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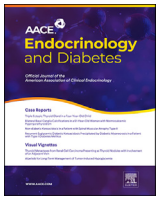

Case Report

Comparison of Fracture Risk Following Semaglutide Treatment vs Sleeve Gastrectomy

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ABSTRACT

Background/Objective: Weight loss in individuals with obesity offers metabolic benefits but may increase fracture risk, potentially influenced by the modality of weight loss. This study aimed to compare fracture risk in patients with obesity treated with semaglutide or sleeve gastrectomy (SG) using a large, real-world electronic health record dataset.
Methods: We conducted a retrospective cohort analysis from 2016 to 2023, using the Atropos Eos electronic health record dataset, representing over 161 million patients seen in community hospitals and large practices in the U.S. Fracture outcomes were compared between adults with obesity treated with semaglutide or SG, using high-dimensional propensity scoring to reduce confounding and enhance group comparability.
Results: We identified 92 405 individuals treated with semaglutide and 16 082 with SG. After high-dimensional propensity score matching, there were 2887 individuals in each group. The mean age was 45 years. Most participants were female (78.5% semaglutide, 77.7% SG) and White (50.3% vs 48.9%, respectively). The Charlson Comorbidity Index was 1.9 for both groups. Over a mean follow-up of 3 years, the semaglutide group experienced 86 fractures (2.98%) compared to 128 (4.43%) in the SG group (hazard ratio 0.74, 95% confidence interval: 0.56-0.98; E-value: 1.2).
Conclusion: Our results indicate a 26% lower fracture risk for the semaglutide group vs SG, suggesting it may help offset the increased fracture risk typically associated with intentional weight loss. However, further research is needed.

Introduction

GLP-1 receptor agonists (GLP1 RA) are becoming increasingly relevant in modern clinical practice due to their significant effects on weight loss and metabolic health. Originally developed for type 2 diabetes, these medications have demonstrated significant efficacy in promoting sustained weight reduction by enhancing satiety, delaying gastric emptying, and reducing appetite through central nervous system pathways. With obesity now recognized as a chronic, relapsing disease that contributes to numerous health complications including cardiovascular disease, sleep apnea, and type 2 diabetes, GLP-1 RA offer a much-needed therapeutic alternative.

Weight loss outcomes with GLP-1 RA vary depending on the specific medication and dosage used. For example, daily subcutaneous liraglutide at 3.0 mg is associated with an average weight loss of approximately 7% after 56 weeks, with a placebo-subtracted reduction of around 5% to 5.4%.[1] In contrast, once-weekly subcutaneous semaglutide at 2.4 mg has demonstrated more substantial effects, with average weight reductions of 15% to 16%[2] over 68 weeks in adults with obesity but without diabetes. Results from the STEP 1 and STEP 3 trials further support semaglutide's efficacy, showing placebo-subtracted weight loss in the range of 10.3% to 12.4%.[2,3]

Abbreviations: BMC, bone mineral content; BMD, bone mineral density; CI, confidence interval; EHR, electronic health record; GLP-1 RA, glucagon-like peptide-1 receptor agonists; hdPS, high-dimensional propensity scoring; HR, hazard ratio; ICD-10, International Classification of Diseases, 10th Revision; LASSO, least absolute shrinkage and selection operator; P1NP, procollagen type 1 N-terminal propeptide; RYGB, Roux-en-Y gastric bypass; SD, standard deviation; SG, sleeve gastrectomy.

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Intentional weight loss in adults with obesity—especially when it is rapid and significant—is typically linked to increased bone turnover and a decline in bone mineral density (BMD), which may heighten the risk of fractures.[4] This association is well documented in cases of weight loss due to caloric restriction[5] and bariatric surgery. The latter is associated with more pronounced effects on bone loss and microarchitectural deterioration, particularly following malabsorptive procedures. Large national cohort studies have shown a significantly increased risk of major osteoporotic fractures following Roux-en-Y gastric bypass (RYGB), but not consistently after sleeve gastrectomy (SG).[6] However, emerging data suggest that SG may also be associated with elevated fracture risk at a lower magnitude,[7] though the extent and long-term impact remains unclear, likely due to shorter durations of follow-up in existing studies.

