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Zoledronic acid for prevention of bone loss in patients receiving bariatric surgery

Yi Liu [a], Maya M. Côté [b], Michael C. Cheney [b], Katherine G. Lindeman [b], Claire C. Rushin [b], Matthew M. Hutter [c,d], Elaine W. Yu [b,c,*]

[a] Department of Medicine, Lahey Clinic, Burlington, MA, USA
[b] Endocrine Unit, Massachusetts General Hospital, Boston, MA, USA
[c] Harvard Medical School, Boston, MA, USA
[d] Department of Surgery, Weight Center, Massachusetts General Hospital, USA

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ABSTRACT

Purpose: Bariatric surgery is an effective treatment for severe obesity but causes substantial bone loss and increased risk of fractures. To date, there have been no studies examining whether pharmacologic treatments can prevent bone loss after bariatric surgery. We performed an exploratory study to examine the preliminary safety and efficacy of zoledronic acid (ZOL), a potent anti-resorptive bisphosphonate, to suppress bone turnover markers (BTM) and prevent declines in bone mineral density (BMD) after Roux-en-Y gastric bypass (RYGB) surgery.

Methods: We performed an open-label pilot study of pre-operative ZOL in postmenopausal women with obesity who were planning RYGB ($n = 4$). A single dose of zoledronic acid 5 mg was given intravenously prior to RYGB. Serum bone biochemistries including C-telopeptide (CTX) and procollagen type 1 N-terminal propeptide (P1NP) were measured at multiple timepoints throughout the 24-week study. BMD was also obtained at the spine and hip by dual-energy x-ray absorptiometry (DXA) and at the trabecular spine by quantitative computed tomography (QCT) at pre-operative baseline and 24 weeks. Results were compared against pre-operative baseline and against changes among RYGB historical controls ($n = 10$).

Results: At 2 weeks after RYGB, there was a nonsignificant trend for CTX and P1NP levels to be lower than baseline levels in the ZOL group. By 24 weeks after RYGB, however, participants who received ZOL had a significant increase in CTX above pre-operative baseline ($+0.228 \pm 0.117$ ng/dL, $p = 0.030$) but this CTX rise was less than that observed in the controls ($+0.601 \pm 0.307$ ng/dL, $p = 0.042$ between groups). Despite ZOL use, participants had significant areal BMD loss at the total hip as compared to pre-operative baseline ($-4.2 \pm 1.5\%$, $p = 0.012$) that was similar in magnitude to total hip BMD loss in the controls ($-5.5 \pm 3.9\%$, $p = 0.005$). There was a suggestion that the ZOL group might be protected against trabecular spine volumetric bone loss as compared to the control group ($+4.8 \pm 8.0\%$ vs. $-5.9 \pm 7.0\%$, $p = 0.075$ between groups). Serum calcium, 25-hydroxyvitamin D, and parathyroid hormone did not change in either group. No hypocalcemia or serious adverse events were reported after ZOL.

Conclusion: In this proof of concept study, a single dose of ZOL prior to RYGB appeared to transiently mitigate but not fully prevent high bone turnover in the acute postoperative period. At 24 weeks after RYGB, our preliminary data suggest that ZOL was not sufficient to prevent bone loss at the hip, although it may preserve bone density at the trabecular spine. Further prospective, controlled studies are needed to confirm our findings and to identify the best strategies for preventing bone loss in bariatric patients receiving RYGB.

1. Introduction

Obesity is a chronic disease that is increasing in prevalence around the world, and constitutes an important threat to public health (N.C.D.R.F. Collaboration, 2017). Roux-en-Y gastric bypass (RYGB) is a highly effective form of bariatric surgery for class 3 obesity that results in

* Corresponding author at: Endocrine Unit, Massachusetts General Hospital, 50 Blossom Street, Thier 1051, Boston, MA 02114, USA.
E-mail address: ewyu@mgh.harvard.edu (E.W. Yu).

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sustainable weight loss (Chang et al., 2014; Angrisani et al., 2017), including for older adults (Petrick et al., 2019). Indeed, one-fifth of all bariatric surgeries are performed for adults aged 56 years and older (Haskins et al., 2018), and there has also been an overall increase in the utilization of bariatric surgery in adults age 60 and older (Gebhart et al., 2015). Women are also three times more likely than men to receive bariatric surgery (Chang et al., 2014).

