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Clinical Research Article

Skeletal effect of semaglutide and tirzepatide in patients with increased risk of fractures

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Abstract

Context **Glucagon-like peptide-1 receptor agonists (GLP1-RA) have potent glucose-lowering and weight loss benefits, but their effects on bone remain unclear.**

Objective **To investigate changes in bone mineral density (BMD) in patients using semaglutide (SEM) and tirzepatide (TIR), a dual agonist of GLP-1/glucose dependent insulinotropic polypeptide.**

Methods **Single-center retrospective study. Adult patients using SEM/TIR for ≥6 months with DXA scans before initiation and at least 6 months after were matched by age, sex, BMI, and diabetes mellitus (DM) to nonusers with at least 2 DXA scans over the same period. The primary outcome was the percentage change in total hip (TH) BMD.**

Results **We included 255 patients using SEM or TIR in the GLP-1 RA group (92% female, mean age 64 ± 9 years, BMI 31.0 ± 5.6 kg/m^2) and 255 controls. After a median follow-up of 17 months, the GLP-1 RA group achieved a median 5% weight loss. Both groups had significant declines in BMD at TH and FN, with a similar magnitude between groups. In the GLP-1RA group, weight loss was directly associated with bone loss at the TH and FN ($r = 0.32$ for TH, $r = 0.17$ for FN, both $P < .01$). Among patients without DM, greater TH bone loss was noted in the GLP-1 RA group compared to controls (−1% vs −0.6%, $P = .04$), whereas TH bone loss was similar between groups among patients with DM.**

Conclusion **SEM/TIR use was associated with greater annualized TH bone loss in patients without DM, whereas TH bone loss was comparable between GLP-1 RA and controls in patients with DM. These findings suggest GLP-1 RA's effects on bone may differ by DM status, with weight loss driving bone loss in patients without DM.**

Keywords semaglutide, tirzepatide, bone loss, osteoporosis, obesity, diabetes

Obesity represents a growing global health challenge, imposing significant morbidity and mortality as well as a substantial economic burden (1). The global prevalence of obesity has increased dramatically from 8.8% in 1990 to 18.5% in 2022 among women and from 4.8% to 14.0% among men (2). Currently, over one billion individuals worldwide are affected by obesity, including 159 million children and adolescents and 879 million adults (2). In the United States, it is projected that 1 in 2 adults will have obesity by 2030 (3).

Incretins, including glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are hormones released by the gastrointestinal tract in response to nutrient intake (4). Two newer incretin-based therapies—semaglutide, a GLP-1 receptor agonist (GLP-1 RA), and tirzepatide, a dual GLP-1/GIP RA, are being increasingly prescribed for weight management due to their high efficacy (5). However, despite their demonstrated effectiveness for weight loss and cardiometabolic benefits, their impact on skeletal health remains largely uncertain.

Previous research has established that weight loss is associated with bone loss in patients using caloric restriction and those who have undergone bariatric surgery (6, 7). While the underlying mechanisms remain unclear, they are likely multifactorial (6, 8). As GLP-1 RA can also produce significant weight loss, concerns have been raised about whether they might negatively impact bone health. Several studies have investigated the skeletal effects of earlier-generation GLP-1 RA and found no negative impact on bone mineral density or fracture risk (9, 10). However,

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these findings may be attributed in part to the limited weight loss achieved with these agents (9, 10). In contrast, semaglutide and tirzepatide produce substantially greater weight loss compared to older GLP-1 RAs, raising questions about their potential musculoskeletal effects (11, 12). For example, a phase 2 trial by Hansen et al reported that 52 weeks of semaglutide treatment in patients without diabetes with osteopenia or prior fractures increased bone resorption markers and reduced BMD at the lumbar spine, total hip, and tibia compared with placebo (12). Given the increasing use of semaglutide and tirzepatide for weight loss, it is important to evaluate the skeletal effects of these newer, more potent agents.

Importantly, diabetes mellitus (DM) represents a distinct clinical context in which skeletal health and weight loss responses may differ (13, 14). Both type 1 DM (T1DM) and type 2 DM (T2DM) are associated with significantly increased fracture risk, though through different pathophysiological mechanisms (13). While T1DM is typically associated with reduced bone mineral density (BMD) (13, 15), T2DM presents paradoxically with preserved or elevated BMD but impaired bone quality compared to the general population (16). Moreover, patients with DM generally experience less weight loss in response to GLP-1 RA therapy compared with individuals without DM, which may mitigate weight-loss–related bone loss (14). These differences suggest that the skeletal effects of semaglutide and tirzepatide may not be uniform across DM and non-DM populations and underscore the need for separate analyses based on DM status.

