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Letter to the Editor

Why Did the "Five-Year Incidence of Progression to Osteoarthritis and Total Joint Arthroplasty in Patients Prescribed Glucagon-Like Peptide 1 (GLP-1) Receptor Agonists" Differ From Previous Randomized Controlled Study?

To the Editor:

We have read the article entitled "Five-year Incidence of Progression to Osteoarthritis and Total Joint Arthroplasty in Patients Prescribed Glucagon-Like Peptide 1 (GLP-1) Receptor Agonists" by Famath A and Lavu M, published in *The Journal of Arthroplasty* on June 8, 2024 (2024; https://doi.org/10.1016/j.arth.2024.06.008). We wish to congratulate the authors on the retrospective publication, which provides a major contribution to the orthopaedic community. It is a persuasive analysis with a large sample size.

Regarding patient selection, we noticed that the authors excluded patients who have pre-existing hip and knee osteoarthritis (OA); however, it was not clear how these patients were excluded. Was it on the basis of imaging (X-rays, magnetic resonance imaging) or clinical assessment? Were there adjudications for the OA diagnosis? Due to the uncertainties surrounding the diagnosis of OA and the possible hidden prevalence of OA at baseline, the most robust conclusion of the article is that there are no differences in total joint arthroplasty rates between the GLP-1 groups and controls. A lack of chart documentation is not evidence of a lack of disease.

In terms of risk of progression, progressing from a lack of prior OA diagnosis of either hip or knee to joint surgery within a 5-year period is somewhat incredulous, especially considering that the average progression from knee pain to total knee arthroplasty is nearly 20 years in the United States, with approximately half managed by the patient and half medically managed.

We have two observations regarding the class of study drugs. Most of the patients are on older generations of GLP-1 agonists. The majority are on liraglutide. Only a few patients (less than 10 in each cohort) from the obese diabetic cohort and the nonobese diabetic cohort were from the newer generation of semaglutide. The older generation of GLP-1 agonists is much less efficacious than the newer GLP-1 agonists in terms of weight loss [1]. Additionally, the majority of the patients were no longer on the study drug by year 5. Only 21% of the nondiabetic obese group remains on GLP-1, and roughly only 40% of the diabetic (obese or nonobese) group remains on GLP-1 by year 5. These two factors combined would explain why there was no substantial weight loss, in terms of body mass index) at two years. Obesity is considered the most modifiable risk factor for knee OA [2]. According to the Shanghai study, weight loss is at least responsible for 30% of the benefits seen with GLP-1 agonists and OA. As acknowledged by the authors, there may not be a sufficient percentage of patients on the study drug (>/ = 50%) to draw definitive conclusions. Without weight loss, how can one expect to see benefits for the knee or the hip?

It is also important to note that the "perceived protective mechanisms of GLP-1-RA in mitigating arthritis progression" are very different from the treatment of OA, as seen by STEP-9 [3] and the Shanghai cohort [4]—which both demonstrated improvements in pain (visual analog scale or numeric rating scale) and function (Western Ontario and McMaster Universities Osteoarthritis Index).

In summary, the results of this retrospective study clearly diverge from those of previous randomized controlled clinical trials. We believe these factors and key elements explain why this study found a greater risk of progression to hip and knee OA among obese and nonobese diabetic GLP-1-receptor agonist users at the 5-year follow-up, namely that these patients likely had an underlying OA condition and study drug compliance was limited.

CRediT authorship contribution statement

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