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ORIGINAL ARTICLE

Clinical Trials and Investigations

Zoledronic acid increases spine bone mass and prevents hip bone loss after bariatric surgery: a randomized placebo-controlled study

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Abstract

Objective: The aim of this study was to investigate the effects of zoledronic acid for the prevention of bone loss after bariatric surgery.

Methods: In this randomized, double-blinded study, 59 patients undergoing Roux-en-Y gastric bypass or sleeve gastrectomy (mean [SD], age: 48.9 [6.3] years, BMI: 42.3 [5.3], 73% female) were randomly assigned (1:1) to receive either zoledronic acid (5 mg; intervention [INT]) or placebo (control [CON]) preoperatively. The primary endpoint was the change in spine volumetric bone mineral density (vBMD) at 12 months after surgery. Secondary outcomes included changes in hip and femoral neck vBMD and areal BMD.

Results: The estimated mean treatment effects of zoledronic acid on the spine and total hip were 6.8 mg/cm^3 (95% CI 1.9–11.7; $p = 0.003$) and 5.0 mg/cm^3 (95% CI: 1.4–8.5; $p = 0.006$), respectively. Bone mass in the spine increased by 2.6% in INT, whereas no changes were observed in CON. Additionally, bone loss in the total hip was prevented in INT compared with CON (vBMD: −0.6% vs. −3.6%; $p = 0.006$).

Conclusions: Zoledronic acid increases bone mass in the spine and prevents bone loss in the hip region after bariatric surgery compared with placebo.

INTRODUCTION

In 2016, more than 600,000 bariatric surgery procedures were performed globally [1]. In addition to long-term weight reduction, bariatric surgery also improves comorbidities related to obesity and lowers mortality rates [2]. However, the two most commonly performed bariatric surgery procedures, Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG), have negative effects on bone metabolism [3–5] and increase the risk of fractures [6–8]. These negative effects on the skeletal system are considered to be multifactorial, in which mechanisms include mechanical unloading, hormonal changes, malnutrition, and changes in body composition [5].

Bariatric surgery causes significant bone loss during the first year after surgery, with declines in bone mineral density (BMD) in the lumbar spine, total hip, and femoral neck ranging from ∼3% to 15% [3, 4, 9–12]. Patients typically reach a plateau in body weight within ∼12 months after surgery, but the accelerated decline in BMD compared with the age-related loss continues despite weight stability [4, 9, 13]. Few studies have performed long-term follow-up, i.e., 5 to 7 years after surgery, and only for RYGB [10, 14]. These studies have shown up to 12%, 17%, and 12% declines in areal BMD (aBMD) in the lumbar spine [10], total hip [14] and femoral neck [10], respectively. One decade after RYGB, more than one-quarter of postmenopausal women and men over age 50 years had developed osteoporosis [15].

Currently, the optimum treatment for preventing bone loss after bariatric surgery is unknown. The efficacy of nutritional supplementation with calcium and vitamin D has been found to be limited [16]. Exercise intervention, including resistance exercise and/or high-impact activities, can attenuate or prevent bone loss in the lumbar spine, hip, and/or femoral neck, although only when adherence is high [17–19]. Therefore, alternative treatments are necessary for preventing bone loss in patients undergoing bariatric surgery.

Bisphosphonates inhibit osteoclast activity and reduce the risk of fractures in patients with osteoporosis [20]. In addition, bone resorption in high bone turnover diseases has been shown to be normalized [21–24]. A recent pilot study with a randomized-controlled design showed promising effects of risedronate for preventing bone loss following SG [25]. Based on these findings, the aim of this study was to assess whether zoledronic acid can prevent bone loss in patients undergoing bariatric surgery. We hypothesized that zoledronic acid will prevent excessive bone resorption and reduce bone loss after bariatric surgery.

Study Importance

What is already known?

- Bariatric surgery is associated with significant bone loss and a 21% to 44% higher risk of fractures compared with that in adults of similar age, sex, and BMI.
- Bisphosphonates, such as zoledronic acid, are commonly used to treat osteoporosis, increase bone mineral density, and reduce fracture risk, and preliminary studies suggest they may also prevent bone loss after bariatric surgery; however, larger studies are needed to confirm this.

What does this study add?

- This study shows that zoledronic acid can effectively prevent bone loss in patients undergoing bariatric surgery.
- Specifically, zoledronic acid increases spine bone mass and prevents bone loss in the total hip region.

How might these results change the direction of research or the focus of clinical practice?

- These results suggest that short-term bone loss after bariatric surgery can be mitigated with zoledronic acid.
- Future research should focus on refining patient selection criteria for this treatment, considering traditional fracture risk factors such as age, gender, postmenopausal status, and bone mass.

METHODS

Study design

This randomized, double-blinded, single-center study was carried out in a public hospital in Denmark and was approved by the Regional Committee on Health Research Ethics for Southern Denmark (project identifier S-20190134). The trial is registered at ClinicalTrials.gov (NCT04742010). The results are reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement. The study protocol has been published elsewhere [26] but is briefly summarized herein. After enrollment and baseline assessment, participants were evenly randomized into two groups: the group receiving zoledronic acid (intervention [INT]) or the group receiving placebo (control [CON]). Participants were administered zoledronic acid or placebo 180 to 7 days prior to surgery, and follow-up assessment was performed 12 months after surgery. Initially, the earliest administration date was set at 59 days prior to surgery; however, we chose to change it to 180 days due to ≈20% of the participants having to be excluded because of surgery delays caused by the COVID-19 pandemic. A single dose of zoledronic acid (range, 1–5 mg) has long-lasting antiresorptive effects, i.e., up to 3 to 5 years [27]; therefore, extending the time from administration to surgery was deemed acceptable.

