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CLINICAL SCIENCE

Glucagon-like peptide-1 receptor agonists as a disease-modifying therapy for knee osteoarthritis mediated by weight loss: findings from the Shanghai Osteoarthritis Cohort

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ABSTRACT

Objective Obesity is a risk factor for knee osteoarthritis (KOA) development and progression. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are indicated for type 2 diabetes mellitus (T2DM) and obesity. However, whether KOA patients can benefit from GLP-1RA therapies has not been sufficiently investigated, especially in the long term.

Methods The Shanghai Osteoarthritis Cohort study is a prospective, observational, multicentre study of >40 000 adults with clinically diagnosed osteoarthritis aged >45 years in Shanghai. We identified all KOA participants with comorbid T2DM enrolled from 1 January 2011 to 1 January 2017. Primary outcome was incidence of knee surgery after enrolment. Secondary outcomes included pain-relieving medication use, number of intra-articular therapies, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and medial femorotibial joint cartilage thickness. To evaluate the effects of GLP-1RA, we performed before-and-after comparison and comparison with participants who had no GLP-1RA exposure.

Results For an intergroup comparison (non-GLP-1RA vs GLP-1RA), more weight loss (adjusted mean difference in weight change from baseline −7.29 kg (95% CI −8.07 to −6.50 kg), p<0.001) and lower incidence of knee surgery (93/1574 (5.9%) vs 4/233 (1.7%), adjusted p=0.014) were observed in the GLP-1RA group. Statistically significant differences in mean change from baseline for the WOMAC total and pain subscale scores were observed (adjusted mean difference in WOMAC total score −1.46 (95% CI −2.84 to −0.08), p=0.038; adjusted mean difference in WOMAC pain subscore −3.37 (95% CI −5.79 to −0.94), p=0.007). Cartilage-loss velocity of the medial femorotibial joint was significantly lower in the GLP-1RA group postadjustment for baseline characteristics (adjusted mean difference −0.02 mm (95% CI −0.03 to −0.002 mm), p=0.004). For the before-and-after comparison within the GLP-1RA group, we observed a significant decrease of symptom-relieving medication consumption and cartilage loss velocity of medial femorotibial joint (after-treatment vs before-treatment: −0.03±0.05 vs −0.05±0.07 mm/year, p<0.001). The association between GLP-1RA exposure and decreased incidence of knee surgery was mediated by weight reduction (mediation proportion: 32.1%), instead of glycaemic control (too small to calculate).

Conclusion With sufficient treatment duration, GLP-1RA therapies might be disease-modifying for KOA patients with comorbid T2DM, possibly mediated by weight loss. Further investigation is needed to elucidate effects of GLP-1RA on disease process, joint structure and patient-reported outcomes of osteoarthritis.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Weight management is considered as a first-line intervention for knee osteoarthritis (KOA). Recent evidence has indicated that glucagon-like peptide-1 receptor agonists (GLP-1RAs), which have effects on reducing weight, provide a small improvement in short-term patient-reported outcomes.

WHAT THIS STUDY ADDS

⇒ Results of this observational study of KOA patients with comorbid type 2 diabetes mellitus indicated long-term effects of GLP-1RAs on KOA progression, with a lower incidence rate of knee surgery in patients receiving GLP-1RAs than in the control group (non-GLP-1RA exposure).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ GLP-1RAs might be potentially disease-modifying OA drugs for KOA, although the benefits might require a long treatment duration.

INTRODUCTION

Osteoarthritis (OA) is a highly prevalent, disabling disease with a tremendous individual and socioeconomic burden.[1] According to the Global Burden of Disease Study 2019,[2] the disease burden of OA has been growing rapidly worldwide over the past decades.[3] Controlling modifiable risk factors, most importantly, maintaining an appropriate weight/body mass index (BMI), is vital for preventing disease development and progression.[4] Multiple guidelines recommend weight control as a basic measure for long-term OA management.[5–7] However, the disease burden of OA associated with a high weight/BMI has remained a continuous upward trend worldwide in the past decades.[8 9] Notably, despite the long-term benefits of weight

control on knee OA (KOA), weight loss via diet modification, physical activities and/or medications only lead to a small improvement in patient-reported outcomes (PROs) of uncertain clinical importance in short term (<2 years).[10 11]

Sustaining weight control in the long term remains a major challenge for the general population including KOA patients.[12–14] Many clinical guidelines recommend adjunctive medications for obese persons, especially those with comorbidities (such as T2DM, cardiovascular diseases and non-alcoholic fatty liver disease).[15–17] Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are a class of medications that are effective treatment for patients with type 2 diabetes mellitus (T2DM) and weight control by stimulating insulin secretion, suppressing glucagon secretion, delaying gastric emptying and decreasing appetite.[18 19] Many GLP-1RAs, including semaglutide, liraglutide and dulaglutide, have been approved for T2DM and weight management.[20] Patients treated with liraglutide therapy lost more body weight than those treated with placebo for at 1 year (a difference of −5.6 kg; 95% CI −6.0 to −5.1 kg).[21] In the STEP 1 trial, semaglutide treatment achieved sustained and clinically important reduction in body weight (estimated treatment difference compared with placebo −12.7 kg; 95% CI −13.7 to −11.7 kg).[22]

Thus, GLP-1RAs are believed to be potential disease-modifying OA drugs for treating OA, with the rationale that GLP-RAs could prevent cartilage loss by reducing the mechanical stress from body weight[23] and PROs by reducing pain sensitivity.[24] To the best of our knowledge, only one clinical study has investigated the efficacy of liraglutide on knee OA (KOA), in which liraglutide did not reduce knee pain compared with placebo at 1 year in KOA patients with obesity or those that are overweight.[11] However, this trial started with a required weight loss of >5% before randomisation and only a small weight loss (<5%) was achieved after liraglutide treatment. This might explain why the results were not significant. Thus, a longer study duration with significant weight loss/maintenance and structural data might be needed to answer this question. In this study, to explore potential disease-modifying effects of GLP-1RAs, we analysed prospectively collected, multicentre, observational data from the Shanghai Osteoarthritis Cohort (SOC) study.

METHODS

Patients

We identified all KOA participants who were enrolled in the SOC study from 1 January 2011 to 1 January 2017. The SOC study prospectively recruited more than 40 000 adults with clinically diagnosed OA aged >45 years from four hospitals in Shanghai. For this study, we included patients with comorbid T2DM at baseline who had at least completed the 5-year follow-up. Patients were eligible for this study if they had baseline bilateral plain radiographs demonstrating Kellgren and Lawrence (K-L) grades 1–3 KOA (K-L grade was recorded according to the more severe side).[25] Participants were excluded from the analyses if they had secondary OA, K–L grade 0 or 4, diabetic vascular diseases, diabetic foot and knee surgery history at baseline. The clinical diagnosis of KOA was performed by clinical specialists in orthopaedic and/or sports medicine. It was determined based on the patient history, physical examination, and laboratory and radiographic findings.[26] These patients were grouped according to whether they received GLP-1RA therapies for the treatment of T2DM. Notably, patients who received GLP-1RA for less than 2 years were also excluded from the analysis (online supplemental figure S1).

Baseline data collection and PROs

Baseline demographic characteristics, including age, sex and weight, were self-reported by the participants. A weight change greater than 5% was considered clinically relevant for KOA.[27] Standard weight-bearing anteroposterior and lateral plain radiographs of the knee were obtained at enrolement, and the K-L scoring system was used to grade the radiographic stages of KOA. The K-L grades were reviewed and rated by an independent radiographic evaluation committee consisting of three radiologists specialising in musculoskeletal radiology. A consensus on the grading was achieved after discussion. When the two knees had different K-L grades, the final readout used in the current study was recorded according to the more severe side (index side). For PROs, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire, a well-validated hip and KOA pain instrument consisting of 24 questions, was used to assess three separate dimensions (pain, physical function and stiffness) in KOA.[28] In this study, for convenience and comparison with previously published literature, all subscales were normalised to scores within a range of 0–100. The minimal clinically important difference (MCID) for the WOMAC total score was 7 (95% CI 4 to 10); pain subscale, 9 (95% CI 6 to 12); function subscale, 6 (95% CI 3 to 9); and stiffness subscale, 7 (95% CI 6 to 9).[29]

Incident knee surgery

Incident knee surgery was defined as all surgical procedures performed to treat KOA after patient enrolment in SOC. In this study, incident knee surgery included total knee arthroplasty, unicompartmental knee arthroplasty, arthroscopic procedures and high tibial osteotomy. Notably, although arthroscopic procedures, including lavage, debridement and arthroscopic partial meniscectomy, are ineffective and even harmful for KOA patients,[30 31] evidence published to date has not led to a major decline in arthroscopic procedures for managing KOA.[32 33] Thus, we also considered incident arthroscopic procedures as meaningful events of poor symptom control in this observational study. We adopted the latest PROs prior to surgery and analysed the structural outcomes using the earliest and latest MRI scans during the study period.

Definition of recommended daily dose and morphine milligram equivalents

To allow direct comparisons of analgesics of different potencies and formulations, we converted the quantities of non-opioid medication use, including acetaminophen and topical and oral non-steroidal anti-inflammatory drugs (NSAIDs) into recommended daily doses (RDDs). RDD was defined as the RDD for treating OA, if applicable. When multiple recommended doses were present, the RDD was calculated by averaging the highest and lowest recommended doses. When no specific recommended dose regarding OA was present, the RDD was calculated by averaging the highest and lowest recommended doses for all indications. The consumption of opioid analgesics was converted into morphine milligram equivalents (MMEs) for each opioid-containing product. The MME conversion factors and RDD of analgesics were collected from various sources, and the details are available in online supplemental table S1 and S2.

Measurement of cartilage loss velocity

We measured the cartilage thickness in the medial femorotibial cartilage plates (tibial and weight-bearing femur): mean cartilage thickness over the total area of the subchondral bone (mm).[34]

The weight-bearing region of the femoral condyles was defined as the area between the intercondylar notch and 60% of the distance to the posterior end of the femoral condyles.[35] The cartilage loss velocity was calculated as follows: cartilage loss velocity (mm/year)=(cartilage thickness at time point A)–(cartilage thickness at time point B)/(duration between time points A and B). To compare the GLP-1RA and non-GLP-1RA groups, we adopted the earliest and latest MRI scans for the index side knee during the study period. We only included patients who underwent at least two MRI scans with a minimal 6-month interval for comparison of cartilage loss. Full imaging methods appear in online supplemental material.

