The weight loss caused by GLP-1 and dual GLP-1/GIP receptor agonists is accompanied by bone loss at the hip and radius in obese diabetic patients.

Matthew Mangan[1], Jeff D Thostenson [2], Elena Ambrogini[1,3,4]

[1]Division of Endocrinology and Metabolism, Center for Musculoskeletal Disease Research, University of Arkansas for Medical Sciences (UAMS), Little Rock, Arkansas; [2]Department of Biostatistics, UAMS; [3] Central Arkansas Veterans Healthcare System, Little Rock; [4] Department of Orthopaedic Surgery, UAMS.

INTRODUCTION

Glucagon-like peptide-1(GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are incretin hormones that stimulate glucose-induced insulin secretion, inhibit glucagon secretion, delay gastric emptying, and reduce food intake and appetite. GLP-1 receptor agonists (GLP-1 RAs) and GLP1-1/GIP dual agonist have transformed the management of type 2 diabetes (T2DM) and obesity by combining effective glucose control with weight loss and weight maintenance. In addition, they have beneficial effects in obstructive sleep apnea, cardiovascular diseases (myocardial infarction, heart failure and stroke), metabolic liver disease, diabetic nephropathy and osteoarthritis. Therefore, they are extensively used even in older patients (Drucker, Nat Rev Drug Discov, 2025).

In T2DM, GLP1- RAs cause various degrees of weight loss after 1 year (Dulaglutide 3-4.5 mg weekly 4-5 %, Exenatide 2 mg weekly 3.7 %, Liraglutide 1.8 mg daily 5 %, and Semaglutide 1-2 mg weekly 6.4-6.9 %, respectively). The GLP-1/ GIP dual agonist Tirzepatide (5-15 mg weekly) cause up to 11.2 % weight loss in diabetic patients. Because of their weight loss efficacy, Liraglutide, Semaglutide and Tirzepatide have been approved for the treatment of obesity without T2DM. Indeed, Liraglutide 3 mg daily causes 8.0% and Semaglutide 2.4 mg weekly 17.6 % weight loss at 1 year, whereas Tirzepatide causes up to 22.5 % weight loss over 72 weeks (Bonora et al, Diabetes Obes Metab, 2021; Brown et al Obes Rev, 2019; Frias et al Lancet Diabetes Endocrinol, 2021; Frias et al, NEJM, 2021; Jastreboff et all, NEJM 2022).

Weight loss leads to bone loss and increases the risk of fractures in overweight or obese women who engage in voluntary weight loss (Compston et al, JBMR, 2016; Selmon et al, JAMA, 2019; Ensrund et al, J Am Geriatr, 2003, Zibellini, JBMR, 2015, Johnson et al, JBMR, 2017). These findings indicate that the effect of incretin-based therapies on weight loss-induced bone loss need to be established. Notably, low Bone Mineral Density (BMD) by Dual X-Ray Absorptiometry (DXA) predicts fracture risk even in the presence of obesity (Premaor et al, JCEM, 2011).

Earlier studies of the effect of GLP-1 agonists on bone mass in diabetics did not show a deleterious effect (Anastasilakis et al, Diabetes Obes Metab, 2025). In many studies, the weight loss was modest, and the study period was less than 1 year. However, more recent evidence indicates that in patients in whom GLP-1 RA causes more substantial weight loss, there is indeed bone loss, mostly at the hip; as well as increased bone remodeling and increased risk of fractures in females of all ages and in males over the age of 75 (Al Refaie et al, Calcified Tissue International, 2024; Hansen et al, eClinical Medicine, 2024; Kushner et al, Obesity, 2025; Karam and Paccou, Obesity, 2025).

OBJECTIVES

Evaluate the relationship between weight loss and BMD changes by DXA in obese diabetic patients treated with GLP-1 receptor agonists (GLP-1 RAs) or GLP1-1/GIP dual agonist for at least one year.

METHODS

- 48 patient retrospective study at the University of Arkansas for Medical Sciences
- Inclusion Criteria: age > 18 years; treatment with GLP-1 receptor agonists (GLP-1 RAs) or GLP1-1/GIP dual agonist for at least one year; BMD measurements by DXA at least 1 year apart while on treatment.
- BMD was measured by DXA (Hologic) at the lumbar spine, proximal femur, and radius.
- Exclusion Criteria : Hemodialysis; treatment for gender dysphoria, multiple myeloma

Figure 1. Timeline

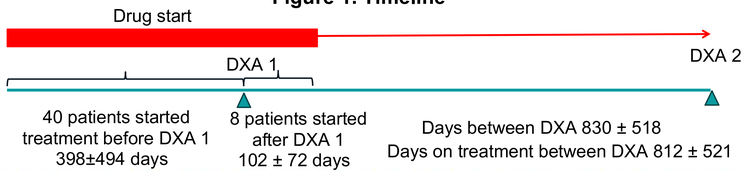

Table 1. Demographic	
Variable	**Mean (SD)**
Age (years) at DXA 1	64.8 (10.2)
Variable	**% (n)**
Sex	
Female	75 (36)
Male	25 (12)
Race	
White	52.1 (25)
African American	45.8 (22)
Other racial groups	2.1 (1)

Table 2. Weights and BMI	
Weight	**Mean (SD)**
At start of the treatment (pounds)	209.5 (49.1)
At DXA 1 (pounds)	205.5 (45.4)
At DXA 2 (pounds)	195.8 (47.4)
Delta weight between start of the treatment and DXA2	-14.3 (26.6)
% weight change between start of the treatment and DXA2	-6.3 (10.7)
Delta weight between DXA 1 and DXA 2	-9.6(17.7)
% weight change between DXA 1 and DXA 2	-4.6 (8.6)
BMI (kg/m^2)	**Mean (SD)**
At start of the treatment	34.2 (6.7)
At first DXA	33.6 (6.1)
At second DXA	32.2 (6.4)