Participants

Patients who were referred to RYGB or SG at the University Hospital of Southern Denmark, Esbjerg, participated in this study. Details

regarding surgery procedures have been published earlier [26]. Inclusion criteria were age ≥35 years and eligibility for bariatric surgery according to the Danish National Guidelines. These include one of the following two criteria: 1) body mass index (BMI) ≥ 35 kg/m^2 and an obesity-related comorbidity of type 2 diabetes, sleep apnea, arthrosis of the hip or knee, polycystic ovary syndrome with an unmet wish for pregnancy, or treatment resistant hypertension; or 2) BMI ≥ 40 kg/m^2 with a significant medical justification for weight loss (other than those mentioned in the first point). Exclusion criteria were current or previous treatment with antiosteoporotic agents; current treatment with oral glucocorticoids or other drugs with effects on bone metabolism; metabolic bone disease (although presence of osteoporosis was allowed); history of medical disorders with known effects on bone metabolism (hypo- and hyperthyroidism were allowed if treated and stable); pregnancy or breastfeeding; chronic kidney disease with estimated glomerular filtration rate (eGFR) < 45 mL/min; hypocalcemia; and hypersensitivity to bisphosphonates, mannitol, or sodium citrate. After inclusion, participants were excluded if eGFR declined to less than 45 mL/min, the participant withdrew consent, or planned surgery was not performed within 180 days from the administration of the study medicine. Fertile women consented to using contraception with intrauterine devices or oral contraceptive pills with estradiol until 1 year after the administration of the study drug. All participants provided informed consent.

Randomization and masking

We randomized participants (1:1) into two groups, i.e., INT or CON, using computer-generated software. We employed block randomization with sizes of two, four, and six and stratified an equal number of participants undergoing RYGB or SG into each study arm. A detailed description of the randomization process, sequence generation, allocation concealment mechanism, implementation, and blinding has been provided elsewhere [26].

Procedures

A single dose of zoledronic acid 5 mg or placebo was administered in a solution containing 100 mL of saline water (0.9% sodium chloride) and slowly infused intravenously (≥15 min). Owing to the risk of anaphylaxis, participants were observed for at least 30 min at the study site after the infusion. The hospital pharmacy, University Hospital of Southern Denmark, prepared the study medicine on the day of administration in a separate location. Fertile women were screened for pregnancy using a urine human chorionic gonadotropin test on the day that they received the study medicine.

In order to ensure sufficient levels of calcium and vitamin D, all participants were advised supplements with calcium (citrate or carbonate) 400 mg twice daily and vitamin D 38 μg daily starting from inclusion and throughout the study. A loading dose of 100,000 IU of vitamin D3 was given orally if serum 25(OH)-vitamin D level was less than 25 nmol/L.

Outcomes

Changes in trabecular volumetric BMD (vBMD; milligrams per centimeters cubed) of the lumbar spine (L1-L2) was the primary outcome of this study. Secondary outcomes were total hip and femoral neck vBMD. We employed non-contrast enhanced abdominal/pelvic quantitative computed tomography (QCT; Siemens SOMATOM FORCE, Siemens Healthcare AG) to assess the changes in vBMD for these bone sites. Patients were scanned in the supine position with the QCTPro calibration phantom positioned beneath them to cover the area from L1 to below the lesser trochanter. The scans were performed as a helical acquisition with the following settings: tube voltage 120 kV (peak); 25 mAs; 38-cm field of vision; 168.5-cm table height; and 2-mm slice thickness and reconstructed at kernel Qr32. The Mindways QCT Pro software was used to conduct a three-dimensional reconstructive analysis of vBMD from the obtained images (Mindways Software Inc.).

Furthermore, we assessed areal BMD (aBMD; grams per centimeters squared) of the lumbar spine (L1-L4), femoral neck, and total hip using dual-energy x-ray absorptiometry (DXA; Hologic Horizon A), and venous blood samples were taken between 7 and 10 am after an overnight fast (minimum of 8 h). Plasma for analyses of bone formation (procollagen type I amino-terminal propeptide [P1NP]) and resorption (carboxy-terminal type I collagen [CTX-1]) markers was stored at −70°C until analysis. CTX-1 and P1NP were measured (iSYS, Immunodiagnostic Systems Ltd.) with coefficient of variation of 8.0% for both analyses. Serum calcium, 25(OH)-vitamin D, and parathyroid hormone (PTH) were measured using standard equipment.

Safety data were collected in accordance with the Good Clinical Practice Guidelines throughout the study. The participants were informed to notify the study site in the case of adverse events or reactions, and in addition, this information was systematically collected 1 and 12 months after surgery. Blood samples were taken 4 weeks after surgery to assess renal function (i.e., eGFR) and the occurrence of hypocalcemia.

Statistical analysis

The statistical procedures have been published elsewhere [26] and are briefly summarized herein. A sample size calculation was based on the change in lumbar spine vBMD 12 months after surgery. It was assumed that trabecular spine vBMD in those receiving zoledronic acid would remain unchanged at 12 months, whereas those receiving placebo would have a decline in vBMD of 12 mg/cm^3 with an SD of 27 [28]. A power analysis showed that a total of 42 participants were needed to detect a significant difference between the groups (repeated measures estimation, power of 0.80, significance level of 0.05, and correlation of 0.86). In order to allow for dropouts, we aimed to include 30 participants in each group.

The intention-to-treat principle was used to analyze the effect of zoledronic acid. A mixed-effects model with repeated measures, including a term for the interaction of group (INT or CON) and time,

was used to assess changes from baseline to 12 months (unadjusted analysis). For the adjusted analysis, the covariates age, gender, and surgery type (randomization factor) were included in the analysis. Changes in absolute values for vBMD and aBMD were correlated with absolute changes in body weight and CTX-1 using Pearson correlation. All analyses were performed using Stata version 18 (StataCorp LLC). We used Fisher exact test to assess the difference in the prevalence of hypocalcemia between groups. The significance level was set at $p < 0.05$.

RESULTS

Participant characteristics

We recruited all participants between February 11, 2021, and November 1, 2022, and details regarding participant flow are displayed in Figure 1. We screened a total of 220 patients, of whom 150 were deemed eligible to participate in this study. We enrolled 81 participants, of whom 64 completed the baseline assessment, 59 were randomized and were administered the study drug, and 53 completed the 12-month visit. Participant characteristics and bone outcomes at baseline are presented in Table 1. The baseline characteristics showed that the groups were well balanced for age, weight, surgery type, and time of administration of the study drug, as well as bone outcomes (Table 1), although a higher number of male individuals was allocated to INT compared with CON.