Therefore, we conducted a study to elucidate the skeletal effects of semaglutide and tirzepatide, aiming to fill the existing gap in knowledge regarding their impact on bone health. We hypothesized that patients treated with semaglutide or tirzepatide would experience greater bone loss compared with age-, sex-, body mass index (BMI), and DM-matched controls.

Methods

Patient population

This retrospective study included adult patients who had 2 or more dual-energy X-ray absorptiometry (DXA) scans at Weill Cornell Medical College between December 2017 and August 2024. Patients who initiated semaglutide or tirzepatide were included in the GLP-1 RA group. Eligible patients had a baseline DXA within 2 years prior to medication initiation and a follow-up DXA at least 6 months after starting therapy. The maintenance dose was determined by the prescription with the largest number of covered days filled during follow-up periods. Maintenance doses of semaglutide 1.7 mg or greater, and tirzepatide 10.0 mg or greater were considered high doses, with all other doses categorized as low doses (17, 18). Controls had at least 2 DXA scans within the 4-year period and no exposure to GLP-1 RA. The study was approved by the Institutional Review Board of Weill Cornell Medical College.

Statistical analysis

Propensity score matching was used to identify a control group matched on age, BMI, sex, and DM status. Patients were then matched using 1:1 nearest neighbor propensity score (PS) matching. Balance was assessed by standardized mean differences, with an acceptable threshold of 0.1. Annualized percentage BMD change at the total hip was used as the primary outcome. Normality testing (Shapiro-Wilk) was performed, and continuous variables were analyzed by Student's *t* test or Wilcoxon rank-sum test, and categorical variables were compared by chi-square test. Linear regression was performed on the primary outcome to detect the interaction effect between GLP-1 RA and DM. The relationship between weight loss and BMD was assessed by Pearson correlation. Two-sided P values $<.05$ were considered to indicate statistical significance. Statistical analysis was performed with SAS (9.4, SAS Institute, United States).

Results

Baseline characteristics

Our study included 255 patients who initiated and used semaglutide or tirzepatide (GLP-1 RA group) for a minimum of 6 months and 255 matched controls. The demographic data for study subjects is summarized in Table 1. The mean age of the subjects was 63.9 ± 9.4 years. The majority were white, and 92% were women. The average baseline BMI was 31.0 ± 5.6 kg/m^2. GLP-1 RA users and controls were of similar height, weight and BMI at baseline. Nineteen percent of patients in the GLP-1 RA group received medications such as glucocorticoids, aromatase inhibitors, or gonadotropin-releasing hormone agonists/antagonists, with no significant difference compared to controls. Within the GLP-1 RA group, 28% of individuals had comorbidities associated with skeletal fragility, such as prior bariatric surgery, prior solid organ transplantation, primary hyperparathyroidism, celiac disease, inflammatory bowel disease, or chronic kidney disease. The prevalence of these conditions was comparable between the 2 groups. The use of antiosteoporotic agents—including bisphosphonates, hormone replacement therapy, denosumab, teriparatide, abaloparatide, romosozumab, and raloxifene—did not differ significantly between the GLP-1 RA group and controls.

Weight loss and GLP-1 RA use

In the GLP-1 RA group, the majority of patients (84%) initiated treatment with semaglutide, while 16% initiated with tirzepatide; 41 patients (16%) switched from semaglutide to tirzepatide during the follow-up period. Overall, 76% of patients were taking a low maintenance dose at the end of the study period. Patients in the high-dose group had a significantly higher baseline BMI (32.9 ± 5.6 vs 30.6 ± 5.6, $P = .01$), but the percent weight loss was similar in the low-dose and high-dose subgroups. The median time from GLP-1 RA initiation to follow-up DXA scan was 17 months. The median percent weight reduction at follow-up was 5.3% (4 kg), and 32% of patients achieved >10% weight loss. Among patients with more than 10% weight loss, the duration of GLP-1 RA use, prevalence of DM, percent receiving high maintenance doses, female sex, and age were similar to those without 10% weight loss. In the control group, BMI was not significantly changed between the baseline and follow-up time periods.