Before-and-after comparison within the GLP-1RA group

For before-and-after comparison, we included patients who had a minimal 2-year follow-up before the start of GLP-1RA therapy. We included 126 of 233 patients from the GLP-1RA group before and after the comparison. For structural comparison, we needed at least two MRI scans for both periods (before and after GLP-1RA therapy).

Statistical analysis

Continuous and categorical variables are presented as means±SD and counts (percentages), unless otherwise indicated (median (quartile)). Univariate analyses were conducted using the t-test (or Mann-Whitney U test) and Pearson's χ^2 test (or Fisher's exact test). Multivariable regression models (linear or logistic regression) were used to compare the mean changes in related variables and knee surgery incidence between the GLP-1RA therapy and non-GLP-1RA therapy groups. All multivariable analyses were adjusted for baseline covariates (age, sex, BMI, K-L grade and WOMAC total score) or other covariates with a $p<0.2$ in univariate analysis. The effects were reported with an adjusted mean difference and its 95% CI.

Considering that the effect of GLP-1RA on outcomes of KOA may primarily rely on the change in weight after receiving GLP-1RA,[36–38] and the poor control of blood glucose may be a risk factor for the progression of OA,[39–42] we established an 'exposure–mediator–outcome' model and viewed weight and hemoglobin A1c (HbA1c) change as a mediator. In this model, the total effect of exposure (GLP-1RA usage) on the outcome (knee surgery) was divided into the 'direct effect' of exposure outcome and the 'indirect effect' on a pathway through the mediator (weight change after using GLP-1RA) (figure 1). We performed a model-based causal mediation analysis to calculate the proportion of 'indirect effect' and its 95% CI (simulated by the quasi-Bayesian Monte Carlo method based on normal approximation[43]) to estimate the proportion of GLP-1RA use to outcomes (knee surgery, cartilage loss velocity and WOMAC pain subscore) effect attributable to the pathway of weight and HbA1c change. The set of pre-exposure covariates (age, sex, WOMAC total score, BMI and K-L grade) satisfied the assumption of confounding adjustment for the exposure–mediator–outcome relationships.

Three sensitivity analyses were conducted. First, to minimise the potential bias due to weight change experienced by participants before GLP-1RA exposure, we conducted an analysis of weight and PROs using the most recent weight and PROs before GLP-1RA usage. Second, to prevent the occurrence of a possible floor effect where differences in score reductions might be difficult to discern, we excluded patients with WOMAC total score lower than 7 (which is the MCID for the WOMAC total score) at baseline. Third, it could find some participants had GLP-1RA exposure before enrolment and we were unable to collect data before enrolment. To partially overcome this problem, we excluded those patients who had GLP-1RA exposure within the initial half year after enrolment in the sensitivity analysis. In addition, we performed subgroup analyses that were stratified based on baseline KL grade and change in weight.

All statistical assessments were performed in a two-sided fashion, and a $p<0.05$ was considered statistically significant. Statistical analysis was conducted using IBM SPSS V.26.0, and the 'mediation' package in R V.4.1.2 was applied for mediation analysis in this study.[44]

RESULTS

We included 1807 clinically diagnosed KOA patients with comorbid T2DM for analysis from the established cohort. GLP-1RA and non-GLP-1RA had 233 and 1574 participants, respectively (table 1).

The enrolment year for participants and the year of initial incident exposure to GLP-1RA of participants are presented in online supplemental table S3 and S4, respectively. The mean treatment duration of GLP-1RAs was 4.9±1.9 years. The GLP-1RA and non-GLP-1RA groups had similar mean weight at baseline (66.0±12.2 vs 65.1±12.3, p=0.31), whereas we observed a substantial reduction in weight in the GLP-1RA group at the last follow-up (change from baseline, GLP-1RA vs non-GLP-1RA, −4.60±8.07 vs 2.69±5.23, p<0.001) (table 2). Clinically relevant gains in weight were observed in 18.5% (43/233) and 45.9% (722/1574) of patients in the GLP-1RA and non-GLP-1RA groups, respectively; clinically relevant reductions in weight were observed in 57.9% (135/233) and 13.4% (211/1574) of the GLP-1RA and non-GLP-1RA groups, respectively (online supplemental table S5). Online supplemental tables S6 and S7 show the results for comparison of outcomes between participants who achieved a clinically significant reduction in weight and those who did not. The baseline demographic and clinical characteristics of the GLP-1RA (n=233) and non-GLP-1RA (n=1574) groups are summarised in table 1; the history of GLP-1RA use

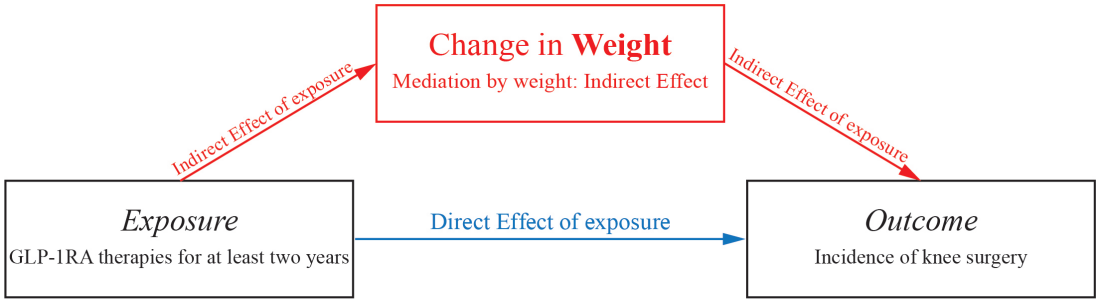

Figure 1 Directed acyclic graph for mediation relationships.

Table 1 Baseline patient characteristics

	GLP-1RA (n=233)	Non-GLP-1RA (n=1574)
Age, years	60.7 (8.7)	61.2 (8.6)
Sex, No. (%)		
Male	59 (25.3%)	429 (27.3%)
Female	174 (74.7%)	1145 (72.7%)
Weight, kg	66.0 (12.2)	65.1 (12.3)
BMI, kg/m^2	25.2 (3.7)	25.1 (3.6)
HbA1c, %	7.3 (1.6)	7.2 (1.5)
Duration of diabetes, years	8.1 (6.0)	8.3 (5.8)
Duration since initial clinically diagnosed KOA, years	5.8 (5.8)	5.5 (5.8)
SBP (mmHg)	129.3 (16.2)	130.5 (16.4)
DBP (mmHg)	79.5 (10.9)	80.1 (11.3)
Current smoker, No. (%)	24 (10.3%)	173 (11.0%)
Use antidiabetes agents, No. (%)		
Oral antidiabetes drugs	218 (93.5%)	1454 (92.4%)
Insulin	148 (63.5%)	991 (63.0%)
Kellgren-Lawrence grade, No. (%)		
Grade I	30 (12.9%)	221 (14.0%)
Grade II	131 (56.2%)	875 (55.6%)
Grade III	72 (30.9%)	478 (30.4%)
Predominantly lateral KOA, No. (%)	42 (18.0%)	298 (18.9%)
WOMAC total score	19.3 (9.7)	19.8 (9.6)
WOMAC pain subscore	18.3 (13.8)	17.4 (12.3)
WOMAC stiffness subscore	18.2 (12.1)	18.3 (15.5)
WOMAC function subscore	19.7 (12.6)	20.7 (11.9)

Data are shown as means (SDs) unless otherwise indicated.
WOMAC questionnaire and all its subscales were normalised to scores within a range of 0–100.
BMI, body mass index; DBP, diastolic blood pressure; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, hemoglobin A1c; KOA, knee osteoarthritis; SBP, systolic blood pressure; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

is shown in online supplemental table S8. Based on the knee radiographs, 42 out of 233 (18.0%) individuals in the GLP-1RA group and 298 out of 1574 (18.9%) individuals in the control group demonstrated predominantly lateral OA.

Comparison of PROs and incident knee surgery between the GLP-1RA and non-GLP-1RA groups

Statistically significant differences were observed in the mean absolute change from baseline for the WOMAC total and pain subscale scores (adjusted mean difference in WOMAC total score −1.46 (95% CI −2.84 to −0.08), p=0.038; adjusted mean difference in WOMAC pain subscore −3.37 (95% CI −5.79 to −0.94), p=0.007). Compared with the non-GLP-1RA (93/1574) group, we observed a substantially lower incidence of knee surgery in the GLP-1RA (4/233) group (5.9% vs 1.7%, adjusted p=0.014) (table 2). Sensitivity analysis of weight and PROs using the most recent weight and PROs before GLP-1RA usage also showed the statistically significant results for WOMAC total and pain subscale scores (adjusted mean difference in WOMAC total score −2.03 (95% CI −3.41 to −0.65), p=0.004; adjusted mean difference in WOMAC pain subscore −3.93 (95% CI −6.29 to −1.56), p=0.001) (online supplemental tables S9). Additionally, sensitivity analyses of PROs and incident knee surgery after excluding patients with low WOMAC total scores at baseline also showed stable results (adjusted mean difference in WOMAC total score −1.49 (95% CI −2.93 to −0.05), p=0.043; adjusted mean difference in WOMAC pain subscore −3.31 (95% CI −5.85 to −0.77), p=0.011; incidence of knee surgery, GLP-1RA vs non-GLP-1RA, 1.9% vs 5.7%, adjusted p=0.026) (online supplemental tables S10-11). The proportion of patients who achieved MCID improvement in the two groups were compared and are presented in online supplemental table S12 and S13. The association between GLP-1RA exposure and WOMAC pain subscore was not mediated by weight reduction and HbA1c change (online supplemental table S14). For the GLP-1RA group, 2 underwent TKA and 2 underwent arthroscopic procedures; for the non-GLP-1RA group, 30 underwent TKA, 1 underwent UKA, 6 underwent HTO, 53 underwent arthroscopic procedures and 3 underwent TKA following arthroscopic procedures (online supplemental table S15).The association between GLP-1RA exposure and decreased incidence of knee surgery was substantially mediated by weight reduction, but much less so by HbA1c change (the mediation proportion for weight reduction was 32.1% for GLP-1RA exposure) (table 3).