Body weight

At the 12-month follow-up, both INT and CON experienced a reduction in body weight: 31.2 kg (95% confidence interval [CI]: −34.8 to −27.5; $p < 0.001$) and 30.4 kg (95% CI: −34.5 to −26.4; $p < 0.001$),

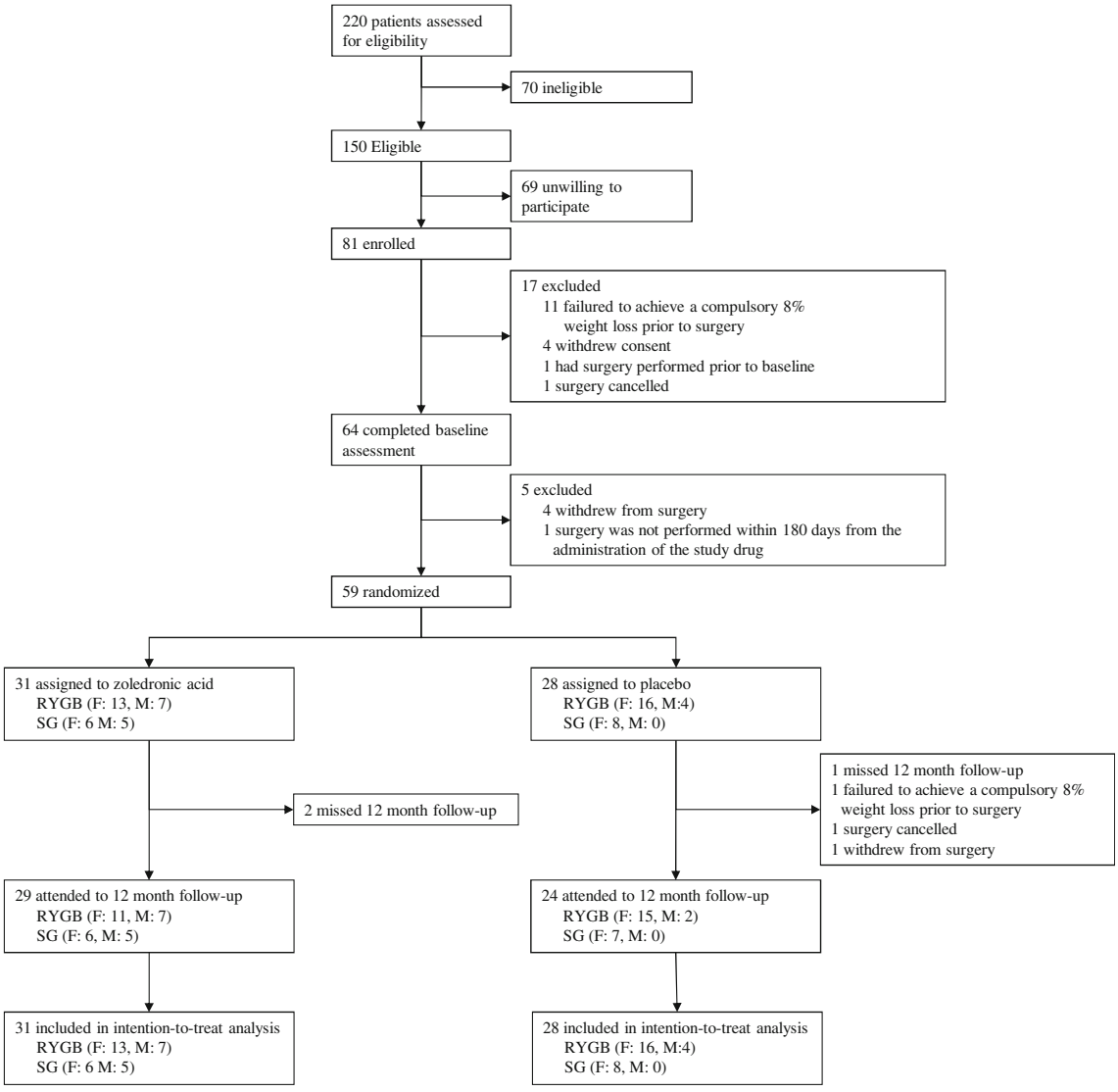

FIGURE 1 Participants' flow diagram. F, female; M, male; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy.

TABLE 1 Participant characteristics at baseline.

	All	INT	CON
N	59	31	28
Surgery type, RYGB/SG	40/19	20/11	20/8
Age, y	48.9 (6.3)	48.5 (6.3)	49.3 (6.5)
Female sex	43 (72.9%)	19 (61.3%)	24 (85.7%)
Male sex	16 (27.1.8%)	12 (38.7%)	4 (14.3%)
Postmenopausal women	19 (32.2%)	8 (44.4%)	11 (45.8%)
Male individuals aged ≥50 y	9 (52.9%)	7 (53.8%)	2 (50.0%)
Height, cm	171 (8.7)	172.3 (8.6)	169.5 (8.4)
Weight, kg	123.7 (18.0)	124.6 (20.9)	122.8 (14.4)
BMI, kg/m^2	42.3 (5.3)	41.8 (5.6)	42.8 (4.8)
Waist circumference, cm	126.8 (11.0)	126.6 (10.8)	123.4 (4.6)
Hip circumference, cm	132.4 (11.4)	130.2 (12.5)	134.8 (9.8)
Systolic blood pressure, mm Hg	131.1 (14.7)	134.4 (17.9)	127.4 (9.0)
Diastolic blood pressure, mm Hg	84.2 (8.9)	86.1 (11.2)	82.1 (4.7)
Administration of the study medication prior to surgery, d	33 (35.7)	26.3 (21.0)	40.4 (46.2)
Calciotropic hormones			
Calcium, mmol/L	2.4 (0.1)	2.4 (0.1)	2.4 (0.1)
25(OH)-vitamin D, nmol/L	72.4 (21.3)	70.1 (19.8)	74.8 (22.8)
PTH, pmol/L	7.8 (3.6)	7.7 (4.3)	7.9 (2.9)
QCT, mg/cm^3			
Trabecular spine vBMD	147.9 (29.2)	151.3 (25.6)	144.0 (32.7)
Trabecular total hip vBMD	163.6 (16.9)	164.5 (15.7)	162.0 (18.5)
Trabecular femoral neck vBMD	165.7 (16.7)	165.2 (17.3)	165.2 (18.6)
DXA, g/cm^2			
Spine aBMD	1.100 (0.14)	1.089 (0.17)	1.113 (0.11)
Total hip aBMD	1.103 (0.12)	1.120 (0.12)	1.085 (0.12)
Femoral neck aBMD	0.902 (0.12)	0.898 (0.12)	0.907 (1.11)
Spine T-score	0.49 (1.29)	0.53 (1.49)	0.39 (1.52)
Total hip T-score	1.20 (0.98)	1.34 (0.99)	1.05 (0.96)
Bone turnover markers			
CTX-1, µg/L	0.26 (0.16)	0.27 (0.15)	0.25 (0.16)
P1NP, µg/L	55.5 (19.5)	55.6 (17.9)	55.5 (21.5)