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Table 1 Baseline characteristics of overall cohort

	GLP-1 RA ($N = 255$)	Control ($N = 255$)	*P* value
Age (years, mean ± SD)	63.7 ± 9.5	64.3 ± 9.4	.58
Female, *N* (%)	234 (92%)	237 (93%)	.62
Ethnicity, *N* (%)			.74
Hispanic	32 (13%)	38 (15%)	
Non-Hispanic	183 (72%)	177 (69%)	
Decline	40 (16%)	40 (16%)	
Race, *N* (%)			<.001
Caucasian	159 (64%)	111 (44%)	
African American	21 (8%)	56 (22%)	
Asian American	9 (4%)	10 (4%)	
Other	66 (26%)	78(31%)	
Baseline BMI (kg/m^2, mean ± SD)	31.0 ± 5.6	30.5 ± 5.68	.22
Baseline weight (kg, Mean ± SD)	82.2 ± 16.8	79.6 ± 15.7	.06
Diabetes mellitus, *N* (%)	112 (44%)	91(35.7%)	.06
T1DM, *N* (%)	7 (3%)	4 (2%)	.34
T2DM, *N* (%)	105 (41%)	87(3%)	.15
Medication with detrimental skeletal potential, *N* (%)	48 (19%)	56 (22%)	.64
Baseline BMD			.53
Normal	76 (30%)	72(28%)	
Osteopenia (*N*, %)	143 (56%)	154 (60%)	
Osteoporosis (*N*, %)	36 (14%)	29 (11%)	
Osteoporosis treatment, *N* (%)	69 (27%)	53 (21%)	.10

Abbreviations: GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; Medication affecting bone loss includes glucocorticoids, aromatase inhibitors, or gonadotropin-releasing hormone agonists/antagonists.

Table 2 Bone mineral density change, osteopenia and osteoporosis at follow up

	GLP-1 RA ($N = 255$)	Control ($N = 255$)	*P* value
Baseline LS BMD (g/cm^2, mean ± SD)	1.12 ± 0.20	1.11 ± 0.20	.63
LS BMD change (%, mean ± SD)	−1.5 ± 7.1[a]	1.4 ± 8.6	.001
Annualized LS BMD change (%, mean ± SD)	−0.5 ± 3.4	0.6 ± 4.5	.001
Baseline FN BMD (g/cm^2, mean ± SD)	0.88 ± 0.15	0.89 ± 0.13	.21
FN BMD change (%, mean ± SD)	−1.6 ± 6.3[a]	−2.1 ± 8.3[a]	.55
Annualized FN BMD change (%, mean ± SD)	−0.6 ± 3.2	−0.8 ± 3.8	.95
Baseline TH BMD (g/cm^2, mean ± SD)	0.95 ± 0.15	0.95 ± 0.13	.72
TH BMD change (%, mean ± SD)	−2.5 ± 4.4[a]	−2.0 ± 3.9[a]	.28
Annualized TH BMD change (%, mean ± SD)	−0.9 ± 1.9	−0.7 ± 1.7	.16

Abbreviations: BMD, bone mineral density; FN, femoral neck; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; LS, lumbar spine; SD, standard deviation.
[a]Indicates a statistically significant within-group difference compared with baseline

BMD change and weight loss

The median follow-up time between the 2 DXA scans was similar in the GLP-1 RA and control groups, at approximately 2.8 years. Both groups demonstrated significant declines in BMD at the total hip and femoral neck on follow-up DXA scans compared to baseline, with the greatest annualized loss at the total hip (Table 2, Fig. 1). The GLP-1 RA group also experienced significant BMD loss at the lumbar spine, which was not observed in the control group. In the GLP-1 RA group, weight loss was significantly associated with BMD loss at the total hip ($r = 0.32$, $P < .01$) and at the femoral neck ($r = 0.17$, $P < .01$), but not at the lumbar spine. When annualized percentage BMD change was examined, weight loss remained significantly associated with total hip BMD loss ($r = 0.26$, $P = .04$), but not with BMD changes at femoral neck (Fig. 2). Patients who lost >10% of their body weight experienced greater total hip BMD loss compared with those who lost <10% (−3.8% vs −1.9%, $P < .01$). No significant differences in annualized BMD at the total hip or femoral neck were noticed between the GLP-1 RA group and control group, although patients in the GLP-1 RA group exhibited greater annualized lumbar spine bone loss than controls (−0.5% vs 0.6%, $P = .001$).