The increasing numbers of older adults and women who are seeking bariatric surgery poses important considerations for post-operative skeletal health. In particular, RYGB is associated with high-turnover bone loss. Significant declines in bone mineral density (BMD), as assessed by dual energy X-ray absorptiometry (DXA) and quantitative computed tomography (QCT), have been demonstrated after RYGB (Schafer et al., 2015a; Bredella et al., 2017; Yu et al., 2015). Postmenopausal women appear to be at particular risk for a higher rate of bone loss after RYGB (Vilarrasa et al., 2011; Schafer et al., 2018). Indeed, 10 years after RYGB, over a quarter of postmenopausal women and men over 50 years had osteoporosis, despite a relatively young cohort (average age 56 years) (Blom-Hogestol et al., 2019). Multiple studies have documented that markers of bone turnover are markedly elevated after RYGB, with elevations being sustained for over 10 years (Bredella et al., 2017; Yu et al., 2016; Schafer et al., 2015b; Lindeman et al., 2018). Studies have also shown increased non-vertebral fracture risk by 43% to 90% after RYGB, including among older patients (Yu et al., 2017; Gagnon and Schafer, 2018; Nakamura et al., 2014). The mechanism of bone loss after RYGB is most likely multifactorial, including skeletal unloading as well as abnormalities in calciotropic hormones and gut hormones (Yu, 2014).

Despite the known negative skeletal effects of bariatric surgery, the optimal management for these patients has not been well elucidated. To our knowledge, there have been no published studies examining whether pharmacologic treatments can prevent bone loss after bariatric surgery. Intravenous zoledronic acid, a potent antiresorptive bisphosphonate, significantly reduces spine, hip, and nonvertebral fracture risk in osteoporosis patients and leads to normalization of bone resorption in high-turnover bone disorders such as Paget's disease, primary hyperparathyroidism, and GnRH-induced hypogonadism (Black et al., 2007a; Khan et al., 2004; Smith et al., 2003; Brufsky et al., n.d.; Michaelson et al., 2007; Reid et al., 2005), as well as in glucocorticoid-induced and transplant-induced osteoporosis (Crawford et al., 2006; Reid et al., 2009). A single dose of zoledronic acid can achieve persistent suppression of bone turnover markers and improvements in bone density for 5 years (Grey et al., 2012a), as well as remissions of Paget's disease for over 5 years (Reid et al., 2011). However, the use of potent bisphosphonates carries a potential risk of hypocalcemia in bariatric populations, who may be prone to decreased calcium absorption and vitamin D deficiency after surgery (Rosen and Brown, 2003).

Given the paucity of data, we conducted an open-label controlled pilot trial to evaluate the preliminary safety and efficacy of preoperative zoledronic acid treatment on bone turnover markers and both areal and volumetric bone density in postmenopausal women undergoing RYGB.

2. Methods

2.1. Study participants

We recruited postmenopausal women with obesity who were planning RYGB at a single academic medical center from October 2018 through March 2019. Participants were excluded if they had a history of medical disorders such as primary hyperparathyroidism, Paget's disease, hyperthyroidism, hypercalcemia, hypocalcemia, severe liver or kidney disease, or history of malignancy within 5 years. Other exclusion criteria were body weight exceeding 400 lbs. (due to limitations of the DXA and CT scanners), and use of medications known to affect calcium and bone metabolism such as bisphosphonates, denosumab, teriparatide, strontium, estrogen, selective estrogen receptor modulators, and loop diuretics. Participants in this interventional protocol were compared to another group of postmenopausal women who participated in a previously published observational study of skeletal health after RYGB (Yu et al., 2014). The study was approved by the Mass General Brigham Human Research Committee (2017P002081), and all participants provided written informed consent. We received a formal Investigational New Drug (IND) Application exemption from the Food and Drug Administration to conduct this protocol. This trial was registered on clinicaltrials.gov (NCT03424239).

2.2. Study protocol

Participants in the interventional protocol had visits at pre-operative baseline, and postoperative 2-week, 12-week and 24-week timepoints. Zoledronic acid 5 mg was given intravenously between 2 and 8 weeks prior to surgery. Control group participants had visits at pre-operative baseline and the postoperative 24-week timepoint. For all participants, fasting morning serum samples were obtained at each study visit. Bone density, body composition, and bionutrition evaluations were assessed as detailed below. Participants in both the zoledronic acid and control groups were counseled to maintain a calcium intake of 1200 to 1500 mg/d and a minimum vitamin D intake of 3000 IU/d through diet and supplements.