Note: Data are presented as means (SD). CON refers to the group treated with placebo, whereas INT refers to the group treated with zoledronic acid.
Abbreviations: aBMD, areal bone mineral density; CON, control; CTX-1, carboxy-terminal type I collagen; DXA, dual-energy x-ray absorptiometry; INT, intervention; P1NP, procollagen type I amino-terminal propeptide; PTH, parathyroid hormone; QCT, quantitative computed tomography; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy; vBMD, volumetric bone.

respectively, with no difference between the groups ($p = 0.79$). This weight loss corresponded to an ∼25% decrease in body weight and mean (SD) loss of about −10.7 (3.5) kg/m^2 in terms of BMI compared with baseline in both groups ($p < 0.001$).

Changes in lumbar spine BMD

The treatment effects of zoledronic acid on BMD at the lumbar spine, total hip, and femoral neck, measured by QCT and DXA, are displayed in Figure 2 and Table 2. Almost identical results were observed for the adjusted and unadjusted analysis; therefore, only data for the adjusted analysis are presented in the text, and the unadjusted analysis is shown in Table 2.

For trabecular spine vBMD and spine aBMD, significant between-group differences in favor of INT were observed: 6.8 mg/cm^3 (95% CI: 1.9 to 11.7; $p = 0.003$) and 0.053 g/cm^2 (95% CI: 0.019 to 0.088; $p = 0.002$), respectively. Compared with baseline, INT had an increase in spine vBMD (2.6%; $p = 0.028$) and preserved aBMD (1.1%; $p = 0.19$), whereas CON had unchanged vBMD (−2.0%; $p = 0.14$) and a 3.3% reduction in aBMD ($p < 0.004$; Figure 2A).

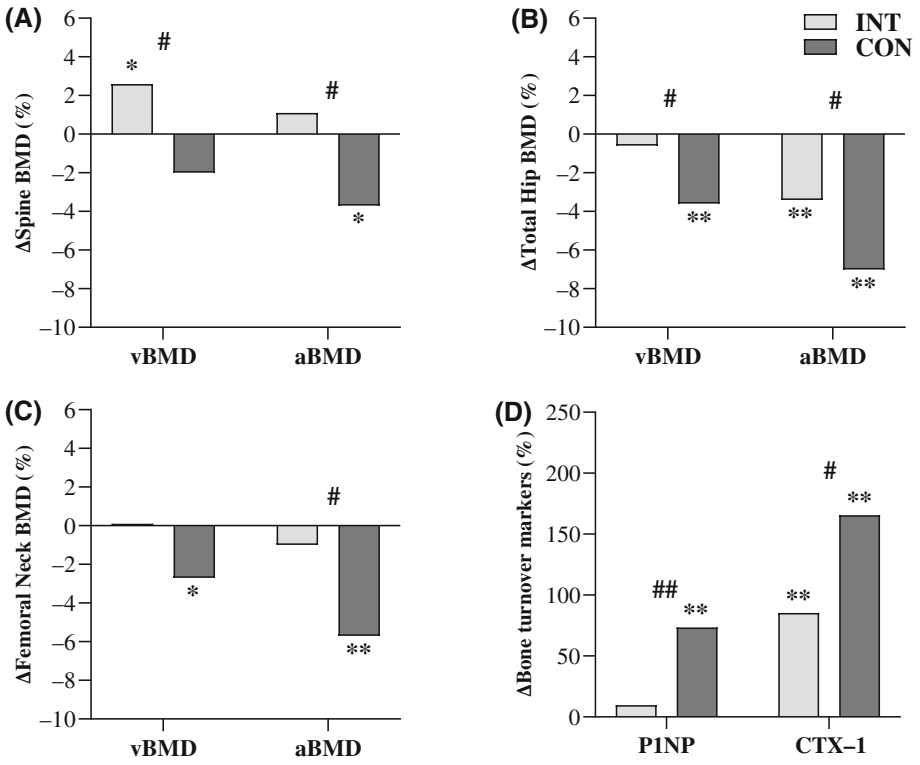

FIGURE 2 Twelve-month mean delta changes from baseline, based on adjusted model means. Light gray and dark gray bars represent the zoledronic acid and placebo groups, respectively. aBMD values are provided in grams per centimeters squared. CTX-1 and P1NP values are provided in micrograms per liter. vBMD values are provided in milligrams per centimeters cubed. Significance levels between groups are denoted as follows: $^{\#}p < 0.05$ and $^{\#\#}p < 0.001$. Significance levels within groups are denoted as follows: $^{*}p < 0.05$ and $^{**}p < 0.001$. aBMD, areal bone mineral density; CON, control; CTX-1, carboxy-terminal type I collagen; INT, intervention; P1NP, procollagen type I amino-terminal propeptide; vBMD, volumetric bone mineral density.

Changes in total hip BMD

For trabecular total hip vBMD and total hip aBMD, significant between-group differences in favor of INT were observed: 5.0 mg/cm^3 (95% CI: 1.4 to 8.5; $p = 0.006$) and 0.040 g/cm^2 (95% CI: 0.013 to 0.066; $p = 0.003$), respectively. vBMD was preserved in INT (−0.6%; $p = 0.46$), whereas CON had a 3.6% reduction ($p < 0.001$). Both groups experienced significant aBMD losses compared with baseline, although losses were larger in CON than INT (aBMD: −3.4% vs. −7.0%; $p = 0.003$; Figure 2B).

Changes in femoral neck BMD

For femoral neck aBMD, a significant between-group difference in favor of INT was observed of 0.043 mg/cm^2 (95% CI: −0.007 to −0.078; $p = 0.018$). CON had a reduction of 2.7% in vBMD ($p = 0.019$) and 5.7% in aBMD ($p < 0.001$), whereas INT had unchanged vBMD (0.0%; $p = 0.99$) and aBMD (−1.0%; $p = 0.46$) compared with baseline (Figure 2C).