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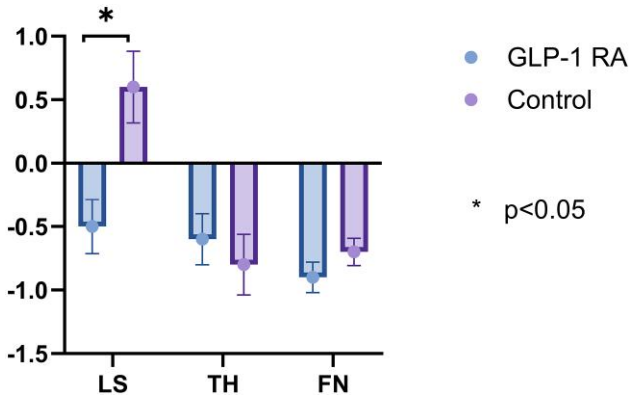


Figure 1 Annualized percentage BMD change between GLP-1 RA group and control group. Values in the bar chart are shown as mean ± SE.

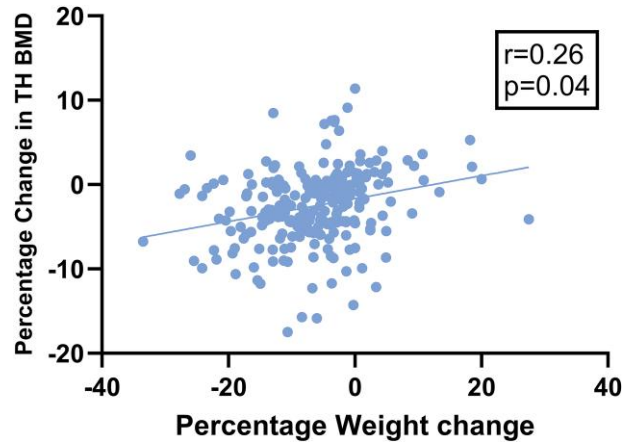


Figure 2 Association of weight loss and annualized percentage change in total hip bone mineral density.
Abbreviations: BMD, bone mineral density; TH, total hip; Wt, weight.

Osteopenia, osteoporosis, and trabecular bone score

At baseline, within the GLP-1 RA group, 56% of patients had osteopenia and 14% had osteoporosis. At follow-up, the prevalence of osteopenia and osteoporosis increased to 60% and 16%, respectively. These findings were comparable to those seen in the control group (Table 1). Baseline *T*-scores were -0.5 ± 1.5 at the lumbar spine, -1.1 ± 1.0 at the femoral neck, -0.4 ± 1.1 at the total hip, and -0.8 ± 1.3 at the forearm, respectively. Trabecular bone scores were similar between the 2 groups at both baseline and follow-up.

Diabetes vs nondiabetes

Among patients in the GLP-1 RA group, 3% had T1DM, 41% had T2DM, and 10% required insulin use, all of which were similar to the control group. In both groups, baseline BMD was highest in patients with T2DM, followed by those without DM, while patients with T1DM had the lowest BMD across all sites. In both groups, the extent of bone loss was similar between patients with and without DM (Table 3). Among patients without DM, the GLP-1 RA group experienced greater annualized bone loss at the lumbar spine and total hip (−0.55% vs 0.62% at lumbar spine, $P < .01$; −1% vs −0.57% at total hip, $P = .04$). In contrast, among patients with DM, TH bone loss was similar between the GLP-1 RA and control groups.

We conducted a subgroup analysis excluding patients on medications that adversely affect bone, those with comorbidities potentially impacting bone health, and those receiving osteoporosis treatment. This subgroup included 113 patients from the GLP-1 RA group and 89 patients from the control group (Table 4). Among them, 60 patients in the GLP-1 RA group and 30 in the control group had DM. Baseline age and BMI were similar in both groups. Among patients without DM (53 in the GLP-1 RA group and 59 in the control group), significantly greater annualized total hip bone loss was noticed in the GLP-1 RA group (−1.1% vs −0.5%, $P = .02$, Fig. 3). In contrast, annualized total hip bone loss was comparable between the GLP-1 RA group and the control group among patients with DM. Similar findings were noticed in analyses restricted to patients with only T2DM. Linear regression model on annualized percentage change in total hip BMD further confirmed that the effects of GLP-1 RA on the outcome differed by DM status (estimated effect of interaction between GLP-1 RA vs DM = 0.88, $P = .047$).

