GLP-1 Receptor Agonists Increase Fracture Risk in Patients with Obesity

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Introduction

GLP-1 receptor agonists (GLP-1 RA) promote insulin secretion and satiety. This class of medication is frequently prescribed to improve glycemic control in patients with type 2 diabetes mellitus (T2DM). These medications also have potential to promote weight loss. Pre-clinical trials suggested that GLP-1 RAs may induce osteoblast stimulation, and thus may decrease the risk of fracture in patients with T2DM. The effect of GLP-1 RAs on bone health in patients without T2DM has not been studied. However, significant rapid weight loss can be associated with decreased muscle mass and sarcopenia, which may increase fracture risk. The purpose of this study was to assess fracture risk in obese patients without diabetes following their use of GLP-1 RAs.

Methods:

A retrospective case-control study was conducted using deidentified data from the TriNetX database. Patients were included based on the diagnosis of obesity between 2018-2022. Patients with diabetes or an A1c >6.5 were excluded. Patients with increased risk of fragility fractures were also excluded: including those with alcohol or nicotine dependence, osteoporosis with or without current pathologic fracture, rheumatoid arthritis, chronic kidney disease, or long term, chronic use of systemic corticosteroids. An initial query based on the above criteria resulted in 1,155,496 patients. Patients with missing demographic factors were then excluded, resulting in 606,364 patients for analysis. This cohort was divided into two groups: (1) patients who were prescribed a GLP-1 RA (n = 28,982) and (2) those without GLP-1 RA use (n = 577,382). Multiple GLP-1 RAs were included (semaglutide, liraglutide, exenatide, dulaglutide, tirzepatide, and lixisenatide). Propensity score matching was performed for two groups of 29,982 patients. The primary outcome was fracture diagnosis following the prescription of a GLP-1 RA within the years 2022-2023. Fracture incidence was compared between groups. Risk and odds ratio with 95% CI's were estimated using multiple logistic regression to account for covariate variability.

Results:

The incidence of fracture was significantly increased in patients diagnosed with obesity without diabetes who were prescribed a GLP-1 RA (3.27%) compared to patients who were not (2.14%) (RR 1.56 CI [1.42, 1.72]; Figure 1). There was no significant association between GLP-1 RA prescription status and fracture location (10 fracture locations assessed between groups; Figure 2a-b).

Conclusions:

The use of GLP-1 RAs are associated with an increased fracture risk obese patients without diabetes. These results contradict previous studies which suggested a protective effect on fracture risk in patients with T2DM prescribed GLP-1 RAs. Further research is necessary to elucidate these trends and guide prescribing of GLP-1 RAs in the setting of obesity.

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Figure 1: Risk of fracture in patients with obesity prescribed GLP1RA

