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Effect of sitagliptin vs. placebo on bone mineralization in women with type 2 diabetes: the SLowDOWN (SitagLiptin in Diabetes for Osteoporosis in WomeN) randomized clinical trial

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Abstract

Background Women with type 2 diabetes have an increased risk of bone fragility and fractures. Experimental models suggest that dipeptidyl peptidase-4 inhibitors (DPP4-Is) may have protective effects on bone, but clinical data remain limited, and randomized trials targeting bone Outcomes are lacking. This study aimed to evaluate the efficacy and safety of 52 weeks of oral sitagliptin treatment in improving bone Outcomes in women with type 2 diabetes.

Methods This multicenter, phase III, superiority, double-blind, randomized, placebo-controlled trial enrolled 132 women with type 2 diabetes in monotherapy with metformin and stable glycemic control. Participants were recruited from diabetes Outpatient clinics at Sapienza University of Rome, Italy, and were randomly assigned to receive sitagliptin or placebo for 52 weeks. The main outcome was a change in bone mineral density (BMD) and bone turnover biomarkers. Both intention-to-treat (ITT) and per-protocol (PP) analyses were conducted.

Results Treatment with sitagliptin preserved the total proximal femur BMD *T* score over 52 weeks (estimated mean difference: −0.02; 95% confidence interval: −0.07; 0.03; $p=0.46$), whereas the placebo group showed a significant reduction (estimated mean difference: −0.13; 95% confidence interval: −0.19; −0.07; $p<0.0001$). The between-group difference was significant in favor of sitagliptin (estimated mean difference: 0.11; 95% confidence interval: 0.03; 0.19; $p=0.0063$). No significant differences were detected in other skeletal sites or bone turnover markers. PP analysis confirmed the results obtained in the ITT analysis. Compared with the placebo, sitagliptin significantly reduced the levels of inflammatory mediators involved in bone metabolism. No within- or between-group differences in glucose control at 52 weeks were reported. No serious adverse events were reported; five mild to moderate adverse events occurred and were equally distributed between the two groups.

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Conclusions Sitagliptin treatment was associated with preservation of total hip *T* score in women with type 2 diabetes, without consistent effects on other bone sites or turnover markers. These findings suggest a potential additional benefit of sitagliptin beyond blood glucose control and warrant confirmation in longer-term studies, also including populations at higher fracture risk.

Trial Registration EudraCT number: 2018–000859-40 (registered 15 March 2018); ClinicalTrials.gov identifier: NCT06770894 (retrospectively registered).

Keywords Type 2 diabetes, Bone mineral density, Sitagliptin, Dipeptidyl peptidase-4 inhibitors, Osteoporosis, Randomized controlled trial, Bone metabolism, Inflammation

Background

Type 2 diabetes mellitus and osteoporosis are major causes of morbidity and mortality, significantly burdening global healthcare systems. Osteoporosis increases dramatically with age, particularly in women in the postmenopausal period, due to estrogen loss [1, 2]. Globally, 200 million women are affected, with the risk of postmenopausal osteoporotic fracture reaching 30–40%, surpassing that of breast, uterine, and ovarian cancer [3, 4]. Diabetes independently increases fracture risk; hyperglycemia, oxidative stress, advanced glycation end products, comorbidities, and medications negatively impact this risk [5–7].

Dipeptidyl peptidase-4 inhibitors (DPP4-Is) are glucose-lowering agents with favorable safety profiles. Evidence from observational studies suggests that treatment with DPP4-Is may mitigate fracture risk by promoting bone formation and inhibiting bone absorption [8, 9]. These effects are likely attributable to the diverse enzymatic and nonenzymatic activities of DPP4 [8]. As a proteolytic enzyme, DPP4 hydrolyzes and modulates the biological activity of various endogenous substrates, which also play roles in bone metabolism [9–12]. Furthermore, DPP4 is expressed on bone cells and secreted by osteoclasts; the modulation of DPP4 secretion from these cells affects glucose regulation in experimental settings, suggesting a promising connection between bone turnover and energy metabolism [13]. Additionally, treatment with DPP4-Is improved osteogenic differentiation and fracture healing in osteoblast cultures and animal models [14].

Despite the substantial amount of experimental evidence available, data from clinical studies are extremely limited [15, 16], with meta-analyses showing either protective [17, 18] or neutral [19] effects on osteoporosis and fracture risk. Thus, the evidence is inconclusive, and randomized clinical trials specifically designed to investigate the effects of DPP4-Is on bone outcomes are lacking.

Therefore, this study aimed to evaluate the efficacy and safety of 52 weeks of sitagliptin therapy on bone Outcomes in women with type 2 diabetes through a randomized, double-blinded, placebo-controlled trial.

Methods

Study design and participants

This multicenter, phase III, double-blinded, randomized, placebo-controlled trial evaluated the safety and efficacy of 52 weeks of 100 mg sitagliptin therapy on bone Outcomes in women with type 2 diabetes. Female participants were recruited between September 24, 2019, and October 13, 2022, from diabetes outpatient clinics at Sapienza University, Rome, Italy. The inclusion criteria were as follows: women ≥ 18 years, type 2 diabetes diagnosis, body mass index (BMI) 20–40 kg/m^2, body weight ≤ 120 kg (DXA limit), HbA1c $< 7.5\%$, stable metformin monotherapy for ≥ 12 weeks, and either postmenopausal, surgically sterilized, or practicing effective contraception if of childbearing potential. The exclusion criteria included the following: treatments affecting bone metabolism (e.g., bisphosphonates, corticosteroids, and hormone replacement therapy); metabolic bone diseases; significant hepatic, renal, or thyroid disorders; the use of non-metformin antidiabetic agents; substance abuse; or the inability to consent. Participants on vitamin D or calcium supplements continued with unchanged doses throughout the entire study duration.