Bone turnover markers

Bone turnover markers are presented in Table 3 and Figure 2D. For P1NP, a significant between-group difference of −34.7 µg/L was observed (95% CI: −49.7 to −19.7; $p < 0.001$). In INT, P1NP remained stable (9.6%; $p = 0.29$), whereas CON had marked increases of 73.4% compared with baseline ($p < 0.001$). Regarding CTX-1, we observed a between-group difference of −0.18 µg/L (95% CI: −0.32 to −0.04; $p = 0.013$), with INT having less pronounced increases of 85.4% ($p < 0.001$) compared with 165.6% ($p < 0.001$) in CON.

Change in markers of calcium homeostasis

Markers of calcium homeostasis are presented in Table 3. For serum calcium, no between-group differences were observed 1 and 12 months after surgery. One month after surgery, INT had increased PTH levels of 2.61 pmol/L (95% CI: 1.13 to 5.09; $p = 0.039$) compared with CON. By 12 months, no differences were observed between the groups ($p = 0.76$), with similar PTH levels compared with baseline ($p = 0.15$ and 0.11, respectively).

TABLE 2 Twelve-month treatment effect estimates on QCT- and DXA-acquired bone metrics.

	INT				CON				Absolute INT − CON	
	Baseline	**12 m**	**Δ**	**Δ%**	**Baseline**	**12 m**	**Δ**	**Δ%**		***p* value**
Spine vBMD										
Unadjusted	151.3 (141.1 to 161.6)	152.5 (142.2 to 162.7)	1.1 (−2.1 to 4.4)	0.8%	144.0 (133.3 to 154.7)	137.9 (127.1 to 148.7)	**−6.1* (−9.7 to −2.5)**	**−4.2%**	**7.2 (2.4 to 12.1)**	**0.004**
Adjusted	149.2 (140.2.6 to 158.2)	153.1 (144.2 to 162.1)	**3.9* (0.4 to 7.4)**	**2.6%**	143.3 (133.9 to 152.7)	140.4 (130.7 to 158.2)	−2.9 (−6.8 to 1.0)	−2,0%	**6.8 (1.9 to 11.7)**	**0.003**
Total hip vBMD										
Unadjusted	164.5 (158.4 to 170.6)	161,9 (155.8 to 168.0)	**−2.6* (−5.0 to −0.2)**	**−1,6%**	162.6 (156.2 to 169.0)	154.7 (148.2 to 161.1)	**−7.9** (−10.5 to −5.2)**	**−4.8%**	**5.3 (1.8 to 8.9)**	**0.003**
Adjusted	162.9 (157.5 to 168.3)	162.0 (156.6 to 167.4)	−0.9 (−3.4 to 1.5)	−0.6%	162.6 (156.9 to 168.2)	156.7 (150.9 to 162.5)	**−5.9** (−8.6 to −3.2)**	**−3.6%**	**5.0 (1.4 to 8.5)**	**0.006**
Femoral neck vBMD										
Unadjusted	165.2 (159.1 to 171.3)	163.4 (157.3 to 169.6)	−1.8 (−5.2 to 1.6)	−1.1%	166.2 (159.8 to 172.6)	159.4 (152.8 to 165.9)	**−6.8** (−10.5 to −3.0)**	**−4.1%**	5.0 (−0.1 to 10.1)	0.056
Adjusted	163.3 (158.3 to 168.3)	163.3 (158.3 to 168.4)	0.0 (−3.4 to 3.4)	0.0%	166.4 (161.1 to 171.6)	161.8 (156.3 to 167.3)	**−4.5* (−8.3 to −0.7)**	**−2.7%**	4.5 (−0.5 to 9.5)	0.079
Spine aBMD										
Unadjusted	1.09 (1.04 to 1.14)	1.10 (1.05 to 1.16)	0.02 (−0.01 to 0.04)	1.4%	1.11 (1.06 to 1.17)	1.08 (1.02 to 1.130)	**−0.04* (−0.06 to −0.01)**	**−3.4%**	**0.05 (0.02 to 0.09)**	**0.003**
Adjusted	1.09 (1.04 to 1.14)	1.10 (1.05 to 1.15)	0.012 (−0.01 to 0.04)	1.1%	1.12 (1.06 to 1.17)	1.08 (1.02 to 1.13)	**−0.04* (−0.069 to −0.015)**	**−3.7%**	**0.05 (0.02 to 0.09)**	**0.002**
Total hip aBMD										
Unadjusted	1.12 (1.08 to 1.16)	1.08 (1.04 to 1.12)	**−0.04** (−0.06 to −0.03)**	**−3.9%**	1.09 (1.04 to 1.13)	1.00 (0.96 to 1.04)	**−0.09** (−0.11 to −0.07)**	**−7.9%**	**0.04 (0.02 to 0.07)**	**0.002**
Adjusted	1.10 (1.070 to 1.148)	1.06 (1.031 to 1.106)	**−0.04** (−0.06 to −0.02)**	**−3.4%**	1.10 (1.06 to 1.13)	1.02 (0.98 to 1.06)	**−0.08** (−0.10 to −0.05)**	**−7.0%**	**0.04 (0.01 to 0.07)**	**0.003**
Femoral neck aBMD										
Unadjusted	0.90 (0.86 to 0.94)	0.89 (0.85 to 0.93)	−0.01 (−0.04 to 0.01)	−1.4%	0.91 (0.87 to 0.95)	0.85 (0.81 to 0.89)	**−0.06** (−0.08 to −0.03)**	**−6.4%**	**0.06 (0.01 to 0.08)**	**0.013**
Adjusted	089 (0.85 to 0.9)	0.88 (0.84 to 0.92)	−0.01 (−0.03 to 0.02)	−1.0%	0.92 (0.88 to 0.96)	0.87 (0.82 to 0.91)	**−0.05** (−0.08 to −0.03)**	**−5,7%**	**0.04 (0.01 to 0.08)**	**0.018**

Note: Estimated treatment effects on 12-month QCT- and DXA-acquired bone metrics based on mixed-model analysis. Values are presented as model unadjusted and adjusted means (95% CI). CON refers to the group treated with placebo, whereas INT refers to the group treated with zoledronic acid. aBMD values are provided in grams per centimeters squared, whereas vBMD values are provided in milligrams per centimeters cubed. Bold text indicates significant results.

