 diabetes mellitus: connections in epidemiology, pathogenesis, and treatments. *Front Endocrinol (Lausanne)*. 2023;14:1161521. Published 2023 Apr 21. doi:10.3389/fendo.2023.1161521

15. Piva SR, Susko AM, Khoja SS, Josbeno DA, Fitzgerald GK, Toledo FG. Links between osteoarthritis and diabetes: implications for management from a physical activity perspective. *Clin Geriatr Med*. 2015;31(1):67-viii. doi:10.1016/j.cger.2014.08.019

16. Lee YS, Jun HS. Anti-Inflammatory Effects of GLP-1-Based Therapies beyond Glucose Control. *Mediators Inflamm*. 2016;2016:3094642. doi:10.1155/2016/3094642

17. Hunter DJ. Pharmacologic therapy for osteoarthritis--the era of disease modification. *Nat Rev Rheumatol*. 2011;7(1):13-22. doi:10.1038/nrrheum.2010.178

18. Kim S, Jeong J, Jung HS, et al. Anti-inflammatory Effect of Glucagon Like Peptide-1 Receptor Agonist, Exendin-4, through Modulation of IB1/JIP1 Expression and JNK Signaling in Stroke. *Exp Neurobiol*. 2017;26(4):227-239. doi:10.5607/en.2017.26.4.227

19. Reed J, Bain S, Kanamarlapudi V. Recent advances in understanding the role of glucagon-like peptide 1. *F1000Res*. 2020;9:F1000 Faculty Rev-239. Published 2020 Apr 6. doi:10.12688/f1000research.20602.1

20. Wong CK, McLean BA, Baggio LL, et al. Central glucagon-like peptide 1 receptor activation inhibits Toll-like receptor agonist-induced inflammation. *Cell Metab*. 2024;36(1):130-143.e5. doi:10.1016/j.cmet.2023.11.009

21. Mert I, Cetinkaya A, Gurler M, et al. Anti-inflammatory potential of liraglutide, a glucagon-like peptide-1 receptor agonist, in rats with peripheral acute

inflammation. *Inflammopharmacology*. 2022;30(3):1093-1105. doi:10.1007/s10787-022-00978-0

22. Halloum W, Dughem YA, Beier D, Pellesi L. Glucagon-like peptide-1 (GLP-1) receptor agonists for headache and pain disorders: a systematic review. *J Headache Pain*. 2024;25(1):112. Published 2024 Jul 12. doi:10.1186/s10194-024-01821-3

23. Gudbergsen H, Overgaard A, Henriksen M, et al. Liraglutide after diet-induced weight loss for pain and weight control in knee osteoarthritis: a randomized controlled trial. *Am J Clin Nutr*. 2021;113(2):314-323. doi:10.1093/ajcn/nqaa328

24. Bliddal H, Bays H, Czernichow S, et al. Once-Weekly Semaglutide in Persons with Obesity and Knee Osteoarthritis. *N Engl J Med*. 2024;391(17):1573-1583. doi:10.1056/NEJMoa2403664

25. Zhu H, Zhou L, Wang Q, et al. Glucagon-like peptide-1 receptor agonists as a disease-modifying therapy for knee osteoarthritis mediated by weight loss: findings from the Shanghai Osteoarthritis Cohort. *Ann Rheum Dis*. 2023;82(9):1218-1226. doi:10.1136/ard-2023-223845

26. George J, Klika AK, Navale SM, Newman JM, Barsoum WK, Higuera CA. Obesity Epidemic: Is Its Impact on Total Joint Arthroplasty Underestimated? An Analysis of National Trends. *Clin Orthop Relat Res*. 2017;475(7):1798-1806. doi:10.1007/s11999-016-5222-4

27. Magruder ML, Yao VJH, Rodriguez AN, Ng MK, Sasson V, Erez O. Does Semaglutide Use Decrease Complications and Costs Following Total Knee Arthroplasty?. *J Arthroplasty*. 2023;38(11):2311-2315.e1. doi:10.1016/j.arth.2023.05.071

28. Magruder ML, Miskiewicz MJ, Rodriguez AN, Mont MA. Semaglutide Use Prior to Total Hip Arthroplasty Results in Fewer Postoperative Prosthetic Joint Infections and Readmissions. *J Arthroplasty*. 2024;39(3):716-720. doi:10.1016/j.arth.2023.12.023

29. Markowicz-Piasecka M, Sadkowska A, Huttunen KM, Podsiedlik M, Mikiciuk-Olasik E, Sikora J. An investigation into the pleiotropic activity of metformin. A glimpse of haemostasis. *Eur J Pharmacol*. 2020;872:172984. doi:10.1016/j.ejphar.2020.172984

30. Li J, Zhang B, Liu WX, et al. Metformin limits osteoarthritis development and progression through activation of AMPK signalling [published correction appears in Ann Rheum Dis. 2020 Sep;79(9):e119. doi: 10.1136/annrheumdis-2019-216713corr1]. *Ann Rheum Dis*. 2020;79(5):635-645. doi:10.1136/annrheumdis-2019-216713

31. Lu CH, Chung CH, Lee CH, et al. Combination COX-2 inhibitor and metformin attenuate rate of joint replacement in osteoarthritis with diabetes: A nationwide, retrospective, matched-cohort study in Taiwan. *PLoS One*. 2018;13(1):e0191242. Published 2018 Jan 31. doi:10.1371/journal.pone.0191242