In subgroup analysis with patients who reached clinically relevant reduction on weight (defined >5%), we observed a trend towards significance for the comparison between GLP-1RA and non-GLP-1RA groups (0/135 (0.0%) vs 6/211 (2.8%), p=0.085) (online supplemental table S16). For sensitivity analysis with only incident users of GLP-1RA (defined as no exposure of GLP-1RA in the initial 6 months after enrolment), compared with the non-GLP-1RA group, we also observed significant differences in mean change from baseline for the WOMAC total and pain subscale scores (adjusted mean difference in WOMAC total score −1.57 (95% CI −3.03 to −0.12), p=0.034; adjusted mean difference in WOMAC pain subscore −3.15 (95% CI −5.70 to −0.60), p=0.016) and a lower incidence of knee surgery in the GLP-1RA group (5.9% vs 1.9%, adjusted p=0.027) (online supplemental table S17).

Comparison of symptom-relieving medication use between the GLP-1RA and non-GLP-1RA groups

We observed numerical but statically nonsignificant decrease in the GLP-1RA group compared with the non-GLP-1RA group in terms of annual consumption of oral NSAIDs and acetaminophen (15.2±13.8 vs 16.9±14.5 RDD/year, p=0.10), topical NSAIDs (21.7±22.7 vs 23.6±22.8 RDD/year, p=0.22), opioids (109.0±190.0 vs 126.2±205.6 MME/year, p=0.20), number of intra-articular therapies (1.07±1.99 vs 1.30±2.12, p=0.10). The GLP-1RA group required fewer number of intra-articular injection of steroids compared with the non-GLP-1RA group (0.13±0.28 vs 0.22±0.39, p<0.001) (online supplemental figure S2, table 2).

Comparison of structural outcomes between the GLP-1RA and non-GLP-1RA groups

We identified 188 and 1267 patients who received at least two MRIs in the GLP-1RA and non-GLP-1RA groups, respectively. The mean duration between the earliest and latest MRI scanning was 4.5±2.1 and 4.3±2.3 years for participants in the GLP-1RA and non-GLP-1RA groups, respectively. Thirty-two out of 188 (17.0%) individuals in the GLP-1RA group and 231 out of 1267 (18.2%) individuals in the control group showed predominantly lateral OA. In this subcohort, cartilage-loss velocity of the medial femorotibial joint was significantly lower in the GLP-1RA group than in the non-GLP-1RA group after adjustment for baseline characteristics, including age, sex, BMI, WOMAC total score and K-L grades (−0.05±0.08 vs −0.07±0.10 mm/year; adjusted mean difference, 0.02 mm (95% CI 0.002 to 0.033), adjusted

Table 2 Comparison of treatment, PROs and incident knee surgery between GLP-1RA and non-GLP-1RA groups

	GLP-1RA (n=233)	Non-GLP-1RA (n=1574)	Adjusted mean difference* (95% CI)	P value	Adjusted P value*
Weight, kg					
At last follow-up	61.4 (14.0)	67.8 (13.6)	-	<0.001	-
Change from baseline	−4.60 (8.07)	2.69 (5.23)	−7.29 (−8.07, −6.50)	<0.001	<0.001
HbA1c, %					
At last follow-up	7.3 (1.5)	7.3 (1.6)	-	0.79	-
Change from baseline	0.02 (1.26)	0.08 (1.23)	−0.05 (−0.22, 0.12)	0.53	0.56
WOMAC total score					
At last follow-up	21.9 (10.3)	23.4 (10.0)	-	0.039	-
Change from baseline	2.65 (14.17)	3.58 (13.99)	−1.46 (−2.84, −0.08)	0.35	0.038
WOMAC pain subscore					
At last follow-up	17.1 (12.6)	19.4 (12.5)	-	0.010	-
Change from baseline	−1.18 (19.00)	2.01 (17.60)	−3.37 (−5.79, −0.94)	0.011	0.007
WOMAC stiffness subscore					
At last follow-up	24.0 (15.8)	24.7 (15.8)	-	0.54	-
Change from baseline	5.79 (21.08)	6.33 (20.43)	−1.05 (−3.35, 1.25)	0.71	0.37
WOMAC function subscore					
At last follow-up	23.1 (12.3)	24.4 (12.3)	-	0.13	-
Change from baseline	3.41 (17.65)	3.72 (17.25)	−0.95 (−2.71, 0.81)	0.80	0.29
Annual consumption of oral NSAIDs and acetaminophen, RDD/year	15.2 (13.8)	16.9 (14.5)	−1.63 (−3.62, 0.36)	0.10	0.11
Annual consumption of topical NSAIDs, RDD/year	21.7 (22.7)	23.6 (22.8)	−1.92 (−5.06, 1.21)	0.22	0.23
Annual consumption of opioids, MME/year	109.0 (190.0)	126.2 (205.6)	−17.07 (−45.09, 10.94)	0.20	0.23
Total no of intra-articular therapies	7.5 (13.4)	9.7 (15.3)	-	0.022	-
Annual no of intra-articular therapies, per year	1.07 (1.99)	1.30 (2.12)	−0.24 (−0.53, 0.05)	0.10	0.10
Annual no of intra-articular injection of steroids, per year	0.13 (0.28)	0.22 (0.39)	−0.087 (−0.14, − 0.036)	<0.001	0.001
Follow-up, years	7.7 (1.5)	7.8 (1.6)	-	0.71	-
Knee surgery	4 (1.7%)	93 (5.9%)	-	0.005	0.014

Data are shown as means (SDs) unless otherwise indicated.
WOMAC questionnaire and all its subscales were normalised to scores within a range of 0–100.
*Mean difference and p value adjusted for age, sex, baseline BMI, baseline Kellgren-Lawrence grade and baseline WOMAC total score.
GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, hemoglobin A1c; MME, milligram morphine equivalents; NSAIDs, non-steroidal anti-inflammatory drugs; PROs, patient-reported outcomes; RDD, recommended daily dose; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

p=0.026) (table 4). For subgroup and sensitivity analyses for (1) patients who reached clinically relevant reduction on weight; (2) incident users of GLP-1RA and (3) with different baseline K-L grades, we have summarised data in online supplemental table S18–20. The association between GLP-1RA exposure and cartilage loss velocity was not mediated by weight reduction and HbA1c change (online supplemental table S21).

Before-and-after comparison within the GLP-1RA group

We observed a significant decrease in pain-relieving medication use after GLP-1RA treatment compared with pretreatment (oral NSAIDs and acetaminophen (post-treatment vs pretreatment, 14.0±12.2 vs 16.8±14.7 RDD/year, p<0.001), topical NSAIDs (16.6±19.6 vs 24.5±24.3 RDD/year, p<0.001), opioids (93.5±182.3 vs 97.7±195.1 MME/year, p=0.70)). Patients required fewer intra-articular therapies (0.76±1.40 vs 1.35±2.67, p<0.001) and fewer intra-articular injections of steroids (0.10±0.21 vs 0.18±0.41, p<0.001) after GLP-1RA therapies. The cartilage loss velocity of the medial femorotibial joint was significantly lower after GLP-1RA treatment compared with the pretreatment level (−0.03±0.05 vs −0.05±0.07 mm/year, n=61, p<0.001) (online supplemental figure S3, table 5).

DISCUSSION

This is the first clinical investigation to examine the long-term effects of GLP-1RA on KOA in patients with comorbid T2DM.

Table 3 Mediation effects for knee outcomes: association of GLP-1RA therapies with the incidence of knee surgery

Exposure: GLP-1RA	Mediator: weight change from baseline Incidence of knee surgery* (95% CI)	P value	Mediator: HbA1c change from baseline Incidence of knee surgery† (95% CI)	P value
Controlled direct effect	−0.027 (−0.050, 0.008)‡	0.095	−0.041 (−0.060, −0.012)‡	0.014
Indirect effect	−0.015 (−0.027, −0.005)	0.004	0.000 (−0.001, 0.002)	0.78
Total effect	−0.042 (−0.061, −0.016)	0.006	−0.040 (−0.060, −0.012)	0.015
Proportion mediated	32.1% (11.0%, 142.8%)	0.010	Proportion too small to calculate—not a mediator	0.78

*The model adjusted for age, sex, baseline BMI, baseline Kellgren-Lawrence grade and baseline WOMAC total score.
†The model adjusted for age, sex, baseline HbA1c, baseline BMI, baseline Kellgren-Lawrence grade and baseline WOMAC total score.
‡Values are unstandardised regression coefficients representing incidence of knee surgery.
BMI, body mass index; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, hemoglobin A1c; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index .

Table 4 Comparison of structural outcomes between the GLP-1RA and non-GLP-1RA groups

	GLP-1RA (n=188)	Non-GLP-1RA (n=1267)	Adjusted mean difference* (95% CI)	P value	Adjusted p value*
Interval of MRI scanning, years	4.5 (2.1)	4.3 (2.3)	-	0.28	-
Cartilage loss, mm	−0.17 (0.20)	−0.20 (0.20)	-	0.044	-
Cartilage loss velocity, mm/year	−0.05 (0.08)	−0.07 (0.10)	0.02 (0.002, 0.03)	0.004	0.026

*Mean difference and p value adjusted for age, sex, baseline BMI, baseline Kellgren-Lawrence grade and baseline WOMAC total score.
BMI, body mass index; GLP-1RA, glucagon-like peptide-1 receptor agonist; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

We noticed significant differences in PROs pertaining to the WOMAC score, both total and pain subscale, between the GLP-1RA and non-GLP-1RA groups. Furthermore, the cartilage loss velocity and knee surgery incidence were both statistically lower in the GLP-1RA group. Importantly, the GLP-1RA group also required fewer intra-articular injections of steroids than the non-GLP-1RA group. The before-and-after comparison within the GLP-1RA group and additional sensitivity analyses further supported our findings.

Weight loss has been reported to be a highly effective approach for patients with OA, particularly those with obesity.[5–7] According to conventional wisdom, a weight change greater than 5% is considered clinically relevant for KOA.[27] In this study, the weight loss after GLP-1RA therapy (such as the use of semaglutide, liraglutide and dulaglutide) was substantial and consistent with previous reports.[45] Our analysis revealed that the effects of GLP-1RA on arthritic knees were largely mediated by weight loss instead of glycaemic control. This observation is as expected because the long-term benefits of weight control in KOA have been well established.[5–7] In contrast, several preclinical studies have revealed that GLP-1RA has anti-inflammatory and antidegradative effects.[46 47] It is reasonable to speculate that GLP-1RA might have direct effects on KOA progression. Nonetheless, the 'direct effects' of GLP-1RA on knee surgery, apart from the weight loss-mediated pathway, did not reach statistical significance (table 3). We also fail to identify statistically significant effects within the weight loss subgroup (online supplemental table S18). Consequently, we hypothesise that benefit of GLP-1RA is mainly associated with weight loss while the direct effects remain unclear.