Randomization and masking

A permuted block randomization list was generated by an independent contract research organization (CORESEARCH s.r.l.) via SAS software (SAS Institute Inc., NC, 27,513) and implemented on a web-based electronic case report form (eCRF); the randomization list was stratified by center for the two recruiting centers, both located at Sapienza University, Italy. Patients, investigators, clinical site staff, and laboratory staff were blinded to treatment assignment throughout the study. The treatment (sitagliptin 100 mg) and placebo were provided to identical blisters. Unblinding procedures were in place according to the study protocol. Study participants had to be immediately unblinded in the case of a medical emergency, suspected unexpected serious adverse reaction (SUSAR), and in the case of a violation of the study protocol.

Procedures

The participants provided written consent and underwent clinical evaluations at baseline and at 24 and 52 weeks, including anthropometric measurements, blood pressure measurements, metabolic and bone marker tests, and systemic DPP4 activity assessments. Study medications were dispensed at baseline and at 24 weeks, with adherence verified through blister returns. Concomitant medications were recorded; antidiabetic therapy changes (with the exception of rescue treatments prescribed by the investigators, such as for clinical indications and the study protocol) were not allowed. As a biochemistry routine, fasting glycemia (FBG, mg/dl), glycosylated hemoglobin (HbA1c, mmol/mol—%), total cholesterol (mg/dl), total cholesterol (mg/dL), high-density lipoprotein cholesterol (HDL, mg/dL), triglycerides (mg/dL), aspartate aminotransferase (AST, IU/L), alanine aminotransferase (ALT, IU/L), and gamma-glutamyl transpeptidase (GGT, mg/dL) were measured via standard laboratory methods. Serum calcium and phosphate were measured centrally by an Integra analyzer (COBAS C, INTEGRA, Roche Diagnostics S.p.A.). Among the circulating markers of bone metabolism, we measured the serum concentrations of parathormone (PTH), type I collagen N-propeptide (P1NP), crosslinked C-terminal telopeptide (CTX), osteopontin (OPN), osteocalcin (OC), osteoprotegerin (OPG), and sclerostin via the multiplex kits Milliplex (Merk Life Science S.r.l., Milan, Italy). Circulating markers of inflammation were investigated by measuring the plasma concentrations of IL (interleukin)−1, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12 (p70), IL-13, IL-15, IL-17, eotaxin, FGF (fibroblast growth factor), G-CSF (granulocyte colony-stimulating factor), GM-CSF (granulocyte–macrophage colony-stimulating factor), IFN-γ (interferon-gamma), CXCL10 (C-X-C motif chemokine Ligand 10), MCP-1 (monocyte chemoattractant protein-1), MIP-α (macrophage inflammatory protein-alpha), MIP-1β (macrophage inflammatory protein-1 beta), PDGF-BB (platelet-derived growth factor-BB), RANTES (regulated on activation, normal T-cell expressed and secreted), TNF-α (tumor necrosis factor-alpha), and VEGF (vascular endothelial growth factor) at baseline and at 24 and 52 weeks via the Human Magnetic Luminex Screening Assay (Bio-Techne). The serum 25(OH) vitamin D concentration (25(OH)D, ng/ml) was measured as an indicator of vitamin D status via an electrochemiluminescence binding assay (Roche Diagnostics S.p.A.). Circulating DPP4 levels were assessed with a Human DPPIV/CD26 Quantikine ELISA Kit (Bio-Techne S.r.l., Milan, Italy). Circulating DPP4 activity (nmol/min/ml) was assessed as described by Matheeussen et al. [20], who measured the 7-amino-4-methylcoumarin (AMC) cleavage rate from the synthetic substrate H-glycyl-prolyl-AMC in plasma samples frozen immediately after separation and stored at − 25 °C for several weeks. To isolate DPP4 activity from other DPP4 family members, a subset of samples was incubated with the selective DPP4 inhibitor sitagliptin (10 mM). The DPP4 activity of each sample was quantified by calculating the residual fluorescence obtained by subtracting the fluorescence of the inhibited sample from that of the noninhibited sample. All the experiments were performed by the same biologist experienced in immunity and metabolic disorders at Sapienza University.

The primary endpoint was bone mineral density (BMD) changes after sitagliptin or placebo, which were measured by dual-energy X-ray absorptiometry (DXA) at baseline and 52 weeks at the lumbar spine (L1–L4) and femoral neck, per the International Society for Clinical Densitometry guidelines [21]. DXA scans were performed by a trained technician via a Hologic Discovery A densitometer (Bedford, MA, USA), with results expressed in g/cm^2. Osteoporosis (T score ≤ -2.5) and osteopenia (T score -2.5 to -1.0) were classified per the WHO criteria. The trabecular bone score (TBS) was calculated via TBS iNsight software (v2.1.2.0).

Outcomes

The primary objective of this study was to test the superiority of 100 mg sitagliptin in addition to metformin versus placebo + metformin in preserving BMD from baseline to the end of treatment (week 52), as estimated by DXA of the lumbar spine and femoral neck.