We also performed a subgroup analysis restricting to patients with class II obesity or higher and found that the distinct effects of GLP-1 RA on TH BMD were even more pronounced (Fig. 3). Among patients with DM and class II obesity or higher, the average annualized TH BMD change was 0.1% in the GLP-1 RA group vs −1.0% in the control group ($P = .20$). In patients without DM and with class II obesity or higher, the GLP-1 RA group experienced greater TH BMD loss than the control group (−2.2% vs −0.5%, $P = .03$).

Discussion

In this study, annualized bone loss at the total hip and femoral neck was similar between the GLP-1 RA and control groups; however, the GLP-1 RA group experienced greater annualized bone loss at the lumbar spine. In the GLP-1 RA group, weight loss was significantly associated with bone loss at both the total hip and femoral neck. After excluding patients receiving osteoporosis treatments and those with medications or comorbidities known to affect bone metabolism, we found that patients without DM treated with semaglutide or tirzepatide experienced significantly greater total hip bone loss compared with controls and such effects were not found in those with DM.

Our study observed a median weight reduction of only 5.3% in the overall cohort with a median follow-up of 17 months, much smaller than the 14.9% to 22.5% reported in clinical trials with semaglutide and tirzepatide (19-22). This is most likely due to several factors. In our cohort, approximately three-quarters of participants were receiving low maintenance doses. Prior studies have shown that weight loss is dose-dependent (19-22). Notably, the 5% weight loss we observed is consistent with findings from a recent meta-analysis of low-dose tirzepatide and a recent real-world study of low-dose semaglutide (18, 23). Our cohort also included patients primarily with class I obesity and previous studies have found that patients with lower

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Table 3 Weight, BMI, and bone mineral density change in patients with DM vs without DM

	GLP-1 RA ($n = 255$)			Control ($n = 255$)		
	DM ($N = 112$)	Non-DM ($N = 143$)	*P*-value	DM ($N = 91$)	Non-DM ($N = 164$)	*P*-value
Baseline weight (kg, mean, SD)	80.0 (16.0)	83.7 (17.3)	.16	78.0 (17.0)	80.2 (14.9)	.07
Weight change (%, mean, SD)	−5.5 (7.8)	−6.7 (9.0)	.47	−1.5 (7.1)	0.4(6.4)	.05
Baseline BMI (kg/m^2, mean, SD)	30.6 (5.7)	31.6 (5.7)	.17	30.2 (6.3)	30.6 (5.3)	.22
BMI change (%, mean, SD)	−5.5 (8.4)	−6.3 (9.2)	.49	−0.6 (8.6)	0.8 (6.6)	.06
Annualized LS BMD change (%, mean, SD)	−0.5 (3.3)	−0.6 (3.4)	.61	0.7 (3.3)	0.6 (5.0)	.91
Annualized FN BMD change (%, mean, SD)	−0.5 (2.6)	−0.6 (3.7)	.49	−0.1 (2.8)	−0.6 (1.8)	.16
Annualized TH BMD change (%, mean, SD)	−0.6 (1.4)	−0.9 (1.4)	.51	−1.1 (1.8)	−0.5 (1.2)	.02

Abbreviations: BMD, bone mineral density; FN, Femoral neck; GLP-1 RA, glucagon-like peptide-1 receptor agonist; LS, lumbar spine; TH, total hip.

Table 4 Weight, BMI, and bone mineral density change in patients with DM vs without DM after excluding confounding factors like comorbidities, osteoporosis medications, and other medications with detrimental skeletal potential