Because GLP-1RAs have a well-established profile in weight management, it is rational to consider that OA patients might benefit from GLP-1RA therapies via reduced mechanical stress and pain sensitivity elicited by overweight.[5–7 20 24] However, a previous trial reported that liraglutide did not reduce knee pain compared with placebo at 1 year in KOA patients that were overweight or obese.[11] Notably, as stated before, the design of this trial is problematic and could not provide a confirmative conclusion. However, a recent trial found a statistically significant correlation between weight loss and pain reduction in the diet and exercise intervention group ($p<0.001$), and the difference in knee pain was statistically significant but small ($p=0.02$) compared with an attention control group at the 18-month follow-up.[10] Therefore, patients with OA might benefit from GLP-1RA therapy for over a longer duration. Thus, in this study, we compared data from patients who received GLP-1RA therapies for at least 2 years with those from the control group. We observed significant effects on the WOMAC total and pain subscale scores during the extended follow-up period. In addition, a larger mean intergroup difference in weight change was noted in this study compared with the previous research,[10 11] which was consistent with earlier finding that substantial weight loss could exert its effect on knee pain improvement.[24]

Notably, different strategies of weight loss, including diet, exercise, and medications, differentially affect body weight, composition, and muscle strength.[48] Although GLP-1RA therapies led to a greater reduction in fat mass, lean body mass was also reduced significantly after treatment due to the treatment-emergent hypocaloric diet.[49 50] However, a longitudinal study demonstrated an increased risk of KOA with obesity and sarcopenic obesity, but not sarcopenia.[51] This might avert part of the worry and concern regarding GLP-1RA therapies. For patients with sarcopenic obesity, physical exercise might be essential to preserve lean body mass, as exercise with weight loss could not

Table 5 Before-and-after comparison within the GLP-1RA group

	Pretreatment (n=126)	Post-treatment (n=126)	Mean difference (95% CI)	P value
Annual consumption of oral NSAIDs and acetaminophen, RDD/year	16.8 (14.7)	14.0 (12.2)	2.80 (1.96, 3.62)	<0.001
Annual consumption of topical NSAIDs, RDD/year	24.5 (24.3)	16.6 (19.6)	7.96 (6.27, 9.65)	<0.001
Annual consumption of opioids, MME/year	97.7 (195.1)	93.5 (182.3)	4.17 (–17.52, 25.86)	0.70
Annual no of intra-articular therapies, per year	1.35 (2.67)	0.76 (1.40)	0.59 (0.27, 0.91)	<0.001
Annual no of intra-articular injection of steroids, per year	0.18 (0.41)	0.10 (0.21)	0.082 (0.038, 0.13)	<0.001

GLP-1RA, glucagon-like peptide-1 receptor agonist; MME, morphine milligram equivalent; NSAIDs, non-steroidal anti-inflammatory drugs; RDD, recommended daily dose.

only decrease ectopic fat but also improve insulin sensitivity.[48] Future trials should consider an add-on design to evaluate the efficacy of GLP-1RA therapies for KOA.

We observed potentially preventive effects of GLP-1RA therapies on articular cartilage in the intergroup and before-and-after comparisons. Articular cartilage is a connective tissue composed of chondrocytes and chondrocyte-producing extracellular matrix.[52] Obesity may impair cartilage homoeostasis and cause systemic and local inflammation, whereas weight loss can improve the quality and quantity of articular cartilage.[53 54] Furthermore, as antianabolic effects of steroids on healthy cartilage are known, the use of intra-articular steroids could result in greater cartilage volume loss compared with placebo.[55 56] Moreover, we observed less progression of knee cartilage loss velocity with fewer number of steroids required in the GLP-1RA group. In addition to indirect effects, GLP-1RA is expressed in normal and OA articular chondrocytes, suggesting that GLP-1RAs might have a direct impact on articular chondrocytes.[57] Preclinical studies have shown that GLP-1RA signalling is associated with apoptosis prevention, anti-inflammatory activity and matrix protection.[23] Future preclinical and clinical investigations may elucidate the underlying mechanisms.

A statistically insignificant decrease was observed for symptom-relieving medication use in the GLP-1RA group compared with the non-GLP-1RA group. This might be because most patients in the GLP-1RA group did not receive GLP-1RA therapies immediately after enrolling in SOC. In contrast, before-and-after comparisons within the GLP-1RA group showed a significant decrease in symptom-relieving medication use except for opioids after GLP-1RA treatment compared with the pretreatment level. Chronic use of opioids is associated with an increased risk of fractures, cardiovascular events, opioid dependence and mortality; opioids were generally considered as second-line choices before intra-articular therapies for KOA.[58 59] Likewise, in this study, opioids were less frequently consumed by participants at about 100 MME per year on average. Thus, the consumption of opioids might not be of clinical importance.

The current study had several limitations. First, because of the large sample size of SOC study, we only had access to routine follow-up on PROs and were unable to perform on-site and routine radiographic follow-up (eg, measured body weight, MRI and X-ray) for our participants owing to limited funding. Future randomised trials are required to validate our findings as this study did not draw any confirmatory conclusions regarding the efficacy of GLP-1RA therapy for KOA. Second, the current study enrolled only KOA patients with comorbid T2DM. Extrapolation of our findings to a general KOA population should be done cautiously, especially given the fact that KOA patients with comorbid T2DM have a higher prevalence of obesity/overweight. Third, the rationale behind the decision to use GLP-1RA was not exactly recorded. Clearly, preferences of the treating physician and patients played important roles regarding this decision. Indication bias (eg, easier access to newer drugs, paying more attention to their health) is inevitable. For structural data, patients who underwent more frequent MRI scans may have been more vigilant about their health. Fourth, because of the observational nature of this study, the switch between different GLP-1RAs occurred frequently during our study period (history of GLP-1RAs use is shown in online supplemental table S8). For example, many patients in this study switched from liraglutide to semaglutide after the latter was made commercially available. Finally, approximately 20% of patients did not have available MRI in this study as MRI examination was not compulsory according to our protocol. Patients underwent MRI examination based on the physicians' recommendations and their preference, resulting in irregular intervals between MRI scans. Therefore, it is not clear whether the cartilage loss in this study was linear or not.

In conclusion, with sufficient treatment duration, GLP-1RA therapies might be disease-modifying for KOA patients with comorbid T2DM. Further investigations are needed to elucidate the effects of GLP-1RA on the disease process, joint structure and PROs of OA.

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REFERENCES

1 Hunter DJ, Schofield D, Callander E. The individual and socioeconomic impact of osteoarthritis. *Nat Rev Rheumatol* 2014;10:437–41.
2 Murray CJL, Aravkin AY, Zheng P, *et al*. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the global burden of disease study 2019. *The Lancet* 2020;396:1223–49.
3 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 & Rheumatology* 2022;74:1172–83. 10.1002/art.42089 Available: https://onlinelibrary.wiley.com/toc/23265205/74/7
4 Reyes C, Leyland KM, Peat G, *et al*. Association between overweight and obesity and risk of clinically diagnosed knee, hip, and hand osteoarthritis: A population-based cohort study. *Arthritis Rheumatol* 2016;68:1869–75.
5 Arden NK, Perry TA, Bannuru RR, *et al*. Non-surgical management of knee osteoarthritis: comparison of ESCEO and OARSI 2019 guidelines. *Nat Rev Rheumatol* 2021;17:59–66.
6 Fernandes L, Hagen KB, Bijlsma JWJ, *et al*. EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. *Ann Rheum Dis* 2013;72:1125–35.
7 Kolasinski SL, Neogi T, Hochberg MC, *et al*. American college of rheumatology/arthritis foundation guideline for the management of osteoarthritis of the hand, hip, and knee. *Arthritis Rheumatol* 2020;72:220–33.
8 Zhao G, Zhu S, Zhang F, *et al*. Global burden of osteoarthritis associated with high body mass index in 204 countries and territories, 1990-2019: findings from the global burden of disease study 2019. *Endocrine* 2023;79:60–71.
9 Liu M, Jin F, Yao X, *et al*. Disease burden of osteoarthritis of the knee and hip due to a high body mass index in China and the USA: 1990-2019 findings from the global burden of disease study 2019. *BMC Musculoskelet Disord* 2022;23:63.
10 Messier SP, Beavers DP, Queen K, *et al*. Effect of diet and exercise on knee pain in patients with osteoarthritis and overweight or obesity: A randomized clinical trial. *JAMA* 2022;328:2242–51.
11 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;113:314–23.
12 Yannakoulia M, Poulimeneas D, Mamalaki E, *et al*. Dietary modifications for weight loss and weight loss maintenance. *Metabolism* 2019;92:153–62.
13 Bray GA, Frühbeck G, Ryan DH, *et al*. Management of obesity. *The Lancet* 2016;387:1947–56.
14 Neogi T, Zhang Y. Epidemiology of osteoarthritis. *Rheum Dis Clin North Am* 2013;39:1–19.
15 Garvey WT, Mechanick JI, Brett EM, *et al*. American association of clinical endocrinologists and american college of endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. *Endocrine PRACTICE* 2016;22:1–203.
16 Wharton S, Lau DCW, Vallis M, *et al*. Obesity in adults: a clinical practice guideline. *CMAJ* 2020;192:E875–91.
17 Kushner RF, Ryan DH. Assessment and Lifestyle management of patients with obesity: clinical recommendations from systematic reviews. *JAMA* 2014;312:943–52.
18 Frías JP, Davies MJ, Rosenstock J, *et al*. Tirzepatide versus Semaglutide once weekly in patients with type 2 diabetes. *N Engl J Med* 2021;385:503–15.
19 Wilding JPH, Batterham RL, Calanna S, *et al*. Once-weekly Semaglutide in adults with overweight or obesity. *N Engl J Med* 2021;384:989–1002.
20 Kalra S, Bhattacharya S, Kapoor N. Contemporary classification of glucagon-like peptide 1 receptor agonists (Glp1Ras). *Diabetes Ther* 2021;12:2133–47.
21 Pi-Sunyer X, Astrup A, Fujioka K, *et al*. A randomized, controlled trial of 3.0 mg of Liraglutide in weight management. *N Engl J Med* 2015;373:11–22.
22 Wilding JPH, Batterham RL, Davies M, *et al*. Weight regain and Cardiometabolic effects after withdrawal of Semaglutide: the STEP 1 trial extension. *Diabetes Obes Metab* 2022;24:1553–64. 10.1111/dom.14725 Available: https://onlinelibrary.wiley.com/toc/14631326/24/8
23 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;32:121–9.
24 Jafarzadeh SR, Neogi T, Stefanik JJ, *et al*. Mediating role of bone marrow lesions, Synovitis, pain sensitization, and depressive symptoms on knee pain improvement following substantial weight loss. *Arthritis Rheumatol* 2020;72:420–7. 10.1002/art.41125 Available: https://onlinelibrary.wiley.com/toc/23265205/72/3
25 Reijman M, Hazes JM, Koes BW, *et al*. Validity, reliability, and applicability of seven definitions of hip osteoarthritis used in Epidemiological studies: a systematic appraisal. *Annals of the Rheumatic Diseases* 2004;63:226–32.
26 Skou ST, Koes BW, Grønne DT, *et al*. Comparison of three sets of clinical classification criteria for knee osteoarthritis: a cross-sectional study of 13,459 patients treated in primary care. *Osteoarthritis and Cartilage* 2020;28:167–72.
27 Wang Q, Runhaar J, Kloppenburg M, *et al*. Diagnosis of early stage knee osteoarthritis based on early clinical course: data from the CHECK cohort. *Arthritis Res Ther* 2021;23:217.
28 Clement ND, Bardgett M, Weir D, *et al*. What is the minimum clinically important difference for the WOMAC index after TKA? *Clin Orthop Relat Res* 2018;476:2005–14.
29 Bellamy N, Hochberg M, Tubach F, *et al*. Development of multinational definitions of minimal clinically important improvement and patient acceptable symptomatic state