In contrast to these weight loss interventions, GLP-1 RA may exert a different effect on bone metabolism. Emerging preclinical evidence and limited clinical studies suggest that these agents may have neutral or even potentially protective effects on bone health.[8] For instance, liraglutide has been associated with increased bone formation markers and reduced bone loss during the weight maintenance phase following diet-induced weight reduction in women with obesity.[9] In this study, 37 healthy women with obesity achieved a 12% weight loss through a low-calorie diet and were then randomized to receive either liraglutide (1.2 mg/d) or no additional treatment for 52 weeks. While both groups maintained their weight loss, the control group experienced a fourfold greater loss in total and appendicular bone mineral content (BMC) compared to the liraglutide group. Furthermore, the liraglutide group showed a significant increase in the bone formation marker P1NP by 16% (7 ± 3 μg/L), whereas the control group experienced a 2% decrease (-1 ± 4 μg/L), a statistically significant difference ($P < .05$).[9]

Similarly, in a 52-week randomized study by Cai et al,[10] exenatide (2.0 mg/wk) was compared to dulaglutide, insulin, and placebo in 65 patients with type 2 diabetes to evaluate changes in BMD, particularly at the total hip. The exenatide group, which included 9 men with a mean age of 63 years and stable body weight, showed a significant increase in BMD at both the femoral neck and total hip compared to placebo. Notably, the total hip BMD increased from 0.95 to 1.03 g/cm^2 ($P = .02$), a clinically relevant improvement, suggesting a potential bone-protective effect of exenatide independent of weight change. In this same trial, dulaglutide was associated with a modest decrease in femoral neck BMD over 52 weeks; however, this reduction was smaller than that seen in the placebo group. Significant BMD loss at the lumbar spine (L1–L4), femoral neck, and total hip occurred in the placebo group, while dulaglutide did not further exacerbate bone loss at these sites.

Despite these promising findings, current clinical evidence regarding the impact of semaglutide and other GLP1 RA on bone health remains limited. Most existing studies have not included bone health as a primary endpoint, have relatively short follow-up periods, or focus on populations with type 2 diabetes or use lower, non-obesity-specific doses. Given these gaps, and the growing use of semaglutide in real-world settings, we aimed to better understand its potential impact on fracture risk by analyzing data from a large real-life clinical database.

Objectives

Given the growing use of GLP-1RA for obesity treatment, understanding their long-term safety profile, particularly with regard to bone health, is critical. Emerging preclinical and limited clinical evidence suggests that GLP-1 RA may have neutral or even protective effects on bone metabolism. Prior studies involving agents such as liraglutide and exenatide have shown favorable impacts on bone turnover markers and BMD. However, the current clinical evidence for semaglutide at obesity-treatment doses remain scarce. Since substantial and rapid weight loss—whether pharmacologic or surgical—is often associated with increased bone loss and fracture risk, it is crucial to assess the real-world skeletal implications of semaglutide. To address this, our objective was to evaluate the fracture risk in patients with obesity treated with semaglutide compared to those who underwent SG, using a large, real-world electronic health record (EHR) database. We hypothesized that semaglutide, owing to its potential bone-sparing properties, would be associated with a lower fracture risk than SG.

Highlights

- Weight loss in obesity can negatively impact bone health
- Semaglutide was linked to 26% lower fracture risk vs sleeve gastrectomy
- Semaglutide may mitigate the increased fracture risk of intentional weight loss

Clinical Relevance:

This study shows semaglutide is associated with a 26% lower fracture risk compared to sleeve gastrectomy in patients with obesity, suggesting a bone-protective effect. These findings may inform treatment decisions for obesity, especially in patients at high fracture risk, thereby reducing skeletal complications.