The secondary objectives were (i) to evaluate the associations between circulating DPP4 activity and serum markers of bone metabolism at baseline and after 24- and 52-week sitagliptin supplementation; (ii) to ascertain whether circulating DPP4 activity is associated with impaired vitamin D availability and, thus, whether chronic DPP4 inhibition induces changes in serum vitamin D levels after treatment; and (iii) to study the relationships between DPP4 activity and systemic markers of inflammation closely related to impaired glucose metabolism at baseline and after 24- and 52-week sitagliptin supplementation.

Statistical analysis

Mixed models for repeated measurements were applied to evaluate the mean difference in the study Outcomes between the intervention and placebo groups after 24 and 52 weeks. Data are reported as estimated means and estimated mean changes from baseline, along with their 95% confidence intervals, throughout the manuscript and additional tables. Paired and unpaired T tests derived from linear mixed models for repeated measurements were applied for within- and between-group

comparisons. Correlations between circulating DPP4 and bone metabolism markers, serum vitamin D, and immunoinflammatory markers were assessed by Pearson's or Spearman's coefficients, as appropriate. Both intention-to-treat and per-protocol analyses were performed. Descriptive data are reported as the means and standard deviations, medians and interquartile ranges (IQRs), or proportions, as appropriate. p values < 0.05 were considered statistically significant for all of the above variables.

The study power was estimated while considering the effect size, since no data on mean-standard deviation (SD) changes in BMD before and after DPP4-Is treatment were available in the Literature. On the basis of the sample size calculation, minimum group sample sizes of 64 individuals each allowed 80% power to be achieved to reject the null hypothesis of zero effect when the population effect size was 0.50, and the significance level (alpha) was 0.05 according to a two-sided two-sample equal-variance t test. An independent contract research organization oversaw data, safety monitoring, and formal analysis, for efficacy. The SLowDOWN study is registered at https://www.clinicaltrialsregister.eu/ no. 2018–000859-40 and at https://clinicaltrials.gov/ no. NCT06770894.

Ethics

This study protocol was approved by the IEC "Comitato Etico AOU Policlinico Umberto I Università Sapienza" (Approval no. 493/19 Rif. 4951—July 7, 2019). No amendments were required during the study. This study was conducted in accordance with the Declaration of Helsinki, version 2013.

Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Primary endpoints

The study participants allocated to the two study arms were balanced for nearly all the characteristics considered (Table 1; Additional file 1: Table S1). The mean ± SD age was 67.5 ± 10.4 years in the treatment group and 65.2 ± 10.5 years in the placebo group ($p = 0.208$). The duration of diabetes was 7.9 ± 6.4 and 7.5 ± 5.9 years ($p = 0.964$), while the HbA1c levels were 6.5 ± 0.6% and 6.4 ± 0.5%, respectively ($p = 0.248$). At baseline, 8 participants (6.1%) were premenopausal (median age 45 years, range 36–52), equally distributed between treatment groups.

The overall compliance for the study treatment was high and comparable between arms in both the

Table 1 Characteristics of the study participants by treatment arm at baseline

	Sitagliptin	Placebo	*p* value
N	66	66	
Age (years)	67.5 ± 10.4	65.2 ± 10.5	0.2085
White ethnicity (%)	65 (98.5)	64 (97.0)	0.5592
HbA1c (%)	6.5 ± 0.6	6.4 ± 0.5	0.2481
T2D duration (years)	7.9 ± 6.4	7.5 ± 5.9	0.9638
Weight (kg)	72.5 ± 11.4	73.6 ± 12.1	0.3339
Waist circumference (cm)	99.4 ± 10.0	100.7 ± 12.3	0.4717
BMI (kg/m^2)	28.5 ± 4.0	28.7 ± 4.1	0.5325
Systolic blood pressure (mmHg)	130.2 ± 12.8	129.1 ± 12.2	0.5598
Diastolic blood pressure (mmHg)	79.9 ± 8.3	79.9 ± 7.3	0.9264
Heart rate (bpm)	75.3 ± 8.7	77.0 ± 9.9	0.3964
Fasting blood glucose (mg/dl)	118.5 ± 20.0	116.3 ± 21.2	0.5107
Glycated hemoglobin (%)	6.5 ± 0.6	6.4 ± 0.5	0.2379
Total cholesterol (mg/dl)	178.8 ± 35.8	178.0 ± 36.6	0.832
HDL cholesterol (mg/dl)	54.7 ± 11.2	54.9 ± 13.1	0.9809
Triglycerides (mg/dl)	127.5 ± 54.7	137.5 ± 63.7	0.4256
LDL cholesterol (mg/dl)	100.9 ± 35.6	97.2 ± 30.7	0.3091
AST (U/L)	21.3 ± 9.5	22.5 ± 9.6	0.4408
ALT (U/L)	20.9 ± 9.8	23.4 ± 11.5	0.3425
Gamma-GT (U/L)	25.2 ± 17.2	30.0 ± 25.5	0.6513
Serum calcium (mg/dl)	9.1 ± 1.5	9.2 ± 1.6	0.8273
Serum phosphate (mg/dl)	4.2 ± 0.7	4.2 ± 0.6	0.5769
PTH (pg/ml)	43.4 ± 29.7	55.0 ± 49.0	0.519
ALP (UI/L)	56.9 ± 15.0	78.7 ± 16.2	0.053
Vitamin D (ng/ml)	29.5 ± 18.9	30.2 ± 16.2	0.4355
Serum creatinine (mg/dl)	0.8 ± 0.2	0.7 ± 0.2	0.0197
Albuminuria (%)			
Normoalbuminuria	24 (92.3)	25 (96.2)	0.552
Microalbuminuria	2 (7.7)	1 (3.8)	
Macroalbuminuria	0 (0.0)	0 (0.0)	
eGFR (ml/min/1.73 m^2)			
MDRD	99.2 ± 34.0	114.5 ± 35.5	0.0148
CKD-Epi	91.0 ± 21.8	100.4 ± 19.3	0.0146
eGFR (CKD-Epi) in classes			
< 30	0 (0.0)	0 (0.0)	0.9901
30–50	1 (1.8)	1 (1.7)	
> 50	56 (98.2)	57 (98.3)	
FT3 (pmol/L)	2.9 ± 0.5	2.9 ± 0.5	0.9572
FT4 (pmol/L)	5.5 ± 5.8	4.0 ± 5.1	0.4639
TSH (pmol/L)	2.6 ± 2.4	2.1 ± 1.5	0.4922
Total bilirubin (mg/dl)	0.5 ± 0.3	0.6 ± 0.4	0.5149
Direct bilirubin (mg/dl)	0.2 ± 0.1	0.2 ± 0.1	0.5162
Indirect bilirubin (mg/dl)	0.3 ± 0.2	0.4 ± 0.4	0.1797