Abbreviations: Δ%, percentage change; aBMD, areal bone mineral density; CON, control; DXA, dual-energy x-ray absorptiometry; INT, intervention; QCT, quantitative computed tomography; vBMD, volumetric bone mineral density.

*$p < 0.05$.

**$p < 0.001$.

TABLE 3 One- and twelve-month treatment effect estimates on bone turnover markers and calcium homeostasis.

	INT				CON				Absolute IN − CON	
	Baseline	**12 m**	**Δ**	**Δ%**	**Baseline**	**12 m**	**Δ**	**Δ%**		***p* value**
P1NP										
Unadjusted	55.6 (47.2 to 63.9)	61.4 (52.8 to 70.1)	5.8 (−4.3 to 16.0)	10.5%	55.7 (46.7 to 64.6)	97.4 (88.0 to 106.9)	**41.7** (30.6 to 52.9)**	**75.0%**	**−35.9 (−50.9 to −20.9)**	**0.000**
Adjusted	55.3 (47.5 to 63.2)	62.4 (54.3 to 70.6)	7.1 (−3.2 to 17.3)	12.8%	55.1 (46.7 to 63.5)	97.2 (88.2 to 106.2)	**42.1** (31.0 to 53.3)**	**76.5%**	**−35.0 (−50.2 to −19.9)**	**0.000**
CTX-1										
Unadjusted	0.27 (0.19 to 0.38)	0.52 (0.44 to 0.61)	**0.25** (0.15 to 0.35)**	**91.3%**	0.26 (0.17 to 0.35)	0.70 (0.61 to 0.80)	**0.44** (0.34 to 0.55)**	**171.2%**	**−0.19 (−0.34 to −0.05)**	**0.008**
Adjusted	0.26 (0.18 to 0.34)	0.53 (0.45 to 0.61)	**0.26** (0.17 to 0.36)**	**101.0%**	0.26 (0.18 to 0.34)	0.71 (0.62 to 0.80)	**0.45** (0.34 to 0.55)**	**172.0%**	**−0.18 (−0.33 to −0.04)**	**0.011**

	INT				CON				Absolute INT − CON	
	Baseline	**1 m**	**Change**	**Δ%**	**Baseline**	**1 m**	**Change**	**Δ%**		***p* value**
Calcium	2.42 (2.39 to 2.44)	2.38 (2.35 to 2.40)	**−0.04* (−0.07 to −0.01)**	**−1.8%**	2.42 (2.39 to 2.45)	2.43 (2.40 to 2.46)	0.01 (−0.02 to 0.04)	0.4%	**−0.05 (−0.09 to −0.01)**	**0.014**
PTH	7.7 (6.5 to 8.9)	8.9 (7.9 to 10.0)	1.18 (−0.04 to 2.39)	15.3%	7.9 (6.7 to 9.1)	6.1 (4.8 to 7.4)	**−1.8* (−3.4 to −0.34)**	**−22.5%**	**2.95 (1.17 to 4.74)**	**0.001**
25 (OH)-vitamin D	69.5 (61.9 to 77.1)	79.9 (72.2 to 87,7)	**10.5* (4.2 to 16.7)**	**15.0%**	74.8 (66.9 to 82.7)	85.3 (76.8 to 93.7)	**10.4* (3.6 to 17.3)**	**13.9%**	0.02 (−9.3 to 9.3)	0.997

	INT				CON				Absolute INT- CON	
	Baseline	**12 m**	**Change**	**Δ%**	**Baseline**	**12 m**	**Change**	**Δ%**		***p* value**
Calcium	2.42 (2.39 to 2.44)	2.37 (2.35 to 2.40)	**−0.05* (−2.1 to 4.4)**	**−1.9%**	2.42 (2.39 to 2.45)	2.41 (2.38 to 2.44)	−0.01 (−9.7 to −2.5)	−0.3%	−0.04 (−0.08 to 0.00)	0.08
PTH	7.7 (6.5 to 8.9)	7.0 (5.8 to 8.2)	−0.7 (−1.9 to 0.5)	−9.0%	7.9 (6.7 to 9.1)	6.9 (5.6 to 8.2)	−1.0 (−2.28 to 0.34)	−12.3%	0.3 (−1.51 to 2.07)	0.762
25(OH)-vitamin D	69.5 (61.9 to 77.1)	84.0 (76. to 91.6)	**14.5** (8.3 to 20.6)**	**20.8%**	74.8 (66.9 to 82.7)	86.7 (78.5 to 94.9)	**11.9** (5.2 to 18.5)**	**15.9%**	2.6 (−6.4 to 11.6)	0.572

Note: Estimated treatment effects on 12-month bone turnover markers (i.e., P1NP and CTX-1) and 1- and 12-month estimated treatment effects on calciotropic hormones (i.e., calcium, PTH, and 25[OH]-vitamin D) based on mixed-model analysis. CON refers to the group treated with placebo, whereas INT refers to the group treated with zoledronic acid. Vitamin D values are provided in nanomoles per liter, calcium values are provided in millimoles per liter, CTX-1 and P1NP values are provided as micrograms per liter, and PTH values are provided as picomoles per liter. The values are presented as model unadjusted and adjusted means with 95% CI. Bold text indicates significant results.

Abbreviations: Δ%, percentage change; CON, control; CTX-1, carboxy-terminal type I collagen; INT, intervention; P1NP, procollagen type I amino-terminal propeptide; PTH, parathyroid hormone.

*$p < 0.05$.

**$p < 0.001$.

TABLE 4 AEs in CON and INT.

	INT	CON	*p* value
AE	35 (1.1 ± 1.6)	27 (0.9 ± 1.0)	0.92
SAE	13 (0.4 ± 1.0)	4 (0.1 ± 0.4)	0.35
AR	19 (0.6 ± 0.6)	7 (0.2 ± 0.4)	0.02
SAR	0	0	

	INT		CON	
	AE	SAE	AE	SAE
Distribution of AEs and SAEs across specific medical categories				
Cardiopulmonary	2	4	0	0
Gastrointestinal	7	9	8	4
Infectious diseases	13	0	6	0
Musculoskeletal	7	0	7	0
Skin	2	0	0	0
Urogenital	4	0	6	0
Description of reported adverse reactions				
Flu-like symptoms	18	6		
Myalgia	0	1		
Syncope	1	0		

Note: AEs, SAEs, and ARs recorded within the first year after surgery. Values are presented as the numbers of occurrences (mean ± SD). Significant differences are based on the Fisher exact test. Additionally, the distribution of AEs, SAEs, and ARs across specific medical categories is presented, detailing the number of occurrences for each group. CON refers to the group treated with placebo, whereas INT refers to the group treated with zoledronic acid. Abbreviations: AR, adverse reaction; AE, adverse event; CON, control; INT, intervention; SAE, serious adverse event; SAR, serious adverse reaction.