Methods

Study Design

We performed a retrospective cohort study utilizing the Atropos Eos EHR database. This database includes structured data on diagnoses, medications, procedures, and visit-level information. The dataset is longitudinal, de-identified, and curated for high continuity and density and includes data from over 161 million patients treated across more than 30 health systems and over 500 hospitals and clinics in the United States. The analysis focused on adults with obesity, comparing fracture incidence between those treated with semaglutide and those who underwent SG between January 2016 and December 2023.

Participants

We included adults aged 18 years or older with a documented diagnosis of obesity, confirmed by at least 90 days of diagnostic history. No minimum follow-up period was required. These subjects received either semaglutide or SG within 1 year of diagnosis, indexed on the date of medication receipt or procedure, respectively.

Individuals with a prior history of fractures were excluded from the analysis. Obesity diagnoses and fracture events were identified using ICD-10 codes extracted from the Atropos Eos database. Fractures were defined using ICD-10 codes from Chapter 19 (S00-S99) in the ICD-10 guidelines, which capture fractures resulting from events such as falls, accidents, or direct trauma. These codes

provide anatomical classification (eg, femur, skull, ankle) and the type of clinical encounter (initial, subsequent, or sequela).

Statistical Methods and Variables

The primary outcome variable was the incidence of fractures at any time during follow-up, identified using ICD-10 codes representing fractures across various anatomical regions. Key covariates included continuous variables such as age, pre-index days, follow-up days, number of encounters and comorbidity score, alongside categorical variables like sex, race, ethnicity, index year, and comorbidities. Covariates were considered to be unbalanced between groups when absolute standardized means were >0.25.[11] To account for confounding in this non-randomized setting and enhance group comparability, we employed high-dimensional propensity score (hdPS) matching.

Propensity scores were derived using logistic regression with LASSO regularization. Matching was performed within a caliper to ensure similarity between groups. For survival outcomes such as time to event, we performed Cox proportional hazards regression. For continuous outcomes that were normally distributed, we utilized linear regression for multivariable modeling. Additionally, the E-value was calculated to assess the strength of an unmeasured confounding factor that would be necessary to change the association between the exposure (semaglutide vs SG) and the outcome (fracture).

Results

We conducted a comprehensive analysis of fracture outcomes in adults with obesity. Between January 2016 and December 2023, 92 405 individuals received semaglutide and 16 082 underwent SG.

A total of 1692 ICD-10 codes were extracted from the Atropos Eos database, with the list majority representing codes in the S00 to S99 range. These included fractures of the skull, spine (cervical, thoracic, lumbar), pelvis, shoulder, upper arm, forearm, hand, wrist, femur, lower leg, ankle and foot.

In the unmatched cohort, individuals in the semaglutide group were older (mean age 50.7 years, SD 13.8) compared to those in the SG group (mean age 44.2 years, SD 12.5) (See Table 1). The semaglutide group also had a lower proportion of females (68.2% vs 81.1%). Race distribution was comparable between groups, with White individuals comprising the largest proportion (55.4% in semaglutide vs 53.7% in SG).

As shown in Table 2, the semaglutide group had a higher prevalence of diabetes (47.7% vs 23.4%), diabetes with complications (18.8% vs 4.9%). Conversely, the SG group had slightly higher rates of mild liver disease (22.8% vs 12.5%).

The primary outcome—incidence of fractures during follow-up—was identified using ICD-10 codes for fractures of the lumbar spine, forearm, femur and other locations. In the unmatched analysis, fracture incidence was 2.55% (2360/92 405) in the semaglutide group versus 5.86% (943/16 082) in the SG group.