Abbreviations. *ALP*, alkaline phosphatase; *ALT*, alanine aminotransferase; *AST*, aspartate aminotransferase; *BMI*, body mass index; *CKD-Epi*, Chronic Kidney Disease Epidemiology Collaboration; *eGFR*, estimated glomerular filtration rate; *FT3*, free triiodothyronine; *FT4*, free thyroxine; *Gamma-GT*, gamma-glutamyl transferase; *GDM*, gestational diabetes mellitus; *HbA1c*, glycated hemoglobin; *HDL*, high-density lipoprotein; *LDL*, low-density lipoprotein; *MDRD*, Modification of Diet in Renal Disease; *PTH*, parathyroid hormone; *T2D*, type 2 diabetes; *TSH*, thyroid-stimulating hormone; *UI*, international unit; *U/L*, units per liter

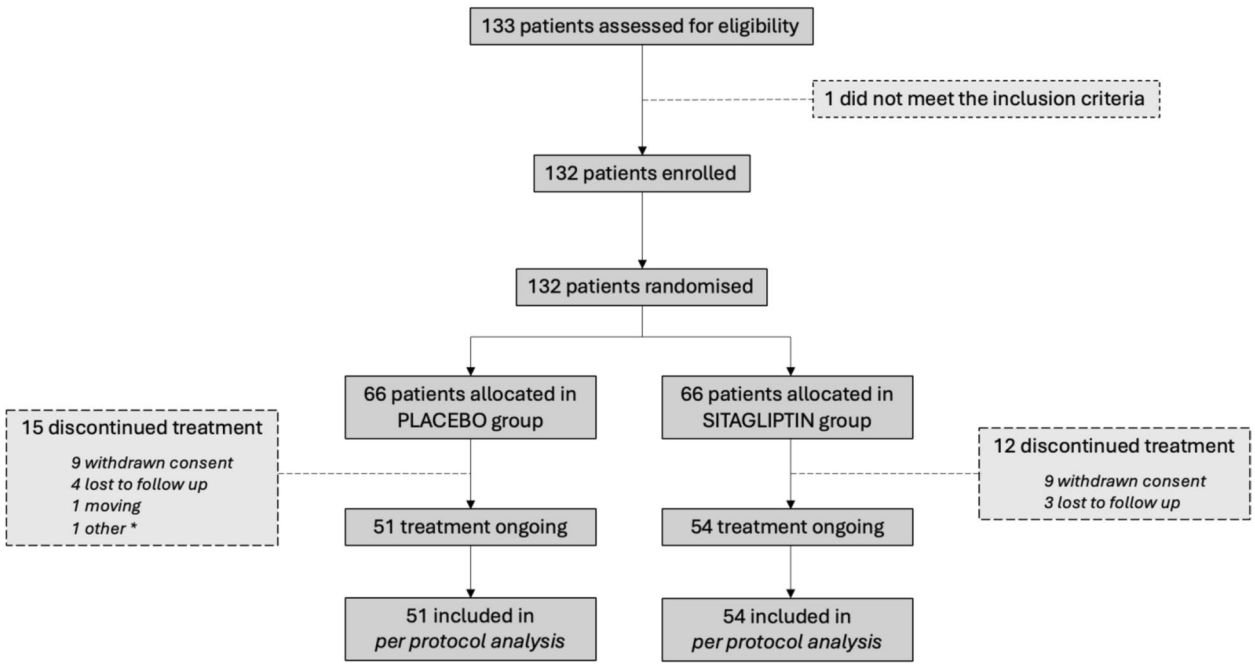

Fig. 1 SLowDOWN trial profile

intention-to-treat (ITT) and per-protocol (PP) analyses (% compliance (mean) for sitagliptin: ITT 88.5 ± 27.5%, PP 93.1 ± 19.6%; placebo: ITT 85.3 ± 30.3%, PP 95.7 ± 9.2%; both $p > 0.05$). The trial profile is shown in Fig. 1.