2.2.1. DXA bone density and body composition

Dual-energy x-ray absorptiometry (DXA) scans of the lumbar spine, total hip, femoral neck, and total body were obtained to assess areal bone mineral density (aBMD) at preoperative baseline and 24-weeks after RYGB (QDR Discovery, Hologic, Inc., Bedford, MA). The short-term precision for this technique is 0.005, 0.006, and 0.009 g/cm^2 for PA spine, total hip, and femoral neck, respectively, at the Massachusetts General Hospital (MGH) Bone Density Center (Lindeman et al., 2020). DXA scans were performed by ISCD-certified technologists and densitometrists. Body composition was measured by DXA to obtain assessments of subtotal (total body excluding head) measurements of fat mass (kg) and lean mass (kg), with mirroring adjustments when necessary.

2.2.2. Quantitative computed tomography (QCT)

QCT scans of the lumbar spine (L1−L2) were obtained to assess trabecular volumetric bone mineral density (vBMD) at preoperative baseline and 24-weeks after RYGB (GE LightSpeed Pro CT scanner, GE Healthcare, Waukesha, WI). Helical scans were acquired with a QCTPro calibration phantom with the following settings: 120 kvP, 100 mA, 1.25 mm slice thickness. 3D reconstructive analysis for trabecular vBMD was performed on QCTPro software (Mindways Software, Inc., Austin, TX). The short-term precision for this technique is 1–2% for vertebral BMD measurements (Lang et al., 1999).

2.2.3. Bone turnover markers

Assays for bone turnover markers and parathyroid hormone (PTH) were performed in batch at the end of the study. Fasting serum levels of type 1 cross-linked C-telopeptide (CTX), a bone resorption marker, were measured by immunoradiometric assay (Immunodiagnostic Systems, Fountain Hills, AZ), with intra- and inter-assay CV of 5.2–6.8% and 5.6–7.4%. Fasting serum procollagen type 1 N-terminal propeptide (P1NP), a bone formation marker, was measured by RIA (Orion Diagnostica, Finland), with intra- and inter-assay CV of 3.5–5.3% and 3.6–5.4%. Serum PTH was measured by chemiluminescent immunoassay (Beckman Coulter, Fullerton, CA) with an intra- and inter-assay CV of 1.6–2.6% and 2.8–5.8%. Additional labs were measured in clinical laboratories using standard clinical assays (i.e. calcium, creatinine: spectrophotometry; 25-hydroxyvitamin D: chemiluminescent immunoassay). Hypocalcemia was defined as <8.6 mg/dL, as per the normal range of our clinical lab assay.

2.2.4. Bionutrition assessments

Height and weight were measured in triplicate using a wall-mounted stadiometer (Harpenden; Seritex) and digital scale (Tanita BWB-800; Tanita Corporation of America, Arlington Heights, IL), respectively. To measure leisure and occupational physical activity, the International Physical Activity Questionnaire (IPAQ) long format was administered by a registered dietitian (Craig et al., 2003). Dietary calcium and vitamin D were assessed through self-reported questionnaires administered by a registered dietitian (van Staveren et al., 1985; Zulkifli and Yu, 1992).

2.3. Statistical analysis

Longitudinal values are reported as mean ± SD unless otherwise noted. The primary outcome of this proof of concept study was comparison of absolute change in CTX in the ZOL vs. control groups as assessed by independent *t*-tests. Absolute changes from baseline within each group were also assessed by one sample t-tests. Exploratory outcomes including 24-week changes in bone density and metabolic bone parameters throughout the study were also evaluated. All analyses were performed using SPSS 26 software (IBM Inc., Armonk, NY). *P* values <0.05 were considered significant, and adjustments for multiple comparisons were not performed given the exploratory nature of this study.

3. Results

3.1. Study cohort and clinical characteristics

We screened 200 patients who were planning bariatric surgery. Among these, 107 were ineligible based on age, sex, and menopause criteria, 37 were ineligible due to comorbidities, and 25 were ineligible due to logistic constraints based on the timing of their surgery. We contacted the remaining 31 patients to discuss the study, of whom 6 underwent screening procedures. Among these, 4 women were eligible and enrolled in our interventional study to receive zoledronic acid (ZOL) prior to RYGB. Our study also included 10 postmenopausal women who had RYGB without ZOL and served as controls. There were no dropouts throughout the study in either group.