in osteoarthritis. *Arthritis Care & Research* 2015;67:972–80. 10.1002/acr.22538 Available: http://doi.wiley.com/10.1002/acr.v67.7
30 Moseley JB, O'Malley K, Petersen NJ, *et al*. A controlled trial of Arthroscopic surgery for osteoarthritis of the knee. *N Engl J Med* 2002;347:81–8.
31 Sihvonen R, Paavola M, Malmivaara A, *et al*. Arthroscopic partial Meniscectomy for a degenerative Meniscus tear: a 5 year follow-up of the placebo-surgery controlled FIDELITY (Finnish degenerative Meniscus lesion study) trial. *Br J Sports Med* 2020;54:1332–9.
32 Stahel PF, Wang P, Hutfless S, *et al*. Surgeon practice patterns of Arthroscopic partial Meniscectomy for degenerative disease in the United States: A measure of low-value care. *JAMA Surg* 2018;153:494–6.
33 Rickert J. On patient safety: Orthopaedic Surgeons must stop performing Arthroscopic partial Meniscectomy on patients with Arthritic knees. *Clin Orthop Relat Res* 2020;478:28–30.
34 Eckstein F, Maschek S, Wirth W, *et al*. One year change of knee cartilage morphology in the first release of participants from the osteoarthritis initiative progression Subcohort: association with sex, body mass index, symptoms and radiographic osteoarthritis status. *Ann Rheum Dis* 2009;68:674–9.
35 Eckstein F, Hudelmaier M, Wirth W. Double echo steady state magnetic resonance imaging of knee Articular cartilage at 3 Tesla: a pilot study for the osteoarthritis initiative. *Annals of the Rheumatic Diseases* 2006;65:433–41.
36 Boer GA, Hay DL, Tups A. Obesity Pharmacotherapy: Incretin action in the central nervous system. *Trends Pharmacol Sci* 2023;44:50–63.
37 Leyland KM, Judge A, Javaid MK, *et al*. Obesity and the relative risk of knee replacement surgery in patients with knee osteoarthritis: A prospective cohort study. *Arthritis & Rheumatology* 2016;68:817–25.
38 Halawi H, Khemani D, Eckert D, *et al*. Effects of Liraglutide on weight, Satiation, and gastric functions in obesity: a randomised, placebo-controlled pilot trial. *Lancet Gastroenterol Hepatol* 2017;2:890–9.
39 Rosa SC, Gonçalves J, Judas F, *et al*. Impaired glucose Transporter-1 degradation and increased glucose transport and oxidative stress in response to high glucose in Chondrocytes from Osteoarthritic versus normal human cartilage. *Arthritis Res Ther* 2009;11:R80.
40 Wang H-J, Giambini H, Chen J-W, *et al*. Diabetes mellitus accelerates the progression of osteoarthritis in streptozotocin-induced diabetic mice by deteriorating bone Microarchitecture, bone mineral composition, and bone strength of Subchondral bone. *Ann Transl Med* 2021;9:768.
41 Schett G, Kleyer A, Perricone C, *et al*. Diabetes is an independent Predictor for severe osteoarthritis: results from a longitudinal cohort study. *Diabetes Care* 2013;36:403–9.
42 Lu C-H, Chung C-H, Lee C-H, *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:e0191242.
43 Imai K, Keele L, Tingley D. A general approach to causal mediation analysis. *Psychol Methods* 2010;15:309–34.
44 Tingley D, Yamamoto T, Hirose K, *et al*. Mediation: R package for causal mediation analysis. *J Stat Softw* 2014;59.
45 Ard J, Fitch A, Fruh S, *et al*. Weight loss and maintenance related to the mechanism of action of glucagon-like peptide 1 receptor agonists. *Adv Ther* 2021;38:2821–39.
46 Mei J, Sun J, Wu J, *et al*. Liraglutide suppresses TNF-A-induced degradation of extracellular matrix in human Chondrocytes: a therapeutic implication in osteoarthritis. *Am J Transl Res* 2019;11:4800–8.
47 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;12:1567.
48 Brennan AM, Standley RA, Anthony SJ, *et al*. Weight loss and exercise Differentially affect insulin sensitivity, body composition, cardiorespiratory fitness, and muscle strength in older adults with obesity: A randomized controlled trial. *J Gerontol A Biol Sci Med Sci* 2022;77:1088–97.
49 McCrimmon RJ, Catarig A-M, Frias JP, *et al*. Effects of once-weekly Semaglutide vs once-daily Canagliflozin on body composition in type 2 diabetes: a Substudy of the SUSTAIN 8 randomised controlled clinical trial. *Diabetologia* 2020;63:473–85.
50 Aroda VR. A review of GLP-1 receptor agonists: evolution and advancement, through the lens of randomised controlled trials. *Diabetes Obes Metab* 2018;20:22–33. 10.1111/dom.13162 Available: http://doi.wiley.com/10.1111/dom.2018.20.issue-S1
51 Misra D, Fielding RA, Felson DT, *et al*. Risk of knee osteoarthritis with obesity, Sarcopenic obesity, and Sarcopenia. *Arthritis Rheumatol* 2019;71:232–7.
52 Dieppe PA, Lohmander LS. Pathogenesis and management of pain in osteoarthritis. *Lancet* 2005;365:965–73.
53 Gersing AS, Schwaiger BJ, Nevitt MC, *et al*. Is weight loss associated with less progression of changes in knee Articular cartilage among obese and overweight patients as assessed with MR imaging over 48 months? data from the osteoarthritis initiative. *Radiology* 2017;284:508–20.
54 Anandacoomarasamy A, Leibman S, Smith G, *et al*. Weight loss in obese people has structure-modifying effects on medial but not on lateral knee Articular cartilage. *Ann Rheum Dis* 2012;71:26–32.
55 McAlindon TE, LaValley MP, Harvey WF, *et al*. Effect of intra-Articular triamcinolone vs saline on knee cartilage volume and pain in patients with knee osteoarthritis: A randomized clinical trial. *JAMA* 2017;317:1967–75.
56 Jüni P, Hari R, Rutjes AWS, *et al*. Intra-Articular corticosteroid for knee osteoarthritis. *Cochrane Database Syst Rev* 2015;2015:CD005328.
57 Chen J, Xie J-J, Shi K-S, *et al*. Glucagon-like Peptide-1 receptor regulates Endoplasmic Reticulum stress-induced apoptosis and the associated inflammatory response in Chondrocytes and the progression of osteoarthritis in rat. *Cell Death Dis* 2018;9:212.
58 Solomon DH, Rassen JA, Glynn RJ, *et al*. The comparative safety of Analgesics in older adults with arthritis. *Arch Intern Med* 2010;170:1968–76.
59 da Costa BR, Pereira TV, Saadat P, *et al*. Effectiveness and safety of non-Steroidal anti-inflammatory drugs and opioid treatment for knee and hip osteoarthritis: network meta-analysis. *BMJ* 2021;375:2321.

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Brief protocol of Shanghai Osteoarthritis Cohort (SOC)

Design

This multicentre, prospective, observational cohort was initiated by the SOC Study Group which consists of researchers from four academic hospitals in Shanghai on clinically diagnosed knee/hip OA, aiming at identifying prognostic factors for incident progression of clinically diagnosed OA. Participants were routinely followed up once per year by phone call. Radiographic and therapeutic data and other clinically relevant information were extracted from institutional Health Information System (HIS) and reported by participants. The study was approved by the medical ethics committees of all participating centres (Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine; Shanghai Changzheng Hospital; Zhongshan Hospital Fudan University; Shanghai Tenth People's Hospital) and informed consent was obtained from all participants. Patients were encouraged to choose SOC centres and/or our collaborated GPs as their primary choices for OA management.

Study population

From January 2011, patients who visited the four medical centres with a clinical diagnosis of HOA/KOA by orthopedic specialists were assessed for eligibility. Inclusion criteria: (1) clinically diagnosed KOA and/or HOA; (2) age > 45 years at enrollment; (3) willing to be followed up at least once per year. Exclusion criteria: (1) any other rheumatic diseases; 2) previous hip or knee joint replacement; (3) osteochondritis dissecans; (4) history of intraarticular lower limb fractures; (5) history of lower limb septic arthritis; (6) malignancy in the past 5 years; (7) understand neither written nor spoken Mandarin.

Criteria for ending follow up: (1) did not complete annual follow-up in two consecutive years; (2) voluntarily withdraw from the study; (3) receiving hip or knee joint replacement.

Baseline variables

At baseline, all demographic and clinical characteristics including current age, age at initial diagnosis of OA, smoking status, weight, height, residential address, phone number, email address (optional), education level (optional), income (optional) and presence of baseline co-morbidities were self-reported by the participants. The baseline Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (normalised to scores within a range of 0–100) was collected. The WOMAC questionnaire is a well-validated instrument consisting of 24 questions with three separate dimensions (pain, physical function, and stiffness) in OA.[1] All participants received blood cell counting, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), antibodies to cyclic citrulline peptide (anti-CCP) tests at enrollment.