After high-dimensional propensity score matching, which yielded 2887 patients per group, baseline characteristics were well balanced. The matched mean age was 45.3 years in both groups, and the proportion of females was similar (78.5% in semaglutide vs 77.7% in SG) (Table 1). Continuous variables, including number of encounters (mean 5.6 vs 5.3) and comorbidity score (mean 1.9 in both groups), were balanced following matching (Tables 1 and 2).

Post-matching, fracture incidence remained lower in the semaglutide group: 2.98% (86/2887) compared to 4.43% (128/2887) in the SG group. Cox proportional hazards modeling demonstrated a significantly lower hazard ratio for fractures in the semaglutide group (HR = 0.74; 95% CI: 0.56–0.98; $P = 0.035$. E-value = 1.2), indicating a 26% reduced risk compared to sleeve gastrectomy (Fig. 1).

Table 1
Baselines demographic characteristics

Characteristic	Unmatched		HdPS matched	
	Sleeve gastrectomy ($N = 16\,082$)	Semaglutide ($N = 92\,405$)	Sleeve gastrectomy ($N = 2887$)	Semaglutide ($N = 2887$)
Female (%)	13 037 (81.1%)	63 025 (68.2%)[a]	2242 (77.7%)	2267 (78.5%)
Age (SD)	44.2 (12.5)	50.7 (13.8) [a]	45.3 (12.8)	45.3 (13.4)
Age groups (%)				
<18 y	0 (0%)	0 (0%)	0 (0%)	0 (0%)
18-29 y	2200 (13.7%)	7197 (7.8%)	349 (12.1%)	397 (13.8%)
30-39 y	4290 (26.7%)	14 850 (16.1%)[a]	698 (24.2%)	683 (23.7%)
40-49 y	4434 (27.6%)	21 365 (23.1%)	804 (27.8%)	766 (26.5%)
50-59 y	3230 (20.1%)	23 762 (25.7%)	630 (21.8%)	590 (20.4%)
60-69 y	1641 (10.2%)	17 884 (19.4%)	335 (11.6%)	358 (12.4%)
70-79 y	284 (1.8%)	6594 (7.1%)	69 (2.4%)	79 (2.7%)
80-89 y	3 (0%)	753 (0.8%)	2 (0.1%)	14 (0.5%)
≥90 y	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Race (%)				
White	8642 (53.7%)	51 175 (55.4%)	1411 (48.9%)	1451 (50.3%)
Other	5331 (33.1%)	30 540 (33.1%)	1106 (38.3%)	1035 (35.9%)
Black	2031 (12.6%)	9154 (9.9%)	348 (12.1%)	368 (12.7%)
Asian	78 (0.5%)	1536 (1.7%)	22 (0.8%)	33 (1.1%)
Hispanic	763 (4.7%)	7185 (7.8%)	168 (5.8%)	238 (8.2%)
Index year (%)				
2015-2019	8567 (53.3%)	5532 (6%)[a]	819 (28.4%)	826 (28.6%)
2020-2023	7515 (46.7%)	86 873 (94%)[a]	2068 (71.6%)	2061 (71.4%)
Pre-index days (SD)	2703 (2857.9)	3557.1 (3120)[a]	2789.6 (2773.9)	3366.9 (3165.5)
Follow-up days (SD)	1600.9 (2259.6)	934.6 (2168.9)[a]	1139.8 (1859.1)	1092.5 (2034.7)
Lost to follow-up (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Number of encounters (SD)	7 (4.1)	4.4 (3.9)[a]	5.3 (4.2)	5.6 (4.5)

Data are presented as mean (standard deviation) or number (%).
[a] Unbalanced characteristics with large differences (absolute mean difference >0.25).