Baseline characteristics of ZOL and control groups are summarized in Table 1. All participants were postmenopausal women and the majority self-identified as non-Hispanic Caucasian. Average age, weight, and BMI were roughly similar in both groups. At the preoperative baseline visit, ZOL and control groups had no differences in bone density at the lumbar spine, total hip, and femoral neck. Baseline laboratory assessments, including CTX and P1NP, were also similar in the two groups.

By 24 weeks after RYGB, the participants in both groups experienced significant and similar weight loss of 25.9 ± 5.7% in the ZOL group ($P < 0.002$ vs baseline), and 23.1 ± 9.8% in the control group ($P = 0.001$ vs baseline; between-group $P = 0.963$) (Table 2). Both groups also experienced similar magnitude of declines in fat mass (ZOL: −16.7 ± 2.2 kg; Control: −15.7 ± 7.1 kg; $P = 0.752$ between groups) and lean mass (ZOL: −7.9 ± 3.6 kg; Control: −9.7 ± 6.2 kg; $P = 0.603$ between groups) (Table 3).

Table 1
Baseline clinical characteristics in postmenopausal women planning RYGB in zoledronic acid and control groups, mean ± SD.

	Zoledronic acid ($n = 4$)	Control ($n = 10$)	P-value
Age (years)	56.0 ± 10.0	59.6 ± 8.6	0.511
Ethnicity			0.510
Hispanic, n (%)	1 (25%)	1 (10%)	
Non-Hispanic White, n (%)	3 (75%)	9 (90%)	
Bionutrition measures			
Weight (lb)	226.0 ± 18.0	248.9 ± 24.5	0.119
BMI (kg/m^2)	40.9 ± 2.0	43.0 ± 4.1	0.347
Subtotal body fat (kg)	46.9 ± 4.2	49.7 ± 2.8	0.209
Subtotal body lean mass (kg)	49.8 ± 5.8	55.4 ± 7.4	0.233
Serum labs			
Calcium (g/dL)	9.4 ± 0.3	9.6 ± 0.3	0.263
Creatinine (mg/dL)	0.72 ± 0.14	0.94 ± 0.30	0.182
25-Hydroxyvitamin D (ng/mL)	39.8 ± 14.8	29.9 ± 9.1	0.149
PTH (pg/mL)	43.5 ± 20.6	51.4 ± 26.4	0.603
CTX (ng/mL)	0.226 ± 0.163	0.264 ± 0.098	0.598
P1NP (ug/L)	35.6 ± 12.5	43.7 ± 21.9	0.508
DXA (g/cm^2)			
Spine aBMD	1.065 ± 0.095	1.154 ± 0.223	0.472
Femoral neck aBMD	0.811 ± 0.124	0.871 ± 0.166	0.537
Total hip aBMD	0.953 ± 0.124	1.062 ± 0.199	0.336
QCT (mg/cm^3)			
Trabecular spine vBMD	114 ± 41	140 ± 30	0.227

3.2. Changes in bone turnover markers

The evolution of biochemical markers of bone turnover during the study is shown in Fig. 1. At 2 weeks after RYGB, we found a trend toward decreased serum CTX in the ZOL group (−0.105 ± 0.088 ng/mL below pre-operative baseline, $P = 0.097$). However, by 24 weeks after RYGB, participants receiving ZOL had a significant increase in CTX above pre-operative baseline (+0.228 ± 0.117 ng/dL, $P = 0.030$). This 24-week

Table 2
Changes from baseline in clinical characteristics and metabolic bone labs after RYGB in zoledronic acid and control groups.