The total femur *T* score did not change significantly after 52 weeks in the sitagliptin group (estimated mean difference − 0.02; 95% CI − 0.07; 0.03; $p = 0.46$), whereas it significantly decreased in the placebo group (estimated mean difference − 0.13; 95% CI − 0.19; − 0.07; $p < 0.0001$). The between-group difference was statistically significant in favor of sitagliptin (estimated mean difference 0.11; 95% CI 0.03; 0.19; $p = 0.0063$). Similarly, the femur neck *T* score did not significantly change after 52 weeks in the sitagliptin group (estimated mean difference − 0.03; 95% CI − 0.11; 0.05; $p = 0.44$), unlike in the placebo group, where a significant decrease was reported (estimated mean difference − 0.08; 95% CI − 0.16; − 0.00; $p = 0.047$). However, the between-group difference did not reach statistical significance ($p = 0.373$). No significant within-group or between-group differences were documented for the BMD at the femur neck, femur total, lumbar spine, or lumbar spine *T* score or TBS. The results of the DXA-derived primary endpoints are reported in Table 2.

No between-group differences emerged for biomarkers of bone metabolism at the end of the study. The serum 25(OH) vitamin D concentration did not differ between the groups at baseline and did not change significantly during the study duration. All between-group differences in bone metabolism markers (ITT population) are shown in Table 3.

Secondary endpoints

Serum DPP4 activity was significantly lower in the sitagliptin group than in the placebo group at 24 weeks (estimated mean difference − 3963.86; 95% CI − 5727.20; − 220,052; $p < 0.0001$) and 52 weeks (estimated mean difference − 2070.25; 95% CI − 3752.09; − 388.41; $p = 0.0168$; Additional file 2: Table S2). No within- or between-group differences in FBG or HbA1c at 52 weeks were reported (Additional file 3: Table S3). Circulating cytokine levels did not differ between the study groups at baseline (Additional file 4: Table S4). Comparisons between groups revealed significantly lower levels of CXCL10, eotaxin, GM-CSF, IL-1α, IL-7, MIP1β, PDGF-BB, and VEGF in the sitagliptin group than in the placebo group at 24 weeks (Additional file 5: Table S5).

Per-protocol (PP) analysis

The overall PP analysis confirmed the results obtained from the ITT analysis, which revealed a statistically significant difference in the total femur *T* score in favor of sitagliptin vs. placebo (estimated between-group differences at 52 + 0.10 weeks; 95% CI 0.02–0.18; $p = 0.0121$). The results of the PP analysis for the primary endpoints are summarized in Additional file 6: Table S6.

Table 2 Primary endpoint: between-group differences in DXA results (ITT population)

	Visit	Sitagliptin			Placebo			Sitagliptin vs. placebo	
		Estimated mean and 95% CI	Estimated mean difference from T0 and 95% CI	Within group *p* value*	Estimated mean and 95% CI	Estimated mean difference from T0 and 95% CI	Within group *p* value*	Between-group difference (estimated mean and 95% CI) (Sita vs. Pl)	Between-group *p* value**
BMD femur neck	0	0.73 (0.70; 0.76)			0.73 (0.70; 0.76)				
	52	0.74 (0.70; 0.78)	0.01 (−0.02; 0.04)	0.2981	0.72 (0.68; 0.76)	−0.01 (−0.04; 0.02)	0.4903	0.02 (−0.02; 0.06)	0.2231
BMD femur neck *T* score	0	−1.07 (−1.31; −0.83)			−1.09 (−1.33; −0.85)				
	52	−1.10 (−1.35; −0.85)	−0.03 (−0.11; 0.05)	0.4365	−1.17 (−1.42; −0.92)	−0.08 (−0.16; −0.00)	0.0471	0.05 (−0.06; 0.16)	0.373
BMD femur total	0	0.88 (0.85; 0.91)			0.88 (0.85; 0.91)				
	52	0.91 (0.87; 0.95)	0.02 (−0.01; 0.05)	0.1149	0.87 (0.83; 0.91)	−0.01 (−0.04; 0.02)	0.4519	0.03 (−0.01; 0.07)	0.1019
BMD femur total *T* score	0	−0.48 (−0.73; −0.23)			−0.50 (−0.75; −0.25)				
	52	−0.50 (−0.75; −0.25)	−0.02 (−0.07; 0.03)	0.4628	−0.63 (−0.88; −0.38)	−0.13 (−0.19; −0.07)	< .0001	0.11 (0.03; 0.19)	0.0063
BMD lumbar spine	0	0.99 (0.95; 1.03)			0.97 (0.93; 1.01)				
	52	1.00 (0.96; 1.04)	0.01 (0.00; 0.02)	0.0861	0.96 (0.92; 1.00)	−0.00 (−0.01; 0.01)	0.6034	0.01 (−0.00; 0.02)	0.1168
BMD lumbar spine *T* score	0	−0.48 (−0.82; −0.14)			−0.72 (−1.06; −0.38)				
	52	−0.43 (−0.78; −0.08)	0.06 (−0.01; 0.13)	0.0857	−0.73 (−1.08; −0.38)	−0.01 (−0.08; 0.06)	0.7646	0.07 (−0.03; 0.17)	0.1573
BMD TBS	0	1.21 (1.18; 1.24)			1.20 (1.17; 1.23)				
	52	1.20 (1.17; 1.23)	−0.01 (−0.04; 0.02)	0.4058	1.20 (1.17; 1.23)	0.00 (−0.03; 0.03)	0.9301	−0.02 (−0.07; 0.03)	0.5188

Abbreviations. *BMD*, bone mineral density; *CI*, confidence interval; *TBS*, trabecular bone score

Safety and tolerability

Sitagliptin was safe and well tolerated. Five nonserious AEs were reported, all of which were resolved. In the sitagliptin group, two mild AEs (fall, diarrhea) and one moderate AE (shoulder pain) occurred. In the placebo group, one severe AE (sciatic pain) and one moderate AE (coxarthrosis) were reported. No deaths occurred.