Table 2
Comorbidities and fracture difference

Characteristic	Unmatched		HdPS matched	
	Sleeve gastrectomy ($N = 16\,082$)	Semaglutide ($N = 92\,405$)	Sleeve gastrectomy ($N = 2887$)	Semaglutide ($N = 2887$)
Charlson comorbidity index (SD)	1.6 (1.9)	2.6 (2.6)	1.9 (2.2)	1.9 (2.2)
Malignancy	605 (3.8%)	5428 (5.9%)	130 (4.5%)	136 (4.7%)
Metastatic solid tumor	58 (0.4%)	700 (0.8%)	15 (0.5%)	16 (0.6%)
Diabetes	3770 (23.4%)	44 069 (47.7%)[a]	870 (30.1%)	1159 (40.2%)
Diabetes with complications	787 (4.9%)	17 340 (18.8%)[a]	219 (7.6%)	357 (12.4%)
Congestive heart failure	618 (3.8%)	5503 (6.0%)	121 (4.2%)	145 (5.0%)
Myocardial infarction	254 (1.6%)	2899 (3.1%)	54 (1.9%)	52 (1.8%)
Peripheral vascular disease	536 (3.3%)	6488 (7.0%)	114 (4.0%)	130 (4.5%)
Chronic pulmonary disease	4174 (26.0%)	21 511 (23.3%)	787 (27.3%)	647 (22.4%)
Cerebrovascular disease	474 (3.0%)	5223 (5.7%)	92 (3.2%)	94 (3.3%)
Dementia	26 (0.2%)	406 (0.4%)	8 (0.3%)	5 (0.2%)
Hemiparaplegia	59 (0.4%)	632 (0.7%)	16 (0.6%)	10 (0.4%)
Mild liver disease	3673 (22.8%)	11 564 (12.5%)[a]	634 (22.0%)	386 (13.4%)
Severe liver disease	48 (0.3%)	461 (0.5%)	13 (0.5%)	15 (0.5%)
Renal disease	608 (3.8%)	7319 (7.9%)	142 (4.9%)	154 (5.3%)
Peptic ulcer disease	372 (2.3%)	1205 (1.3%)	79 (2.7%)	41 (1.4%)
Rheumatic disease	555 (3.5%)	3041 (3.3%)	110 (3.8%)	84 (2.9%)
HIV	37 (0.2%)	341 (0.4%)	13 (0.5%)	6 (0.2%)
Fracture anytime on follow-up	943 (5.9%)	2360 (2.6%)	128 (4.4%)	86 (3.0%)

Data are presented as mean (standard deviation) or number (%).
[a] Unbalanced characteristics with large differences (absolute mean difference >0.25).

Discussion

This retrospective cohort study compared fracture outcomes from real-world data in obese adults treated with semaglutide ($n = 92\,405$) versus sleeve gastrectomy ($n = 16\,082$) from January 2016 to December 2023.

Our most notable finding is the significantly lower incidence of fractures in the semaglutide group (2.55% unmatched, 2.98% hdPS matched) compared to the sleeve gastrectomy group (5.86% unmatched, 4.43% hdPS matched), with a hazard ratio of 0.74 (95% CI: 0.56–0.98, $P = 0.035$), indicating a 26% reduced fracture risk for semaglutide users. This difference persisted despite baseline disparities, such as the semaglutide group being older (mean age 50.7 vs 44.2 years) and having higher prevalence of comorbidities like diabetes (47.7% vs 23.4%) and diabetes with complications (18.8% vs 4.9%).

To address potential bias, we employed propensity score matching to balance baseline characteristics between cohorts, reducing confounding due to differences in age (mean 50.7 vs 44.2 years), sex (68.2% vs 81.1% female), and comorbidities like diabetes (47.7% vs 23.4%) in the unmatched semaglutide and SG groups, respectively. After matching, each group included 2887 patients, with improved balance in covariates (eg, mean age 45.3 in both groups).