All KOA participants underwent weightbearing semi-flexed posteroanterior knee radiographs with a standard protocol. [2] Briefly, each participant was instructed to position their knee facing a vertical table, with their toes touching the table and weight evenly distributed between both legs. The feet were rotated externally by approximately 10° and images were captured using a horizontal X-ray beam that was centred on the joint line. The captured image was assessed by a senior radiologist. If necessary, the participant was then instructed to reposition his or her knee and receive one or more replicate exposures until obtaining a satisfactory image. All hip radiographs for HOA patients were obtained with the patient in a weight-bearing position. The X-ray beam was arranged in an anterior-posterior orientation, parallel to the horizon and at a right angle to the table. Pelvis radiographs were

executed with approximately 15° of internal foot rotation and with the X-ray beam aimed at the upper border of the pubic symphysis. In the case of hip anterior-posterior views, approximately 15° of internal foot rotation was likewise necessary, but the X-ray beam was targeted at the joint space.[3] The K-L grades were then reviewed and rated by an independent radiographic evaluation committee consisting of three radiologists specialising in musculoskeletal radiology.

MRI Scanning and Measurement

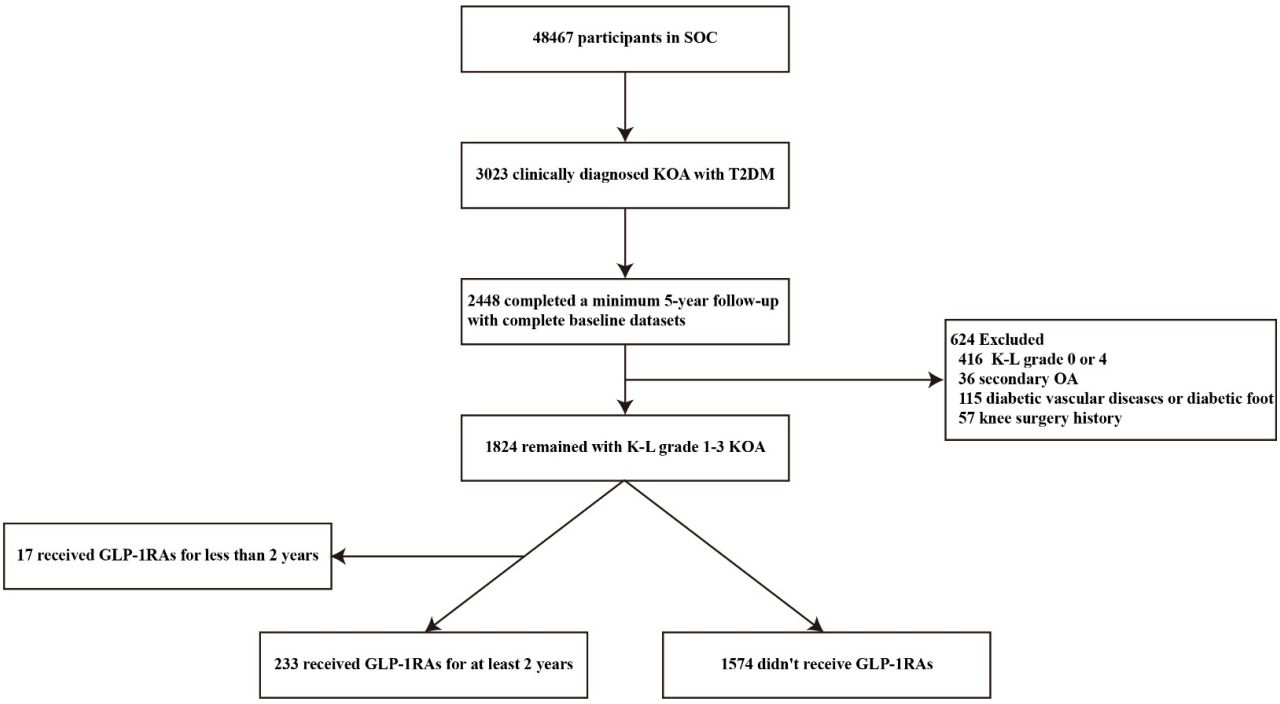
We did not perform routine MRI scanning for each participant. All MRI scanning in this study was performed by the decision of patient after consulting with his or her treating physician. To obtain qualified MRI data for our research purpose, the participants were requested to contact the researchers when they planned to receive an MRI scanning. The researchers would arrange an appropriate time and site for the participant to receive the MRI scanning. All the imaging data were acquired using 3.0T clinical MRI scanners from Siemens. The pulse sequence parameters for the protocol of double-echo steady-state (DESS) MRI series of knee were 384×307 (phase) matrix; 140 (mm) field of view; 0.7 (mm) slice thickness; 25° flip angle; 16.3/4.7 (ms/ms) repetition time/echo time; 185 (kHZ) bandwidth. The pulse sequence parameters for the protocol of DESS MRI series of hip were flexible body-matrix; 192 (mm) field of view; 0.6 (mm) slice thickness; 25° flip angle; 14.8/5 (ms/ms) repetition time/echo time; 260 (kHZ) bandwidth.

Images of the target knee were imported into Stradview (University of Cambridge Department of Engineering, Cambridge, UK), which was used for semi-automatic cartilage segmentation. Two trained readers independently and manually drew initial contours for the tibia and femur every three slices, from which a 3D isosurface was generated for each bone separately. The cartilage surfaces were then automatically measured in every slice and checked manually. To calculate the mean cartilage thickness, the minimum Euclidean distance of each point at the bone–cartilage interface towards the cartilage surface was averaged. The imaging readers were blinded to treatment and order of the image acquisition. The final readout was obtained by averaging the two independent readouts.

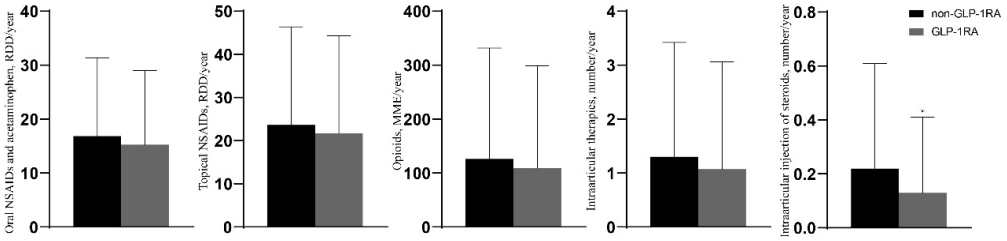
Other Information Collected during Routine follow up

Participants were routinely followed up once per year by phone call to obtain following information: (1) any incident knee/hip surgery; (2) any incident knee/hip surgery in purpose of treating OA; (3) WOMAC score; (4) body weight; (5) drug consumption in treatment of OA (recorded and reported by patients); (6) any physical therapies for OA management (optional); (7) any alternative treatments for OA management (optional).

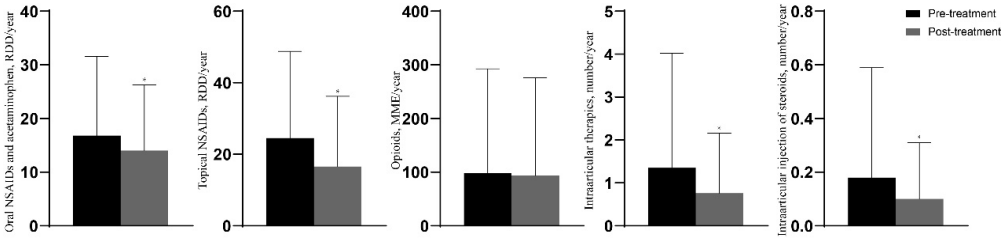
Supplemental figure S1. Flow chart of the study



Supplemental figure S2: Comparison of symptom-relieving medication use between the non-GLP-1RA and GLP-1RA groups. *, P<0.05.



Supplemental figure S3 Before-and-after comparison of symptom-relieving medication use within the GLP-1RA group. *, P<0.05.



Supplemental table S1. List of acetaminophen, oral NSAIDs, topical NSAIDs and their recommended daily doses (RDD)

Drug		
Acetaminophen	Acetaminophen	1250 mg
Oral NSAID	Aceclofenac	125 mg
Oral NSAID	Acemetacin	90 mg
Oral NSAID	Celebrex	200 mg
Oral NSAID	Choline Magnesium Trisalicylate	3275 mg
Oral NSAID	Dexibuprofen	800 mg
Oral NSAID	Dexketoprofen	68.75mg
Oral NSAID	Diacerein	75 mg
Oral NSAID	Diclofenac Sodium	112.5 mg
Oral NSAID	Diflunisal	375 mg
Oral NSAID	Etoricoxib	45 mg
Oral NSAID	Etodolac	800 mg
Oral NSAID	Fenbufen	800 mg
Oral NSAID	Flurbiprofen	175 mg
Oral NSAID	Ibuprofen	600 mg
Oral NSAID	Imidazole salicylate	1875 mg
Oral NSAID	Imrecoxib	200 mg
Oral NSAID	Indometacin	62.5 mg
Oral NSAID	Ketoprofen	200 mg
Oral NSAID	Lornoxicam	24 mg
Oral NSAID	Loxoprofen sodium	270 mg
Oral NSAID	Meloxicam	11.25 mg
Oral NSAID	Nabumetone	1500 mg
Oral NSAID	Naproxen	875 mg
Oral NSAID	Nimesulide	150 mg
Oral NSAID	Oxaprozin	400 mg
Oral NSAID	Piroxicam	20 mg
Oral NSAID	Rofecoxib	18.75mg
Oral NSAID	Sulindac	400 mg
Topical NSAID	Diclofenac Sodium	110 mg
Topical NSAID	Etofenamate	150 mg
Topical NSAID	Flurbiprofen	80 mg
Topical NSAID	Ibuprofen	212.5 mg
Topical NSAID	Ketoprofen	60 mg
Topical NSAID	Loxoprofen sodium	100 mg
Topical NSAID	Piroxicam	36 mg

Supplemental table S2. List of opioid analgesics and morphine milligram equivalents (MME)[4]

Opioid analgesic	MME conversion factor
Bezitramide	60
Codeine	0.15
Dextromoramide	4
Dextropropoxyphene	0.1
Diamorphine (Injection)	3
Diamorphine (Oral formulation)	1
Dihydrocodeine	0.25
Dipipanone	0.5
Fentanyl (Film)	180
Fentanyl (Nasal spray)	160
Fentanyl (Patch)	100
Fentanyl (Tablet)	130
Hydrocodone	1
Hydromorphone	5
Ketobemidone	2
Levorphanol	11
Meptazinol	0.03
Morphine (Injection)	2
Morphine (Oral formulation)	1
Nalbuphine	1
Nicomorphine	1
Oxycodone	1.5
Oxymorphone	3
Pentazocine	0.37
Pethidine (Injection)	0.24
Pethidine (Oral formulation)	0.1
Piritramide	0.75
Tapentadol	0.4
Tilidine	0.1
Tramadol	0.1
Trimeperidine	0.5

Supplemental table S3. Enrollment year for participants in the GLP-1RA and non-GLP-1RA groups

	2011	2012	2013	2014	2015	2016	Total	P value
GLP-1RA (n)	54	51	44	37	38	9	233	0.55
Non-GLP-1RA (n)	315	303	291	296	283	86	1574	

Supplemental table S4. The year of initial incident exposure to GLP-1RAs of participants in the GLP-1RA group

	2011	2012	2013	2014	2015	2016	2017	2018	2019	Total
Number	5	17	19	35	45	45	44	19	4	233

Data of GLP-1RA exposure before enrollment is missing.