Discussion

This randomized controlled trial explored the potential effects of the DPP4 inhibitor sitagliptin on bone mineral density and related biomarkers in women with type 2 diabetes, a population at increased risk of osteoporosis and fractures. In this selected cohort with normal or mildly reduced baseline BMD, sitagliptin treatment was associated with preservation of the total femur *T* score over 52 weeks, with a between-group significant difference in favor of sitagliptin of 0.11 (95% CI: 0.03–0.19, $p=0.0063$). No significant difference was observed in other skeletal sites or bone turnover markers.

At the end of the trial, glucose control and other metabolic parameters were comparable between the groups, and no serious adverse events were reported. This is the first double-blind, placebo-controlled RCT specifically evaluating the effects of chronic DPP4-Is treatment on bone health in patients with type 2 diabetes. Poor glucose control, metabolic legacy, and treatment with certain glucose-lowering agents, i.e., insulin, sulfonylureas, and thiazolidinediones, are known to negatively impact bone health in people living with diabetes [5]. Therefore, for the purpose of this trial, we exclusively enrolled individuals with type 2 diabetes who were maintaining stable treatment with metformin alone at the maximum tolerated dose and who achieved good glucose control. Furthermore, to investigate the specific effects of sitagliptin on bone metabolism, we excluded individuals with a confirmed diagnosis of osteoporosis and those requiring anti-osteoporotic treatment from this trial. This approach allowed us to focus our investigation on the impact of sitagliptin while mitigating potential interference from

Table 3 Between-group differences in bone metabolism markers (ITT population)

	Visit	Sitagliptin			Placebo			Sitagliptin vs. placebo	
		Estimated mean and 95% CI	Estimated mean difference from T0 and 95% CI	Within group *p* value*	Estimated mean and 95% CI	Estimated mean difference from T0 and 95% CI	Within group *p* value*	Between-group difference (estimated mean and 95% CI) (Sita vs. Pl)	Between-group *p* value**
P1NP	0	33.80 (30.37; 37.23)			29.48 (26.03; 32.93)				
	24	38.14 (26.27; 50.01)	4.33 (−7.79; 16.45)	0.485	30.37 (18.54; 42.20)	0.90 (−11.19; 12.99)	0.8849	3.44 (−13.69; 20.57)	0.6947
	52	32.07 (28.26; 35.88)	−1.74 (−6.29; 2.81)	0.4562	29.09 (25.24; 32.94)	−0.39 (−4.99; 4.21)	0.8686	−1.35 (−7.82; 5.12)	0.6842
CTX	0	0.25 (0.22; 0.28)			0.26 (0.23; 0.29)				
	24	0.27 (0.24; 0.30)	0.02 (−0.02; 0.06)	0.3777	0.27 (0.24; 0.30)	0.01 (−0.03; 0.05)	0.7064	−0.01 (−0.07; 0.05)	0.7128
	52	0.29 (0.25; 0.33)	0.05 (0.00; 0.10)	0.05	0.28 (0.24; 0.32)	0.02 (−0.03; 0.07)	0.3632	−0.03 (−0.09; 0.03)	0.4459
OPN	0	16,644.26 (13,892.90; 19,395.62)			14,689.99 (11,902.68; 17,477.30)				
	24	20,576.43 (16,728.25; 24,424.61)	3932.17 (96.82; 7767.52)	0.0464	20,664.04 (16,547.63; 24,780.45)	5974.05 (1847.43; 10,100.67)	0.0052	−2041.89 (−7675.62; 3591.84)	0.4786
	52	18,964.79 (15,877.75; 22,051.83)	2320.54 (−750.49; 5391.57)	0.1408	19,828.66 (16,783.29; 22,874.03)	5138.67 (2092.91; 8184.43)	0.0012	−2818.14 (−7143.40; 1507.12)	0.2037
OC	0	8837.68 (7579.61; 10,095.75)			7799.63 (6523.25; 9076.01)				
	24	9155.06 (7283.52; 11,026.60)	317.38 (−1703.14; 2337.90)	0.7586	7040.97 (5023.11; 9058.83)	−758.66 (−2927.02; 1409.70)	0.494	1076.04 (−1887.79; 4039.87)	0.4779
	52	8118.10 (6646.31; 9589.89)	−719.57 (−2376.68; 937.54)	0.3962	9300.30 (7842.10; 10,758.50)	1500.67 (−155.09; 3156.43)	0.0779	−2220.25 (−4562.80; 122.30)	0.0653
OPG	0	555.03 (498.94; 611.12)			534.02 (477.22; 590.82)				
	24	507.39 (430.50; 584.28)	−47.64 (−122.25; 26.97)	0.2128	572.84 (490.80; 654.88)	38.82 (−41.50; 119.14)	0.3451	−86.46 (−196.08; 23.16)	0.1244
	52	532.43 (469.96; 594.90)	−22.60 (−82.23; 37.03)	0.4589	568.91 (507.20; 630.62)	34.88 (−24.25; 94.01)	0.2495	−57.48 (−141.46; 26.50)	0.1819
Sclerostin	0	1274.76 (−321,996; 324,545.3)			1339.57 (−319,355; 322,034.3)				
	24	1411.56 (−321,859; 324,682.3)	136.80 (−301.07; 574.67)	0.5416	1299.38 (−319,396; 321,994.3)	−40.18 (−517.29; 436.93)	0.8692	176.98 (−470.60; 824.56)	0.5933
	52	1042.06 (−322,229; 324,312.7)	−232.70 (−595.89; 130.49)	0.2119	1373.57 (−319,321; 322,068.3)	34.00 (−329.79; 397.79)	0.855	−266.70 (−780.76; 247.36)	0.3115
Vitamin D	0	29.47 (25.50; 33.44)			30.39 (26.44; 34.34)				
	24	29.99 (24.91; 35.07)	0.52 (−4.19; 5.23)	0.83	30.99 (25.91; 36.07)	0.60 (−4.14; 5.34)	0.8032	176.98 (−470.60; 824.56)	0.5933
	52	29.13 (24.87; 33.39)	−0.34 (−4.15; 3.47)	0.86	31.07 (26.79; 35.35)	0.69 (−3.17; 4.55)	0.7275	−266.70 (−780.76; 247.36)	0.3115