Table 3. Drug used	
	% (n)
Liraglutide	35.4 (17)
Semaglutide	35.4 (17)
Tirzepatide	4.2 (2)
Dulaglutide	39.6 (19)
Exenatide	8.3 (4)

Table 4. Drugs accounted in the analysis	
	% (n)
Bisphosphonates	22.9 (11)
Denosumab	4.2 (2)
Estrogen deprivation therapy	25 (12)
Androgen deprivation therapy	2.1 (1)
Prednisone (stable dose)	10.4 (5)

RESULTS

Figure 2. Linear Regression between weight loss and BMD changes

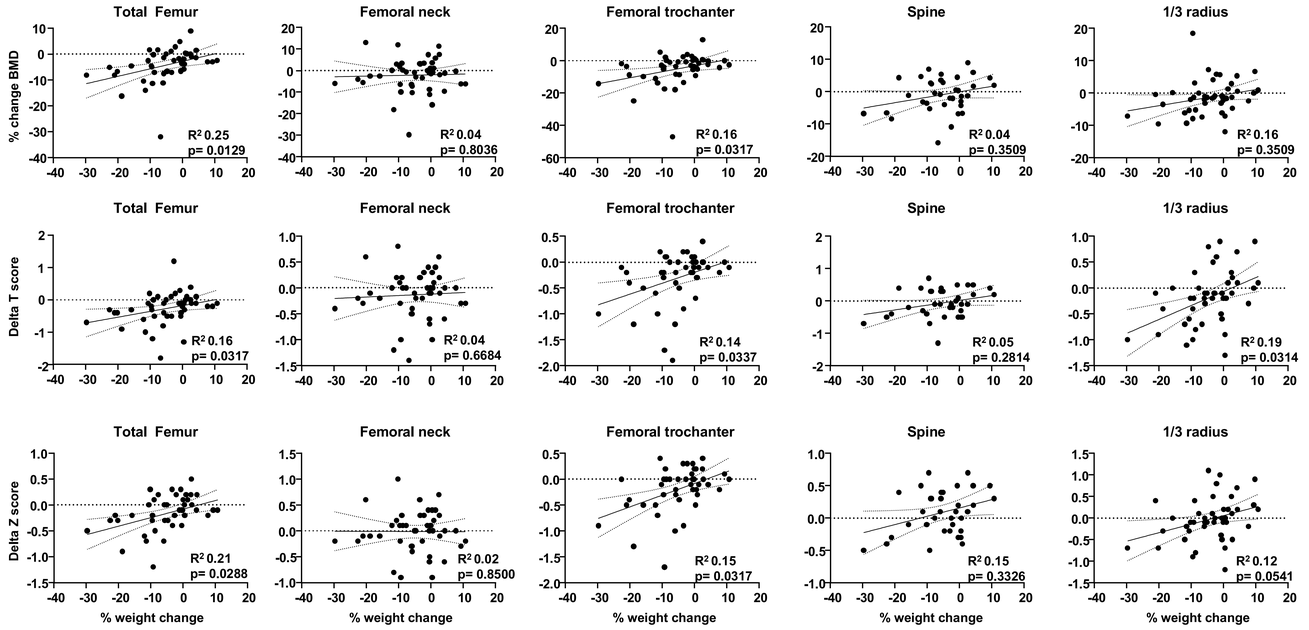

Table 5. Total Femur		
	Mean	**SD**
BMD DXA (g/cm^2)	0.943	0.178
BMD DXA 2 (g/cm^2)	0.912	0.183
T score DXA 1	-0.445	1.209
T score DXA 2	-0.650	1.200
Z score DXA 1	0.530	1.203
Z score DXA 2	0.442	1.098

Table 6. Femoral Neck		
	Mean	**SD**
BMD DXA (g/cm^2)	0.747	0.150
BMD DXA 2 (g/cm^2)	0.738	0.159
T score DXA 1	-1.319	1.101
T score DXA 2	-1.404	1.120
Z score DXA 1	-0.017	1.086
Z score DXA 2	0.036	1.010

Table 7. Femoral Trochanter		
	Mean	**SD**
BMD DXA (g/cm^2)	0.675	0.139
BMD DXA 2 (g/cm^2)	0.645	0.143
T score DXA 1	-0.647	1.150
T score DXA 2	-0.911	1.122
Z score DXA 1	0.228	1.117
Z score DXA 2	0.091	1.019

Table 8. Lumbar spine		
	Mean	**SD**
BMD DXA (g/cm^2)	1.045	0.183
BMD DXA 2 (g/cm^2)	1.013	0.152
T score DXA 1	-0.484	1.714
T score DXA 2	-0.761	1.382
Z score DXA 1	1.045	1.690
Z score DXA 2	0.895	1.453

Table 9. Radius 1/3		
	Mean	**SD**
BMD DXA (g/cm^2)	0.694	0.118
BMD DXA 2 (g/cm^2)	0.682	0.117
T score DXA 1	-0.515	1.627
T score DXA 2	-0.715	1.595
Z score DXA 1	1.163	1.561
Z score DXA 2	1.085	1.585

Figure 3. Scatterplots representing the linear regression between % weight change and % BMD change between the two DXA. The regression line and 95% confidence intervals are included. The R squared and the multiple comparison adjusted p values are shown .

CONCLUSIONS

- In diabetics, GLP-1 or dual GLP-1/GIP RAs-induced weight loss is linearly associated with bone loss at the hip and forearm.
- Bone mass should be monitored during treatment particularly in patients who lose ≥10 % of weight and bone protective management should be considered for those who are at high risk for fractures.

ACKNOWLEDGEMENTS

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