Weeks	Baseline	Absolute change at 2-week visit	Absolute change at 12-week visit	Absolute change at 24-week visit	Between group at 24-week visit P-value
Weight (lb)					
ZOL	226.0 ± 18.0	−16.4 ± 5.0[a]	−39.2 ± 7.5[a]	−58.2 ± 11.9[a]	0.963
Control	248.9 ± 24.5	n/a	n/a	−58.8 ± 26.0[a]	
BMI (kg/m^2)					
ZOL	40.9 ± 2.0	−3.7 ± 1.7[b]	−7.1 ± 0.8[a]	−10.6 ± 1.7[a]	0.725
Control	43.0 ± 4.1	n/a	n/a	−9.9 ± 4.0[a]	
Ca (mg/dL)					
ZOL	9.4 ± 0.3	−0.1 ± 0.3	+0.3 ± 0.3	−0.1 ± 0.5	0.335
Control	9.6 ± 0.3	n/a	n/a	+0.1 ± 0.4	
Creatinine (mg/dL)					
ZOL	0.72 ± 0.14	−0.04 ± 0.04	−0.12 ± 0.11	−0.10 ± 0.07[b]	0.617
Control	0.94 ± 0.30			−0.14 ± 0.17[a]	
25(OH)D (ng/mL)					
ZOL	39.8 ± 14.8	+2.5 ± 15.3	+11.5 ± 14.1	+9.5 ± 19.3	0.414
Control	29.9 ± 9.1	n/a	n/a	+1.9 ± 12.7	
PTH (pg/mL)					
ZOL	43.5 ± 20.6	+30.8 ± 18.2[a]	+3.2 ± 7.0	+11.3 ± 17.2	0.200
Control	51.4 ± 26.4	n/a	n/a	−4.4 ± 19.9	
CTX (ng/mL)					
ZOL	0.226 ± 0.163	−0.105 ± 0.088[b]	+0.072 ± 0.142	+0.228 ± 0.117[a]	0.042
Control	0.264 ± 0.098	n/a	n/a	+0.601 ± 0.307[a]	
P1NP (ug/L)					
ZOL	35.6 ± 12.5	−14.5 ± 10.1 [b]	−11.8 ± 12.1	+4.6 ± 16.2	0.058
Control	43.7 ± 21.9	n/a	n/a	+30.8 ± 22.0[a]	

Note that data were not available (n/a) for Control group at 2- and 12-week timepoints.
[a] *P*-value <0.05 for within-group comparison vs pre-operative baseline.
[b] *P*-value <0.10 for within-group comparison vs pre-operative baseline.

Table 3
Changes from baseline in body composition and bone mineral density after RYGB in zoledronic acid and control groups.

Weeks	Baseline	Absolute change at 24-week visit	Between group at 24-week visit P-value
DXA body composition			
Subtotal fat (kg)			
ZOL	46.9 ± 4.2	−16.7 ± 2.2[a]	0.752
Control	49.7 ± 2.8	−15.4 ± 7.1[a]	
Subtotal lean mass (kg)			
ZOL	49.8 ± 5.8	−7.9 ± 3.6[a]	0.603
Control	55.4 ± 7.4	−9.7 ± 6.2[a]	
DXA bone density (g/cm^2)			
Spine aBMD			
ZOL	1.065 ± 0.095	+0.003 ± 0.074	0.768
Control	1.154 ± 0.223	−0.008 ± 0.054	
Femoral neck aBMD			
ZOL	0.811 ± 0.124	−0.038 ± 0.032[b]	0.780
Control	0.871 ± 0.166	−0.031 ± 0.047[b]	
Total hip aBMD			
ZOL	0.953 ± 0.124	−0.039 ± 0.014[a]	0.387
Control	1.062 ± 0.199	−0.059 ± 0.041[a]	
QCT trabecular spine vBMD (mg/cm^3)			
ZOL	113.7 ± 41.4	+4.9 ± 7.8	0.075
Control	139.5 ± 30.0	−9.1 ± 10.4	

[a] *P*-value <0.05 for within-group comparison vs pre-operative baseline.
[b] P-value ≤0.10 for within-group comparison vs pre-operative baseline.

CTX rise in the ZOL group was less than that observed in the untreated controls (+0.601 ± 0.307 ng/dL above pre-operative baseline, $p < 0.001$; between-group $P = 0.042$). P1NP changes in the ZOL group at the 2-week postoperative timepoint mirrored that of CTX, with a suggestion of decreased levels compared to baseline (−14.5 ± 10.1 μg/L, $P = 0.063$). By 24 weeks after RYGB, participants in ZOL group had P1NP levels that had approximately returned to baseline levels (+4.5 ± 16.2 μg/L, $P = 0.613$). In the untreated control group, serum P1NP rose significantly above pre-operative baseline at 24 weeks (+30.8 ± 22.0 μg/L, $P = 0.003$).