preexisting bone conditions or concurrent osteoporosis therapies. Moreover, since a significant proportion of fractures occur in older women with osteopenia, optimizing bone health in this population is of primary importance [22].

To the best of our knowledge, no previous RCT has investigated the effects of DPP4-Is on bone mineralization in individuals with type 2 diabetes. Data from meta-analyses have reported either protective [17, 18] or neutral [19] effects of chronic DPP4-Is treatment on fracture risk; however, none of these findings is derived from clinical trials specifically designed for testing bone health outcomes in patients with diabetes [17–19, 23].

In Our study, patients with type 2 diabetes in the two arms had comparable fracture histories at baseline, with no fractures occurring during the trial. As per study design, no participants had osteoporosis or were on anti-osteoporotic treatments. Compared with the sitagliptin group, the placebo group presented a significant decrease in BMD at the total femur site, with an annual decrease in BMD (~ 1.13%), which is consistent with previous reports [24, 25]. At other skeletal sites, BMD changes in the placebo group were small and non-significant, which limits the likelihood of detecting significant between-group differences for a drug expected to exert a protective rather than osteogenic effect.

In our study, treatment with sitagliptin significantly reduced circulating DPP4 activity at 24 and 52 weeks, along with decreased chemokine levels at 24 weeks. Experimental evidence has shown that DPP4 plays a role in immune-inflammatory processes and bone metabolism by modulating substrates such as CXCL10 and GM-CSF, which influence osteogenic differentiation and cytokine production [9–11, 26–29]. Previous studies described eotaxin and CXCL10 as endogenous substrates of the DPP4 enzyme [9], and their circulating levels were significantly reduced by 24 weeks of teneligliptin treatment in a small clinical study [10]. The DPP4 enzyme promotes the expression of colony-stimulating factors, such as GM-CSF, which take part in the pathogenesis of inflammatory diseases [27]. DPP4 activity also contributes to the development of chronic complications of diabetes by regulating the VEGF/VEGFR axis through its proteolytic activity [11]. DPP4-truncated proteins can influence the production and release of cytokines such as IL-1, IL-6, and CSFs through a cascade mechanism [26]. This concept extends to the potential regulation of bone metabolism by DPP4; consequently, chronic DPP4 inhibition may affect bone remodeling by influencing chemokines, interleukins, and other cytokines involved in bone mineralization processes. Thus, the observed decrease in BMD loss following sitagliptin treatment reported in the present study may be at least partly attributed to a modulation of the inflammatory pattern associated with skeletal health in the actively treated group compared with the placebo group.

Other mechanisms, including the upregulation of gut hormones such as glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptides 1 and 2, may also be associated with BMD preservation, according to initial experimental evidence [29]. Further studies with longer follow-up periods are warranted to elucidate the mechanisms and clinical implications of sitagliptin on bone health comprehensively.

Overall, this study suggests that 52 weeks of sitagliptin treatment may help preserve total hip BMD *T* score in women with type 2 diabetes at low risk of osteoporosis, with a significant advantage over placebo. While preliminary, these findings point to a potential added value of sitagliptin beyond glycemic control and may constitute a valuable basis in the context of a randomized controlled trial for future investigations in broader cohorts, including individuals at higher fracture risk.

The absence of significant differences in glucose control or metabolic parameters between the groups after treatment underscores the potential specific effects of sitagliptin on bone metabolism. Moreover, sitagliptin has a well-known favorable safety profile and high tolerability, and data from this trial confirmed a very low incidence of side effects/adverse events associated with its use.