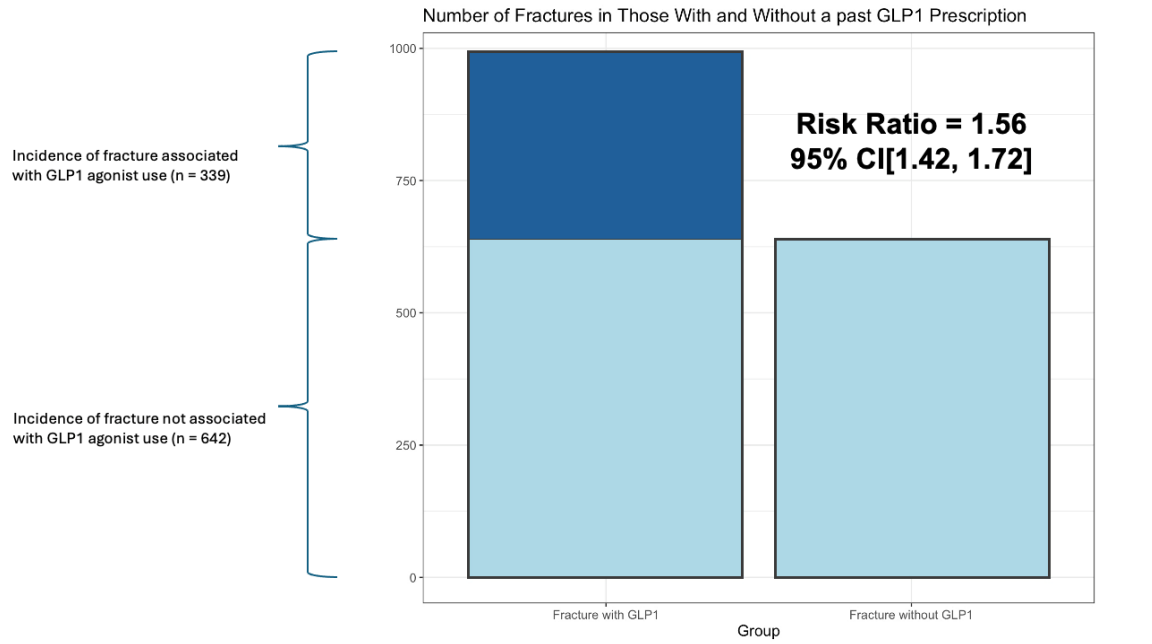

Figure 2a: Fracture location

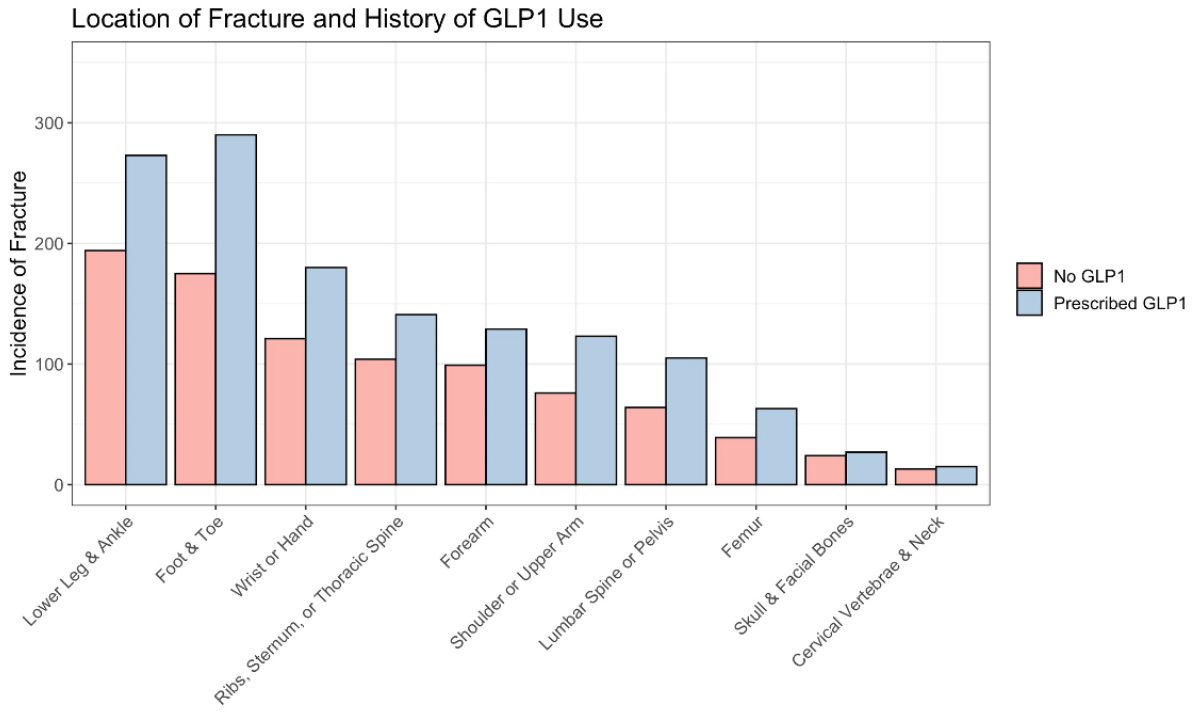

Figure 2b: Odds ratio for fracture type