Supplemental table S5. Clinically relevant change on weight in patients of the GLP-1RA and non-GLP-1RA groups

	GLP-1RA (n = 233)	**Non-GLP-1RA (n = 1574)**	***P* value**
Clinically relevant change on weight*			
Gain	43 (18.5%)	722 (45.9%)	<0.001
Stable	55 (23.6%)	641 (40.7%)	
Reduction	135 (57.9%)	211 (13.4%)	

* A weight change greater than 5% is considered as clinically relevant.

Supplemental table S6. Comparison of treatment, PROs and incident knee surgery between participants who achieved a clinically significant reduction in weight and those who did not.

	Reduction in weight (n = 346)	**Non-reduction in weight (n = 1461)**	**Adjusted mean difference* (95% CI)**	**P value**	**Adjusted p value***
Weight, kg					
Baseline	64.5 (12.5)	65.4 (12.2)		0.22	
Change	-7.35 (4.31)	3.90 (4.31)	-11.26 (-11.77, -10.76)	<0.001	<0.001
WOMAC total score					
Baseline	19.6 (9.2)	19.8 (9.7)		0.76	
Change	2.65 (13.26)	3.65 (14.18)	-1.17 (-2.35, 0.006)	0.23	0.051
WOMAC pain subscore					
Baseline	17.8 (13.1)	17.4 (12.3)		0.60	
Change	1.21 (18.56)	1.69 (17.63)	-0.58 (-2.65, 1.49)	0.65	0.58
WOMAC stiffness subscore					
Baseline	18.8 (14.3)	18.2 (15.3)		0.50	
Change	4.37 (19.81)	6.71 (20.66)	-2.42 (-4.37, -0.46)	0.057	0.016
WOMAC function subscore					
Baseline	20.2 (11.3)	20.7 (12.2)		0.55	
Change	2.87 (16.27)	3.87 (17.53)	-1.20 (-2.69, 0.30)	0.34	0.12
Follow-up, years	7.7 (1.6)	7.8 (1.6)	..	0.68	..
Knee surgery	4 (1.7%)	91 (6.2%)	..	0.001	0.002

Data are shown as means (SDs) unless otherwise indicated. WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index. WOMAC questionnaire and all its subscales were normalised to scores within a range of 0–100.

* Mean difference and P value adjusted for age, sex, baseline BMI, baseline Kellgren-Lawrence grade, and baseline WOMAC total score.

Supplemental table S7. Comparison of structural outcomes between participants who achieved a clinically significant reduction in weight and those who did not

	Reduction in weight (n = 287)	**Non-reduction in weight (n = 1168)**	**Adjusted mean difference* (95% CI)**	**P value**	**Adjusted p value***
Interval of MRI scanning, years	4.2 (2.2)	4.3 (2.3)	..	0.52	..
Cartilage loss, mm	-0.19 (0.20)	-0.20 (0.20)	..	0.29	..
Cartilage loss velocity, mm/year	-0.06 (0.09)	-0.07 (0.10)	0.01 (-0.005, 0.02)	0.25	0.25

* Mean difference and P value adjusted for age, sex, baseline BMI, baseline Kellgren-Lawrence grade, and baseline WOMAC total score.

Supplemental table S8. History use of GLP-1RAs during study period

	No.
Liraglutide	168 (72.1%)
Dulagopeptide	95 (40.8%)
Semaglutide	171 (73.4%)
Other (e.g. Losenatide, Risenatide, Exenatide)	45 (19.3%)

Supplemental table S9. Sensitivity analysis of PROs between the GLP-1RA (based on the latest follow-up before GLP-1RA usage) and non-GLP-1RA groups

	GLP-1RA (n = 233)	**Non-GLP-1RA (n = 1574)**	**Adjusted mean difference* (95% CI)**	**P value**	**Adjusted p value***
Weight, kg					
Baseline	66.5 (12.2) †	65.1 (12.3)		0.11	
Change	-5.10 (6.93)	2.69 (5.23)	-7.78 (-8.54, -7.03)	<0.001	<0.001
WOMAC total score					
Baseline	19.9 (8.2) †	19.8 (9.6)		0.90	
Change	2.06 (11.97)	3.58 (13.99)	-2.03 (-3.41, -0.65)	0.077	0.004
WOMAC pain subscore					
Baseline	18.9 (11.8) †	17.4 (12.3)		0.071	
Change	-1.76 (15.25)	2.01 (17.60)	-3.93 (-6.29, -1.56)	0.001	0.001
WOMAC stiffness subscore					
Baseline	18.7 (11.0) †	18.3 (15.5)		0.68	
Change	5.31 (16.43)	6.33 (20.43)	-1.49 (-3.75, 0.77)	0.39	0.20
WOMAC function subscore					
Baseline	20.5 (11.0) †	20.7 (11.9)		0.78	
Change	2.65 (15.17)	3.72 (17.25)	-1.68 (-3.43, 0.078)	0.33	0.061
Follow-up, years	5.4 (1.7) ††	7.8 (1.6)	..	<0.001	..
Interval time†††, years	0.46 (0.28)	..	..	..	..

Data are shown as means (SDs) unless otherwise indicated. WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index. WOMAC questionnaire and all its subscales were normalised to scores within a range of 0–100.

* Mean difference and P value adjusted for age, sex, baseline BMI, baseline Kellgren-Lawrence grade, and baseline WOMAC total score.

†The baseline weight and PROs were defined as the data collected at the latest follow-up before the administration of GLP-1RA for the GLP-1RA group.

†† The interval between the initiation of GLP-1RA usage and the latest follow-up for the GLP-1RA group.

††† The interval between the latest follow-up before the initial exposure of GLP-1RA and the initiation of GLP-1RA usage.

Supplemental table S10. Sensitivity analysis of PROs and incident knee surgery after excluding patients with WOMAC total score lower than 7 at baseline

	GLP-1RA (n = 214)	**Non-GLP-1RA (n = 1459)**	**Adjusted mean difference * (95% CI)**	**P value**	**Adjusted p value***
Weight (Change from baseline), kg	-4.40 (8.04)	2.63 (5.21)	-7.02 (-7.83, -6.20)	<0.001	<0.001
HbA1c (Change from baseline), %	0.01 (1.16)	0.07 (1.23)	-0.05 (-0.23, 0.13)	0.55	0.58
WOMAC total score (Change from baseline)	1.27 (13.59)	2.35 (13.50)	-1.49 (-2.93, -0.05)	0.27	0.043
WOMAC pain subscore (Change from baseline)	-1.91 (19.03)	1.29 (17.56)	-3.31 (-5.85, -0.77)	0.014	0.011
WOMAC stiffness subscore (Change from baseline)	4.21 (20.87)	5.12 (20.29)	-1.31 (-3.72, 1.11)	0.54	0.29
WOMAC function subscore (Change from baseline)	1.86 (17.16)	2.33 (16.76)	-0.97 (-2.80, 0.86)	0.70	0.30
Follow-up, years	7.7 (1.5)	7.8 (1.6)	..	0.32	..
Knee surgery	4 (1.9%)	83 (5.7%)	..	0.019	0.026

Data are shown as means (SDs) unless otherwise indicated. WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index. WOMAC questionnaire and all its subscales were normalised to scores within a range of 0–100.

* Mean difference and P value adjusted for age, sex, baseline BMI, baseline Kellgren-Lawrence grade, and baseline WOMAC total score.

Supplemental table S11. Sensitivity analysis of structural outcomes after excluding patients with WOMAC total score that lower than 7 at baseline

	GLP-1RA (n = 173)	**Non-GLP-1RA (n = 1175)**	**Adjusted mean difference* (95% CI)**	**P value**	**Adjusted p value***
Interval of MRI scanning, years	4.5 (2.1)	4.3 (2.3)	..	0.31	..
Cartilage loss, mm	-0.18 (0.20)	-0.21 (0.20)	..	0.077	..
Cartilage loss velocity, mm/year	-0.05 (0.08)	-0.07 (0.10)	0.02 (0.001, 0.03)	0.009	0.038

* Mean difference and P value adjusted for age, sex, baseline BMI, baseline Kellgren-Lawrence grade, and baseline WOMAC total score.

Supplemental table S12. Comparison of patients who reaching the MCID improvement of WOMAC total score in the GLP-1RA and non-GLP-1RA groups *

	GLP-1RA (n = 233)	**Non-GLP-1RA (n = 1574)**	**P value**
Improvement	61 (26.2%)	347 (22.0%)	0.16
No improvement	172 (73.8%)	1227 (78.0%)	

*The MCID for the WOMAC total score was 7.

Supplemental table S13. Comparison of patients who reaching the MCID improvement of WOMAC pain subscore in the GLP-1RA and non-GLP-1RA groups *

	GLP-1RA (n = 233)	**Non-GLP-1RA (n = 1574)**	**P value**
Improvement	81 (34.8%)	443 (28.1%)	0.038
No improvement	152 (65.2%)	1131 (71.9%)	

*The MCID for the WOMAC pain subscore was 9.