This study has limitations that must be acknowledged. First, a statistically significant between-group difference was observed exclusively for the total proximal femur *T* score, whereas absolute BMD values at the same site and all other skeletal regions did not achieve statistical significance. Nevertheless, the pattern of change across sites was directionally consistent, favoring sitagliptin over placebo. The use of *T* scores, which are standardized against reference populations, may confer greater sensitivity to subtle changes over a relatively short observation period. The study cohort was restricted to women with type 2 diabetes who had normal or only mildly reduced BMD at baseline and were not receiving osteoporosis treatment, in order to minimize confounding from preexisting skeletal disease or its management. While this design enhanced internal validity, it also reduced the expected rate of bone loss over 12 months, thereby Limiting the magnitude of detectable between-group differences. Given the observed variability, the minimum difference detectable with 80% power in this sample was close to the effect size identified at the total hip, which may partly explain the absence of significant findings at other skeletal sites. These considerations support an interpretation of the total hip result as hypothesis-generating and emphasize the need for replication in larger studies with

longer follow-up and in populations at higher fracture risk.

Second, the study population specifically included women with type 2 diabetes on stable metformin therapy. This choice was aimed at minimizing heterogeneity and treatment-related confounding; however, it limits the generalizability of the results, particularly to male individuals or those receiving different antidiabetic regimens.

Moreover, while a panel of bone-related inflammatory cytokines were assessed to explore potential mechanistic pathways, several markers did not significantly change in response to sitagliptin. This may reflect either the complexity of the role of DPP4 in immune regulation or the limited sensitivity of systemic biomarkers to capture localized changes in bone remodeling. However, further mechanistic studies are needed to elucidate the biological pathways underlying our results.

Finally, another study limitation could be the relatively short treatment period. Although this timeframe may not be sufficient to assess long-term effects on fracture risk, it still captures short-term changes in bone mineral density under pharmacological intervention. The results observed, while not fully conclusive, may offer clinically relevant indications to guide future studies with longer treatment durations and extended observation periods. Similarly, studies conducted in different populations—such as patients with pronounced osteoporosis—might reveal more pronounced differences, especially in other skeletal districts.

Conclusions

In conclusion, the SLowDOWN trial provides novel data on the potential effects of DPP4-Is on bone health in the context of a specifically designed RCT addressing women's specific frailties, such as osteoporosis and fractures, the risk of which further increases in the presence of diabetes.

Our data are consistent with the hypothesis that sitagliptin may help preserve bone health in women with type 2 diabetes, a population at increased risk of osteoporosis, particularly when used in early stages to prevent bone deterioration. While preliminary, these findings add evidence to the potential effects of chronic DPP4-I treatment on bone metabolism. If confirmed, they may contribute to inform and to orient clinical decision-making within the wide range of therapeutic options for diabetes care, with significant implication for multiple approach to diabetes treatment.

Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
AMC	7-Amino-4-methylcoumarin
AST	Aspartate aminotransferase
BMD	Bone mineral density
BMI	Body mass index
CI	Confidence interval
CTX	Crosslinked C-terminal telopeptide
DPP4	Dipeptidyl peptidase-4
DPP4-Is	Dipeptidyl peptidase-4 inhibitors
DXA	Dual-energy X-ray absorptiometry
eCRF	Electronic case report form
FBG	Fasting blood glucose
G-CSF	Granulocyte colony-stimulating factor
GGT	Gamma-glutamyl transferase
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HbA1c	Glycated hemoglobin
HDL	High-density lipoprotein cholesterol
IFN-γ	Interferon gamma
IL	Interleukin
ITT	Intention-to-treat
OC	Osteocalcin
OPG	Osteoprotegerin
OPN	Osteopontin
P1NP	Type I collagen N-propeptide
PDGF-BB	Platelet-derived growth factor BB
PP	Per-protocol
PTH	Parathyroid hormone
RCT	Randomized controlled trial
SUSAR	Suspected unexpected serious adverse reactions
TBS	Trabecular bone score
TNF-α	Tumor necrosis factor alpha
VEGF	Vascular endothelial growth factor
25(OH)D	25-Hydroxyvitamin D

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-04363-w.

Additional file 1: Table S1 Other characteristics of study participants by treatment arm at baseline.

Additional file 2: Table S2 Secondary endpoints: between-group differences in DPP4 concentration and activity (ITT population).

Additional file 3: Table S3 Between-group differences in metabolism and clinical parameters (ITT population).

Additional file 4: Table S4 Mean baseline values of cytokines by study arm.

Additional file 5: Table S5 Between-group differences in bone metabolism markers (ITT population).

Additional file 6: Table S6 Primary endpoint: between-group differences in DXA results (PP population).

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Authors' contributions
Contributors. MGC, MGB, IB and SM conceived the study. MGC, MGB, SM and AN had full access to the source study data and took responsibility for the integrity of the data. MCG and IB handled submission and updates to the Ethics Committee and coordinated the acquisition/management of the experimental drug. IB, TF, FAC, SD, GP, ER, EB, and VV were involved in patient recruitment and data collection. FS, FAC, EA and OG performed the centralized lab analyses. AN completed the statistical analyses and the final study report. MGC, MGB, SM, NN and AL contributed to the interpretation of results and provided critical revision of the manuscript for important intellectual content. All the authors contributed to the concept and design of the study, development of the protocol, and interpretation of the data. MGC was the principal investigator of this study. IB wrote the first draft of the manuscript. All the authors were involved in the decision to submit this manuscript for publication. All authors read and approved the final manuscript.

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Data availability
The data that support the findings of this study are available upon request from the corresponding author MGC.

Declarations

Ethics approval and consent to participate
This study protocol was approved by the IEC "Comitato Etico AOU Policlinico Umberto I Università Sapienza" (Approval no. 493/19 Rif. 4951—July 7, 2019). No amendments were required during the study. This study was conducted in accordance with the Declaration of Helsinki, version 2013.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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