GLP1 Receptor Agonist Use Is Associated With Increased Risk of Osteoporosis, Gout, and Osteomalacia in Adults With Type 2 Diabetes and Obesity

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INTRODUCTION:
Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have become central to the treatment of type 2 diabetes mellitus (T2DM) and obesity, with proven benefits in glycemic control, weight loss, and cardiometabolic risk reduction. Despite emerging hypotheses suggesting possible skeletal benefits, long-term effects of GLP-1 RA exposure on bone and joint health remain poorly understood. Mechanistic studies have raised concerns about altered calcium homeostasis and bone turnover, but real-world outcomes data are lacking. Recent studies have demonstrated potentially protective effects of GLP-1-RAs in this domain, but with limited power and generalizability. This study aimed to evaluate the five-year risk of osteoporosis, gout, and osteomalacia in patients with T2DM and obesity treated with GLP-1 RAs compared to matched controls, using a large multi-institutional electronic medical record (EMR)–derived database.
METHODS:
We performed a retrospective cohort study using a federated EMR-derived national database. Adults aged 18 years or older with concurrent diagnoses of T2DM and obesity (BMI ≥30 kg/m²) were included. Patients who received GLP-1 RAs, including semaglutide, liraglutide, dulaglutide, or exenatide, were identified and matched 1:1 to GLP-1 RA-naïve controls using propensity score matching. Matching covariates included age, sex, race, BMI, hemoglobin A1c, tobacco use, and comorbid conditions such as chronic kidney disease, rheumatoid arthritis, and baseline osteoporosis. Patients were followed for five years from the index date of GLP-1 RA initiation or matched entry date. The primary outcomes were incident diagnoses of osteoporosis, gout, and osteomalacia. Risk ratios (RRs) and 95% confidence intervals (CIs) were calculated; statistical significance was defined as $p<0.05$.
RESULTS:
After matching, cohort sizes were 73,483 patients per group with balanced baseline characteristics. At five years, patients exposed to GLP-1 RAs had a significantly increased risk of osteoporosis compared to controls (4.1% vs. 3.2%; RR 1.29, 95% CI 1.22–1.36; $p<0.001$). Similarly, the incidence of gout was elevated among GLP-1 RA users (7.4% vs. 6.6%; RR 1.12, 95% CI 1.08–1.16; $p<0.001$). The greatest relative risk increase was observed for osteomalacia, with a five-year incidence of 0.2% among GLP-1 RA users versus 0.1% in the control group (RR 2.55, 95% CI 1.83–3.55; $p<0.001$). All differences in absolute and relative risk reached statistical significance.
DISCUSSION AND CONCLUSION: In this large matched cohort study of adults with T2DM and obesity, treatment with GLP-1 RAs was independently associated with significantly increased five-year risk of osteoporosis, gout, and osteomalacia compared to non-users. These findings contradict recent assertions of musculoskeletal protection and suggest that GLP-1 RA exposure may confer increased long-term skeletal risk. As these agents are increasingly prescribed for both diabetic and non-diabetic indications, clinicians should consider bone health surveillance and monitor for delayed-onset complications in at-risk populations.

Table 1. Five-Year Incidence of Bone and Joint Disorders in GLP-1 RA Users Versus Matched Controls

Outcome	GLP-1 RA Cases (N)	GLP-1 RA Incidence (%)	Control Cases (N)	Control Incidence (%)	Risk Ratio (RR)	95% CI	P-Value
Osteoporosis	2955	4.1	2284	3.2	1.29	1.22–1.36	<0.001
Gout	5407	7.4	4832	6.6	1.12	1.08–1.16	<0.001
Osteomalacia	125	0.2	49	0.1	2.55	1.83–3.55	<0.001