Our results suggest that semaglutide may confer a protective effect against fractures compared to sleeve gastrectomy. This

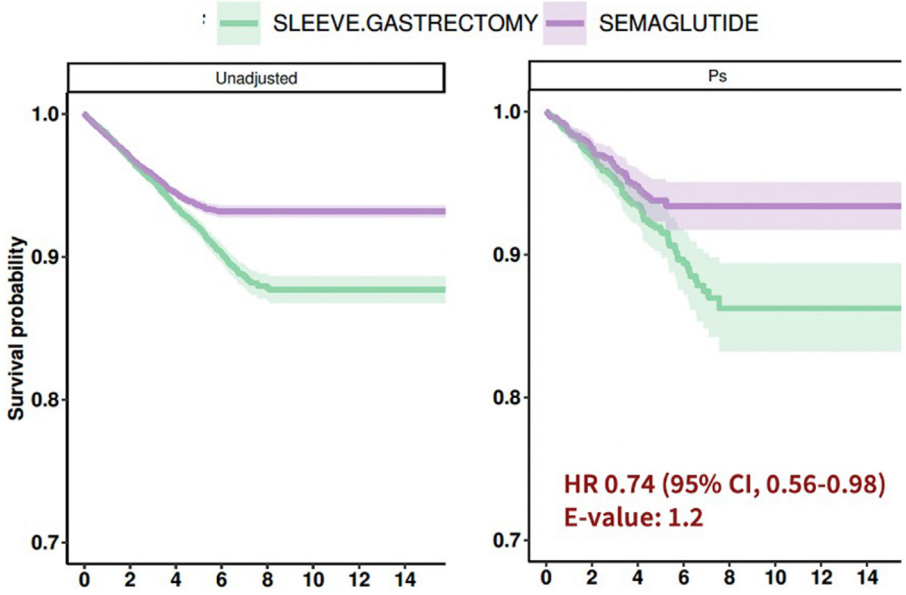

Fig. Survival free of fractures after semaglutide or sleeve gastrectomy: Cox proportional hazards modeling was used to compare fracture free survival between the 2 groups. The E-value was calculated to evaluate the potential impact of unmeasured confounding variables on the results.

finding is clinically significant, as obesity and diabetes are associated with increased fracture risk due to factors such as altered bone metabolism, increased mechanical stress, and fall risk, which may be exacerbated post-bariatric surgery due to rapid weight loss and potential nutrient deficiencies affecting bone health.

Preclinical data in obese mice demonstrate that semaglutide preserves bone mass despite substantial weight loss, whereas sleeve gastrectomy leads to significant bone loss and deterioration of bone microarchitecture, even when both interventions achieve similar weight reduction.[12] Mechanistically, semaglutide may offer bone-protective effects by directly influencing bone cells, promoting osteoblast proliferation and osteogenic differentiation through activation of the Wnt/LRP5/β-catenin signaling pathway, as demonstrated in in vitro studies and animal models.[13,14]

In our study, the lower fracture risk with semaglutide could be attributed to a direct mechanism of GLP-1 RA that is not yet fully understood. Although changes in BMI were not objectively quantified in our study, we hypothesize that the gradual weight loss associated with semaglutide may help preserve bone mineral density, in contrast to the more rapid weight loss and potential malabsorptive effects associated with SG,[15,16] which may induce negative calcium balance, increased bone turnover, and sustained reductions in BMD.

At baseline, 47.7% of individuals in the semaglutide group had diabetes. According to the American Diabetes Association, people with type 2 diabetes have a 1.79-fold higher risk of hip fractures and a 35% greater incidence of vertebral fractures compared to individuals without diabetes, with overall lifetime fracture risk increased by 40% to 70%.[17] This heightened risk is attributed to impaired bone microarchitecture, reduced bone strength, and accelerated bone loss, despite BMD often being 5% to 10% higher in this population.[17] Although we did not stratify our cohort by diabetes status, we hypothesize that the GLP-1 RA semaglutide may also offer bone-protective benefits in individuals with this condition.