Predictors of skeletal changes after bariatric surgery

For CON, we observed that the postoperative absolute weight loss was correlated with the absolute declines in total hip aBMD ($r = 0.65$; $p < 0.001$) and femoral neck aBMD ($r = 0.60$; $p = 0.002$), whereas such correlations were not present in INT. In both groups, weight loss was not correlated with changes in spine vBMD or aBMD. For CTX-1, we observed an inverse correlation with change in spine aBMD ($r = -0.44$; $p = 0.017$) in INT and CON ($r = -0.49$; $p = 0.017$), and, additionally in CON, CTX-1 was also inversely correlated with the changes in total hip ($r = -0.49$; $p = 0.017$) and femoral neck ($r = -0.48$; $p = 0.02$).

Safety

Table 4 displays the reported adverse events, serious adverse events, and adverse reactions recorded from inclusion to 1 year after surgery, and these did not differ between the groups. Hypocalcemia was found in two participants in INT 1 month after surgery (RYGB, $n = 2$), whereas all had normal levels at 12 months. The prevalence of hypocalcemia did not differ between the groups ($p = 0.50$). The prevalence of elevated PTH levels (>9.2 pmol/L) was significantly higher in INT compared with CON 1 month after surgery (11 vs. 2; $p = 0.013$), with no difference at 12 months (6 vs. 3; $p = 0.43$). The number of adverse reactions, predominantly flu-like symptoms, was significantly higher in INT compared with CON ($p = 0.02$). No serious adverse reactions were reported.

DISCUSSION

In this randomized, placebo-controlled study investigating the effects of zoledronic acid after bariatric surgery, we found that a single infusion of zoledronic acid increased spine bone mass and prevented bone loss in the hip region, whereas those receiving placebo had significant bone loss in the hip region. These results confirm our hypothesis that zoledronic acid can prevent bone loss after bariatric surgery. Furthermore, our safety data were reassuring, indicating that treating patients undergoing bariatric surgery with zoledronic acid is safe.

In the present study, we observed that CON had declines in BMD 1 year after surgery for the spine, hip, and femoral neck, ranging from 2.7% to 7.0% (except for spine vBMD), despite supplements with calcium and vitamin D. This is consistent with previous findings [3, 11, 12]. We observed that a single infusion of zoledronic acid had bone-sparing effects on different skeletal sites. Spine vBMD was increased, whereas spine aBMD was preserved. For the hip region, the bone loss were either prevented or reduced. These results are consistent with those from a pilot study, which showed that patients who had risedronate administered for 6 months following SG prevented bone loss in the spine, and this effect persisted at 12 months after surgery [25].

Supervised exercise consisting of resistance exercise and/or high-impact activities are treatment modalities that have shown promising effects for the prevention of bone loss after bariatric surgery in randomized-controlled studies. Intention-to-treat analyses showed that bone loss in the spine [18], total hip [19] and femoral neck [19] was attenuated within the first year following RYGB ($n = 61$) [18] or RYGB/SG ($n = 63$) [19]. Per-protocol analysis showed that high adherence to these types of exercise regimens (two to three sessions weekly of 60–70 min) has effects similar to bisphosphonates observed in our study and others [25] with bone loss in the spine [17, 18] and femoral neck [18], whereas loss in the hip is blunted [17] or unaffected [18]. Although bisphosphonates and exercise with high adherence appear to have equal efficacy for preventing bone loss, exercise has several limitations such as a low adherence rate [17–19], the need for trained staff for supervised exercise, and the requirement for specialized equipment, as well as the fact that some patients might face challenges when engaging in exercise due to injuries or physical limitations. We acknowledge that exercise has many health benefits; however, exercise as a treatment strategy is unsuitable for many patients. In contrast, we had 100% adherence to a single intravenous dose of zoledronic acid.

We observed that rises in CTX-1 levels in CON 1 year after surgery were associated with reductions in BMD for all bone sites. In

INT, this association was only found for the lumbar spine. Furthermore, the rise in CTX-1 was blunted in INT compared with CON. These results are consistent with the well-known mechanism by which bisphosphonates prevent bone loss through the inhibition of osteoclast activity. Additionally, mechanical unloading induced by weight loss is a strong determinant for bone resorption after bariatric surgery [5]. In accordance, we found a strong association between body weight reduction and reduced BMD in CON. However, such associations were absent following treatment with zoledronic acid, indicating that antiresorptive treatment mitigates the impact of mechanical unloading on bone resorption.

Safety

Our safety data indicate that treating patients undergoing bariatric surgery with zoledronic acid is safe. Hypocalcemia is a concern when using antiresorptive agents in these patients in part because the absorption of calcium from the gut is lower due to the malabsorptive and/or restrictive effects of surgery. In addition, bone turnover is markedly increased after bariatric surgery, and treatment with an antiresorptive agent that lowers bone resorption and the efflux of calcium to the circulation could lead to hypocalcemia. This could mimic a hungry bone syndrome seen in other high bone turnover diseases in which bone resorption is rapidly reduced, such as parathyroidectomy in primary hyperparathyroidism or thyroidectomy in hyperthyroidism. In this respect, our findings were reassuring because hypocalcemia was only found in two participants in INT 1 month after surgery without the need for specific treatment. Serum calcium was normal in all participants when assessed 12 months after surgery. Similar findings were observed in patients treated with risedronate after SG [25]. We observed a significantly higher number of adverse reactions, predominantly caused by flu-like symptoms in patients administered zoledronic acid compared with placebo, which is a well-known side effect of zoledronic acid. None of these was considered serious or unexpected [20].