	DM			Non-DM		
	GLP-1 RA ($N = 60$)	Control ($N = 30$)	*P*-value	GLP-1 RA ($N = 53$)	Control ($N = 59$)	*P*-value
Baseline weight (kg, mean, SD)	80.1 (15.7)	79.7 (20.8)	.27	83.1 (14.3)	81.2 (15.4)	.53
Weight change (%, mean, SD)	−5.6(7.9)	−0.9 (6.3)	.002	−5.4 (8.1)	0.0 (5.3)	<.001
Baseline BMI (kg/m^2, mean, SD)	31.3 (5.6)	31.2(7.6)	.34	32.1 (5.4)	30.9 (5.6)	.18
BMI change (%, mean, SD)	−5.5 (8.6)	−1.0 (6.2)	.006	−5.7 (8.1)	0.3 (5.8)	<.001
Annualized LS BMD change (%, mean, SD)	−0.7 (2.3)	0.4 (2.6)	.20	−0.1 (2.6)	0.4 (3.9)	.26
Annualized FN BMD change (%, mean, SD)	−0.2 (2.3)	−0.9 (2.1)	.16	−0.1 (2.8)	−0.6(1.8)	.86
Annualized TH BMD change (%, mean, SD)	−0.6 (1.4)	−0.9 (1.4)	.51	−1.1 (1.8)	−0.5 (1.2)	.02

Abbreviations: BMD, bone mineral density; DM, diabetes mellitus; FN, Femoral neck; GLP-1 RA, glucagon-like peptide-1 receptor agonist; LS, lumbar spine; TH, total hip

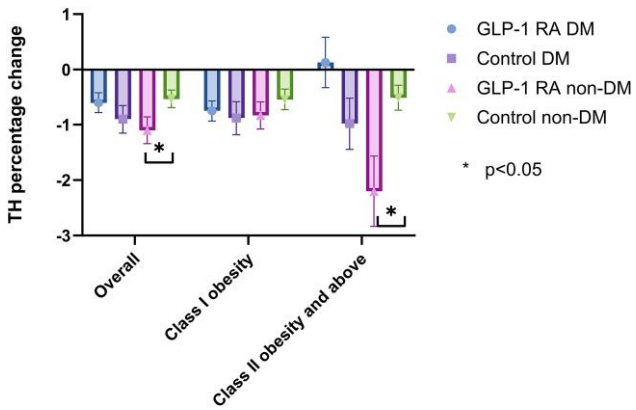


Figure 3 Annualized total hip bone mineral density change in DM vs non-DM patients after excluding confounding factors like comorbidities, osteoporosis medications, and other medications with detrimental skeletal potential. Values in the bar chart are shown as mean ± SE.

baseline BMIs tend to have less weight loss (24, 25). In addition, our cohort included 41% of patients with T2DM and previous studies have shown that patients with T2DM tend to have less weight loss than those without (14). Furthermore, the mean age of our study population was 63.9 years, and prior studies have reported that participants over 65 years of age receiving tirzepatide experienced numerically lower weight loss compared with the overall study population (26).

Several studies have examined the effects of GLP-1 RA therapy on bone, but the findings remain controversial. In our study, we found distinct effects of GLP-1 RA on bone among patients with and without DM. Among patients without DM, we found that patients taking GLP-1 RA experienced more substantial bone loss at the total hip compared with the control group. This finding is consistent with 2 previous studies that included more than 50 patients without DM and provided follow-up BMD measurements (12, 27), while other smaller studies on patients without DM were limited by sample size or the absence of longitudinal BMD data (10, 15-17). In a phase 2 randomized clinical trial, Hansen et al demonstrated that 52 weeks of semaglutide treatment in patients without DM but with osteopenia or prior fractures led to increased bone resorption markers, lower lumbar spine and total hip areal BMD, and reduced tibial volumetric BMD compared with placebo (12). Jensen et al found that liraglutide monotherapy resulted in greater reductions in hip and spine BMD than exercise alone, despite comparable weight loss among adults aged 18-65 years without DM; this effect was not observed when liraglutide was combined with exercise (27). The greater total hip

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bone loss observed among patients without DM in the GLP-1 RA group was most likely related to weight loss, as we identified a significant association between weight loss and bone loss. This finding was similar to previous studies showing that total hip BMD is particularly susceptible to weight loss regardless of method, including dietary modification, exercise, and bariatric surgery (28-30). The hip may be especially vulnerable because of its higher proportion of cortical bone and greater mechanical unloading with weight reduction (31).