While the mechanisms responsible for this protective effect are still being clarified in humans, studies in mouse models of diabetes have shown that 4 weeks of semaglutide treatment had a largely neutral effect on bone mass and microarchitecture, with only minor reductions in cortical thickness and no significant changes in bone turnover markers.[13]

We believe that the implications of this attenuated fracture risk with semaglutide are substantial. Semaglutide could be a preferred option for obese patients at high risk for fractures, particularly older individuals or those with comorbidities like diabetes, potentially reducing healthcare costs and morbidity associated with fractures. However, the low E-value we obtained highlights the need for caution, as unmeasured factors (eg, physical activity, bone density, rate and magnitude of weight loss or nutritional status) could influence results. Clinicians should weigh these potential benefits against other considerations, including semaglutide's side effect profile and cost, as well as the surgical risks and long-term nutritional requirements of sleeve gastrectomy. Finally, since this study focused solely on semaglutide, caution is recommended when generalizing the findings to other GLP-1 RA.

Future research should include prospective studies incorporating bone density assessments, nutritional evaluation, and longer follow-up durations to confirm these findings and to better understand the underlying mechanisms of semaglutide's potential bone-protective properties in the context of obesity management.

Limitations

Although this retrospective study cannot establish causality, it provides valuable clinical insights. The relatively low E-value observed suggests that unmeasured confounders—such as nutritional status, physical activity, and rate and magnitude of weight loss,—could influence the results and should be considered when interpreting our findings. Specifically, dietary information, such as milk and dairy product consumption before or after undergoing SG or initiating semaglutide, were not available in the EHR. Consequently, we were unable to assess the potential impact of diet on our outcomes. In addition, the rate of weight loss following sleeve gastrectomy is substantially greater than that observed with semaglutide based on prior studies. At 12 months, sleeve gastrectomy typically results in a 23% to 32% reduction in total body weight,[18,19] whereas semaglutide achieves an 8% to 15% reduction depending on the population studied and treatment adherence.[18,20] This difference in weight loss magnitude may also have influenced our results.

Despite these limitations, the analysis has several notable strengths that support the reliability of the conclusions. We employed hdPS matching to adjust for confounding variables, enhancing the comparability of treatment groups. Requiring a minimum of 90 days of diagnostic history helped reduce information bias by ensuring that all patients had adequate longitudinal data. Outcomes were defined consistently across cohorts, minimizing misclassification bias, and indexing patients by the date of treatment initiation helped eliminate immortal time bias.

Since this was a retrospective cohort study using an existing, comprehensive dataset, we included all eligible patients based on pre-defined inclusion/exclusion criteria. After matching, key continuous variables such as the number of medical encounters (mean 5.6 in semaglutide vs 5.3 in SG) and comorbidity score (mean 1.9 in both groups) were well balanced. Thus, the large sample size and rigorous matching approach enhanced the robustness of our findings.

Conclusions

This retrospective cohort study, using the Atropos Eos EHR database, found that semaglutide was associated with a 26% lower risk of fractures compared to sleeve gastrectomy in adults with obesity (HR = 0.74, 95% CI: 0.56-0.98, $P = .035$) after propensity score matching. Despite the possibility of unmeasured confounding, we believe this study contributes meaningful real-world evidence that can help guide clinical decision-making, particularly for patients with obesity who may be at increased risk for bone health complications due to increased fall risk and compromised bone quality, altered bone microarchitecture, and disrupted bone remodeling secondary to proinflammatory cytokines and adipokines produced by adipose tissue.[21]

Future prospective studies incorporating BMD and bone resorption markers are warranted to validate these results and elucidate underlying mechanisms.

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Conflicts of interest

The authors JAN, YM, DES, JYW and SHK declare no conflict of interest. CWP and GH are employed by Atropos Health.

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Author Contributions

JAN and SHK were involved in the conception and design of the study. CWP and GH performed the statistical analyses, and all authors (JAN, CWP, GH, YM, DES, JYW, SHK) were involved in the interpretation of the results. JAN wrote the first draft of the manuscript, and all authors edited, reviewed, and approved the final version of the manuscript. JAN is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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