Clinical applications and future research directions

Zoledronic acid is a relatively inexpensive treatment that is easy to adhere to. Our findings demonstrate that zoledronic acid can be used for the prophylactic management of bone loss in patients undergoing bariatric surgery. In a clinical setting, however, it is unclear whether patients undergoing bariatric surgery should receive bone-protecting treatments in addition to supplements with calcium and vitamin D. Despite substantial bone loss within the first year after surgery, these patients generally have T-scores much greater than the osteoporotic range [3, 29]. This could lead to the conclusion that prophylactic management of bone loss is unnecessary. In the years following surgery, however, the age-related decline in BMD is accelerated, and bone resorption remains increased for as long as 7 years after RYGB [5, 13, 30]. Postmenopausal women, in particular, have greater bone loss within the first year after RYGB compared with premenopausal women and men [11]. Twenty-five percent of postmenopausal female and male individuals aged 50 years or older had developed osteoporosis 10 years after RYGB surgery [15]. Furthermore, it is evident that fracture risk is increased as early as 2 years after surgery [6, 7], and this risk appears to increase further with time from surgery [6, 7]. In addition to declining bone mass, the increase in fracture risk may relate to the high bone turnover state that follows bariatric surgery, in which excessive bone resorption leads to deterioration of trabecular and cortical bone structures that are both important determinants of bone strength independent of bone mass. Altogether, this indicates that prophylactic treatment of bone loss may be relevant in patients undergoing bariatric surgery. Treatment is likely not indicated in all who are set for bariatric surgery, and the decision to treat could be guided by common risk factors for fracture such as age, gender, postmenopausal status, and BMD. Although evidence in terms of fracture risk reduction is not available, candidates for zoledronic acid could be postmenopausal women and men who are older than age 50 years with a hip T-score ≤ 1.0. Furthermore, surgery type may be an additional risk factor because RYGB is associated with greater bone loss in the hip region compared with SG [3, 4]. Our subgroup analysis on the response to zoledronic acid between RYGB and SG showed that only RYGB had a significant increase in CTX-1 compared with SG (134% vs. 4%; $p < 0.001$; data not shown). Over time, this increased bone resorption may lead to greater bone loss in RYGB compared with SG. However, caution is warranted when interpreting these results, as the subgroup analysis may have introduced imbalances between groups in terms of age, gender, and menopause status, which could have influenced the outcome. In this setting, treatment with zoledronic acid can be used to prevent or blunt the rapid bone loss in the first year after surgery and limit the increase in bone turnover and, thereby, potentially preserve bone structure. Whether treatment with zoledronic acid translates into longer-term protection against bone loss or fracture remains to be explored. Moreover, despite the blunted rise in CTX-1 in INT, CTX-1 was still 85.4% higher than baseline levels at the 12-month follow-up. This indicates that a single preoperative infusion of zoledronic acid (5 mg) is insufficient to fully suppress bone turnover in patients undergoing bariatric surgery. More frequent administration might be necessary to fully protect against bone loss, and such regimens could be explored in future studies.

Strengths and limitations

This study has several strengths. It is the first, to our knowledge, sufficiently powered, double-blinded, randomized-controlled study that explores whether bisphosphonates can prevent bone loss in patients undergoing bariatric surgery. We achieved a satisfactory 90% adherence rate, with 53 out of 59 participants completing the 12-month follow-up assessment. The inclusion of both QCT and DXA measurements is a further strength because QCT measurement is less influenced by obesity and changes in body composition in terms of

providing accurate vBMD values. The accuracy and precision of DXA measurement are compromised by obesity and extreme changes in body composition [31]. However, DXA is the commonly used clinical method to assess bone loss and fracture risk and serves as a clinically relevant surrogate outcome [32]. One limitation of this study is the heterogeneous group in terms of age, gender, and menopausal status. This makes it difficult to extrapolate whether treatment with zoledronic acid should be provided to all patients or to specific patients with distinct attributes, such as postmenopausal women or patients with specific risk factors for fractures. Another limitation is that incorporating both RYGB and SG in this present study might affect the generalizability of the study's results. We acknowledge that RYGB and SG may have different effects on bone health, as evidenced by greater bone loss in the hip region for RYGB [3, 4]. We addressed this by stratifying groups with equal numbers of RYGB and SG in each group. Additionally, there was an imbalance in the gender distribution between INT and CON, with a higher proportion of men in INT. This imbalance may have biased the results, as men are generally known to experience less bone loss than women after bariatric surgery. Also, postmenopausal women may have larger bone loss compared with premenopausal women [11]. However, a sensitivity analysis in INT indicated that men and women responded similarly to zoledronic acid, and the same was observed in the comparison between pre- and postmenopausal women (data not shown). Although these analyses suggest that the treatment effect was similar across gender and menopausal status, this remains a limitation that might have influenced the overall results.

CONCLUSION

In summary, the results of this study demonstrate that zoledronic acid increases bone mass in the spine and prevents bone loss in the hip after bariatric surgery. In a clinical setting, selected patients with an increased risk of fracture can safely be offered prophylactic treatment with zoledronic acid to prevent bone loss.O

AUTHOR CONTRIBUTIONS

Søren Gam, Stinus Gadegaard Hansen, Bibi Gram, Claus Bogh Juhl, and Anne Pernille Hermann contributed substantially to the concept and design of the study. Søren Gam and Stinus Gadegaard Hansen were responsible for trial management. Martin Weber Kusk was responsible for the protocol and setup for the QCT measurement. Simon Lysdahlgaard was responsible for the majority of quantitative computed tomography scans. Søren Gam performed the statistical analysis and wrote and edited the first draft of the manuscript with input from all authors. All authors reviewed and commented on drafts of the paper and approved the final version.

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CONFLICT OF INTEREST STATEMENT

Søren Gam reports support for attending meetings and travel from the Esbjerg Internationalization Fund for Travel Grants and William Demant Foundation. Claus Bogh Juhl reports receiving honoraria for lectures and educational events from Novo Nordisk A/S, as well as serving on an advisory panel for the company. Additionally, he reports serving as the local principal investigator on studies sponsored by Novo Nordisk A/S and Bayer. Anne Pernille Hermann reports receiving payment or honoraria for lectures, presentations, and participation in speaker bureaus from UCB and Amgen Inc. She also reports support for attending meetings and travel, including conference fees and travel support from UCB. The other authors declared no conflicts of interest.

CLINICAL TRIAL REGISTRATION

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DATA AVAILABILITY STATEMENT

The deidentified data collected for this study will be made available to the public upon reasonable request to corresponding author.

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