However, we did not identify such an effect in patients with DM, suggesting that the skeletal impact of GLP-1 RA may differ based on DM status. Li et al conducted a 24-week randomized controlled trial in 62 treatment-naive patients with DM receiving exenatide, insulin, or pioglitazone, and found that patients in the exenatide group lost an average of 4.7 kg without changes in lumbar spine or total hip BMD at follow-up (32). In another randomized controlled trial, Hygum reported no change in BMD among T2DM patients treated with liraglutide 1.8 mg for 26 weeks despite a 4-kg weight loss, whereas the placebo group showed a decline in total hip BMD from baseline (33). However, a recent longitudinal study by Al Refaie et al reported significant declines in lumbar spine and total hip BMD after 12 months of liraglutide or semaglutide use among patients with T2DM, though the absence of a matched control group limits interpretation, as the BMD reduction may be related to aging, medication effects, or weight loss (34). A key strength of our analysis was the inclusion of a matched control group with comparable baseline BMI, age, sex, and BMD at all sites, which allowed us to demonstrate that GLP-1 RA attenuated bone loss among patients with DM. The preservation of bone among patients with DM receiving GLP-1 RA could be explained in several ways. In vitro studies demonstrate that GLP-1 RAs exert bone-protective effects by promoting osteoblast activity through RANK/OPG signaling, inhibiting osteoclastogenesis through PI3K/AKT pathways, and attenuating advanced glycation end product-mediated impairment of osteogenic proliferation and differentiation (35, 36). In a mouse model of T2DM, no differences in bone turnover markers or bone microstructural parameters assessed by micro-CT were observed between mice treated with tirzepatide, semaglutide, or controls, except for a lower cortical thickness in the semaglutide-treated group (37). In addition, improvements in glycemic control associated with GLP-1 RA use may partially mitigate the observed weight loss-related BMD loss. Finally, because patients with T2DM, who comprised the majority of the DM group, often exhibit normal or elevated BMD compared to those without DM, our neutral findings may suggest that BMD is insufficient to assess skeletal health in this population (13). In T2DM, fracture risk is driven largely by impaired bone quality rather than bone quantity, highlighting the need for future studies to incorporate bone quality measures to better define the skeletal effects of GLP-1 RA (16).

Our study has several limitations. This is a retrospective, single-center study, which inherently limits our ability to control follow-up intervals between DXA scans; however, follow-up duration was comparable between groups, and annualized BMD change was used as the primary outcome. We could not standardize medication doses, and frequent switching between semaglutide and tirzepatide due to intolerance, insurance issues, or drug shortages prevented a direct comparison between the 2 medications. We did not assess HbA1c levels or other DM medications that could potentially affect bone outcomes in patients with DM. While information on changes in lean mass and total body mass would have been valuable, we had insufficient data for whole-body composition scans, as these are often not covered by insurance. In addition, lifestyle factors such as dietary calcium and vitamin D intake and physical activity were not available. The study was conducted at a single academic institution, limiting the study population's heterogeneity. The majority of participants had class I obesity; however, we performed a subgroup analysis of patients with class II obesity or higher and found that the distinct effect of GLP-1 RAs on total hip BMD change based on DM status was more pronounced in those with more severe obesity. Because our inclusion criteria required at least 2 DXA scans and routine osteoporosis screening with DXA is not commonly performed in men, the study included a predominantly female population. Our study also included a higher proportion of Caucasian patients in the GLP-1 RA group than in the control group, which may reflect racial disparities in access to GLP-1 RA. In addition, patients receiving osteoporosis treatment, medications known to negatively affect bone, and comorbidities that may influence bone health were included in the initial analysis to ensure an adequate sample size for propensity score matching without imposing excessive restrictions, although this could introduce residual confounding. Therefore, we performed subgroup analyses excluding patients with these factors, and the overall conclusions remained unchanged. These results may indicate that inclusion of participants on bone-active medications did not materially affect our conclusions. Finally, the relatively small cohort size and limited duration of follow-up constrained our ability to assess fracture incidence.

In conclusion, patients receiving semaglutide or tirzepatide with modest weight loss experienced similar bone loss during follow-up compared with age-, BMI-, sex-, and DM-matched controls, with the greatest decline observed at the total hip. Among these patients, weight loss was significantly associated with bone loss at the total hip and femoral neck. Subgroup analyses revealed differences according to DM status: in patients without DM treated with semaglutide or tirzepatide, annualized total hip bone loss was significantly greater than in controls, whereas no such effect was observed in patients with DM. Further prospective, controlled studies are warranted to confirm these findings and guide clinical management.

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Data availability

De-identified data will be made available upon reasonable request.

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