Supplemental table S14. Mediation effects for knee outcomes: association of GLP-1RA therapies with WOMAC pain subscore

Exposure: GLP-1RA	**Mediator: Weight change from baseline Change of WOMAC pain subscore from baseline* (95% CI)**	***P* value**	**Mediator: HbA1c change from baseline Change of WOMAC pain subscore from baseline** (95% CI)**	***P* value**
Controlled direct effect	-3.76 (-6.58, -0.98)†	0.005	-3.34 (-5.94, -0.76)†	0.012
Indirect effect	0.45 (-0.59, 1.50)	0.40	0.007 (-0.061, 0.010)	0.85
Total effect	-3.31 (-5.84, -0.78)	0.008	-3.33 (-5.94, -0.75)	0.012
Proportion mediated	Proportion too small to calculate--not a mediator	0.41	Proportion too small to calculate--not a mediator	0.85

*The model adjusted for age, sex, baseline BMI, baseline Kellgren-Lawrence grade, and baseline WOMAC total score.

**The model adjusted for age, sex, baseline HbA1c, baseline BMI, baseline Kellgren-Lawrence grade, and baseline WOMAC total score.

†Values are unstandardised regression coefficients representing change of WOMAC pain subscore from baseline.

Supplemental table S15. Incident knee surgery between the GLP-1RA and non-GLP-1RA Groups

	GLP-1RA (n = 233)	**Non-GLP-1RA (n = 1574)**
TKA	2 (0.9%)	30 (1.9%)
UKA	0 (0.0%)	1 (0.1%)
HTO	0 (0.0%)	6 (0.4%)
Arthroscopic procedures	2 (0.9%)	53 (3.4%)
TKA following arthroscopic procedures	0 (0.0%)	3 (0.2%)

TKA, total knee arthroplasty; UKA, unicompartmental knee arthroplasty; HTO, high tibial osteotomy.

Supplemental table S16. Subgroup comparison of PROs and incident knee surgery among participants who reached clinically relevant reduction on weight* between the GLP-1RA and non-GLP-1RA groups

	GLP-1RA (n = 135)	**Non-GLP-1RA (n = 211)**	**Adjusted mean difference* (95% CI)**	**P value**	**Adjusted p value****
WOMAC total score (Change from baseline)	2.17 (13.48)	2.96 (13.14)	-2.10 (-4.29, 0.09)	0.59	0.060
WOMAC pain subscore (Change from baseline)	-0.48 (18.69)	2.30 (18.44)	-3.27 (-7.25, 0.71)	0.17	0.11
WOMAC stiffness subscore (Change from baseline)	4.63 (20.30)	4.21 (19.54)	-0.87 (-4.60, 2.86)	0.85	0.65
WOMAC function subscore (Change from baseline)	2.67 (16.74)	3.00 (15.99)	-1.90 (-4.67, 0.87)	0.85	0.18
Follow-up, years	7.8 (1.5)	7.7 (1.6)	..	0.69	..
Knee surgery	0 (0.0%)	6 (2.8%)	..	0.085	Not applicable†

Data are shown as means (SDs) unless otherwise indicated. WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index. WOMAC questionnaire and all its subscales were normalised to scores within a range of 0–100.

* A weight change greater than 5% is considered as clinically relevant.

** Mean difference and P value adjusted for age, sex, baseline BMI, baseline Kellgren-Lawrence grade, and baseline WOMAC total score.

† Lack of fitting in the regression mode.

Supplemental table S17. Sensitivity analysis of PROs and incident knee surgery after excluding patients had GLP-1RA exposure within the initial six months after enrollment

	GLP-1RA (n = 206)	**Non-GLP-1RA (n = 1574)**	**Adjusted mean difference* (95% CI)**	**P value**	**Adjusted p value***
Weight (Change from baseline), kg	-4.54 (8.11)	2.69 (5.23)	-7.23 (-8.05, -6.41)	<0.001	<0.001
HbA1c (Change from baseline), %	0.02 (1.25)	0.08 (1.23)	-0.05 (-0.23, 0.13)	0.53	0.56
WOMAC total score (Change from baseline)	2.84 (14.11)	3.58 (13.99)	-1.57 (-3.03, -0.12)	0.48	0.034
WOMAC pain subscore (Change from baseline)	-0.87 (18.81)	2.01 (17.60)	-3.15 (-5.70, -0.60)	0.028	0.016
WOMAC stiffness subscore (Change from baseline)	5.83 (20.71)	6.33 (20.43)	-1.34 (-3.76, 1.08)	0.74	0.28
WOMAC function subscore (Change from baseline)	3.58 (17.46)	3.72 (17.25)	-1.14 (-2.99, 0.72)	0.92	0.23
Follow-up, years	7.8 (1.6)	7.8 (1.6)	..	0.69	..
Knee surgery	4 (1.9%)	93 (5.9%)	..	0.014	0.027

Data are shown as means (SDs) unless otherwise indicated. WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index. WOMAC questionnaire and all its subscales were normalised to scores within a range of 0–100.

* Mean difference and P value adjusted for age, sex, baseline BMI, baseline Kellgren-Lawrence grade, and baseline WOMAC total score.

Supplemental table S18. Subgroup comparison of structural outcomes among participants who reached clinically relevant reduction on weight* between the GLP-1RA and non-GLP-1RA groups

	GLP-1RA (n = 113)	**Non-GLP-1RA (n = 174)**	**Adjusted mean difference* (95% CI)**	**P value**	**Adjusted p value**
Interval of MRI scanning, years	4.6 (2.2)	4.0 (2.2)	..	0.018	..
Cartilage loss, mm	-0.17 (0.20)	-0.20 (0.19)	..	0.41	..
Cartilage loss velocity, mm/year	-0.05 (0.07)	-0.07 (0.10)	0.01 (-0.008, 0.04)	0.16	0.22

* A weight change greater than 5% is considered as clinically relevant.

Supplemental table S19. Sensitivity analysis of structural outcomes after excluding patients had GLP-1RA exposure within the initial six months after enrollment

	GLP-1RA (n = 165)	**Non-GLP-1RA (n = 1267)**	**Adjusted mean difference* (95% CI)**	**P value**	**Adjusted p value***
Interval of MRI scanning, years	4.5 (2.1)	4.3 (2.3)	..	0.25	..
Cartilage loss, mm	-0.17 (0.20)	-0.20 (0.20)	..	0.057	..
Cartilage loss velocity, mm/year	-0.05 (0.08)	-0.07 (0.10)	0.02 (0.001, 0.03)	0.008	0.026

* Mean difference and P value adjusted for age, sex, baseline BMI, baseline Kellgren-Lawrence grade, and baseline WOMAC total score.

Supplemental table S20. Subgroup comparison of structural outcomes with baseline KL grade between the GLP-1RA and non-GLP-1RA groups

	GLP-1RA	**Non-GLP-1RA**	**Adjusted mean difference* (95% CI)**	**P value**	**Adjusted p value***
Interval of MRI scanning, years					
KL grade I†	5.0 (2.2)	4.3 (2.2)	..	0.17	..
KL grade II††	4.6 (2.0)	4.2 (2.3)	..	0.13	..
KL grade III†††	4.1 (2.2)	4.4 (2.3)	..	0.47	..
Cartilage loss, mm					
KL grade I†	-0.16 (0.19)	-0.22 (0.21)	..	0.18	
KL grade II††	-0.18 (0.21)	-0.20 (0.20)	..	0.52	..
KL grade III†††	-0.16 (0.20)	-0.21 (0.20)	..	0.067	..
Cartilage loss velocity, mm/year					
KL grade I†	-0.04 (0.06)	-0.07 (0.11)	0.03 (-0.019, 0.07)	0.21	0.25
KL grade II††	-0.06 (0.08)	-0.07 (0.11)	0.01 (-0.008, 0.04)	0.24	0.21
KL grade III†††	-0.05 (0.07)	-0.07 (0.10)	0.02 (-0.004, 0.05)	0.091	0.090

* Mean difference and P value adjusted for age, sex, baseline BMI, baseline Kellgren-Lawrence grade, and baseline WOMAC total score.

† GLP-1RA group (n=22) and non-GLP-1RA group (n=179).

†† GLP-1RA group (n=105) and non-GLP-1RA group (n=709).

††† GLP-1RA group (n=61) and non-GLP-1RA group (n=379).

Supplemental table S21. Mediation effects for knee outcomes: association of GLP-1RA therapies with cartilage loss velocity

Exposure: GLP-1RA	**Mediator: Weight change from baseline Cartilage loss velocity* (95% CI)**	***P* value**	**Mediator: HbA1c change from baseline Cartilage loss velocity** (95% CI)**	***P* value**
Controlled direct effect	0.015 (0.001, 0.030)†	0.040	0.018 (0.005, 0.030)†	0.006
Indirect effect	0.003 (-0.004, 0.010)	0.45	0.000 (-0.0003, 0.001)	0.62
Total effect	0.018 (0.006, 0.030)	0.007	0.018 (0.006, 0.030)	0.006
Proportion mediated	Proportion too small to calculate--not a mediator	0.46	Proportion too small to calculate--not a mediator	0.62

*The model adjusted for age, sex, baseline BMI, baseline Kellgren-Lawrence grade, and baseline WOMAC total score.

**The model adjusted for age, sex, baseline HbA1c, baseline BMI, baseline Kellgren-Lawrence grade, and baseline WOMAC total score.

†Values are unstandardised regression coefficients representing cartilage loss velocity.

Reference

1. Clement ND, Bardgett M, Weir D, Holland J, Gerrand C, Deehan DJ. What is the Minimum Clinically Important Difference for the WOMAC Index After TKA? *Clin Orthop Relat Res* 2018; 476(10): 2005-14.
2. Peterfy C, Li J, Zaim S, et al. Comparison of fixed-flexion positioning with fluoroscopic semi-flexed positioning for quantifying radiographic joint-space width in the knee: test-retest reproducibility. *Skeletal Radiol* 2003; 32(3): 128-32.
3. Maheu E, Cadet C, Marty M, et al. Reproducibility and sensitivity to change of various methods to measure joint space width in osteoarthritis of the hip: a double reading of three different radiographic views taken with a three-year interval. *Arthritis Res Ther* 2005; 7(6): R1375-85.
4. Ju C, Wei L, Man KKC, et al. Global, regional, and national trends in opioid analgesic consumption from 2015 to 2019: a longitudinal study. *Lancet Public Health* 2022; 7(4): e335-e46.