3.3. Changes in serum calcium and other labs

Serum calcium and 25(OH)-vitamin D levels were largely stable throughout the 24-week study in both groups (Fig. 2). No participants developed hypocalcemia at any timepoint. Although there were no clear differences in serum calcium or 25(OH)-vitamin D at 2 weeks after RYGB, serum PTH was transiently elevated above baseline in ZOL group (+30.8 ± 18.2 pg/mL, $p = 0.043$, Fig. 2C). By 24 weeks, serum PTH in the ZOL group was similar to pre-operative baseline, and no different than in the controls which experienced stability of PTH. There was no evidence of increasing creatinine in the ZOL group, and in fact there was a tendency toward minor reduction in creatinine levels in both groups during the postoperative period (Table 2).

3.4. Changes in spine and total hip bone mineral density

24-week changes in bone density are shown in Fig. 3. Despite ZOL use, participants had significant bone loss at the total hip as compared to pre-operative baseline (−4.2 ± 1.5%, $P = 0.012$) that was similar in magnitude to total hip aBMD loss in the controls (−5.6 ± 3.9%, $P = 0.005$). At the femoral neck, there was a trend toward decreased bone density in both the ZOL group (−4.5 ± 3.3%, $P = 0.100$) and the control group (−3.6% ± 5.2%, $P = 0.105$) when compared to baseline. In contrast, we did not find a significant within-group change in either group at the lumbar spine as assessed by DXA. However, in QCT analyses, there was a suggestion that the ZOL group was protected against trabecular spine volumetric bone loss as compared to the control group (ZOL +4.8 ± 8.0% vs. control −5.9 ± 7.0%, $P = 0.075$).

4. Discussion

Despite the beneficial outcome of weight loss, RYGB inadvertently results in detrimental high-turnover bone loss (Schafer et al., 2015a; Yu et al., 2015). The marked and persistent elevation in bone resorption far exceeds the increases in bone resorption that occur in the settings of non-surgical weight loss, menopausal transition, or immobilization (Zibellini et al., 2015; Sowers et al., 2013; Belavy et al., 2016). In this pilot study, we provide preliminary data about the impact of preoperative zoledronic acid treatment on bone turnover in postmenopausal women receiving RYGB. Our data suggest that zoledronic acid may suppress bone turnover transiently, but that this effect is not sustained. Indeed, by 24 weeks after surgery, serum CTX in the ZOL group had risen to levels exceeding preoperative baseline in all ZOL participants, albeit the CTX rise was lower than that observed in the untreated RYGB control group. Furthermore, these changes occurred in conjunction with a significant

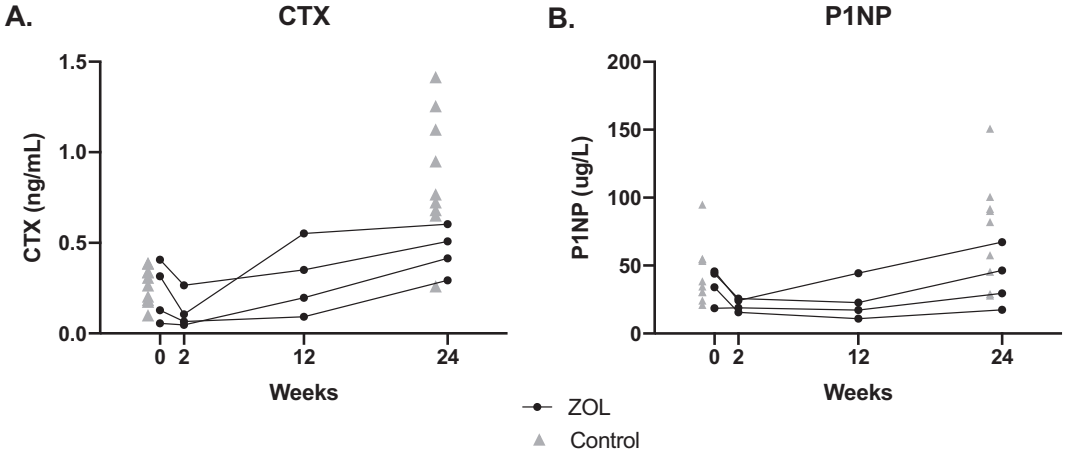

Fig. 1. Bone turnover markers in the 24 weeks after RYGB in zoledronic acid (ZOL) and control groups. Panels show serum CTX (A) and P1NP (B) at pre-operative baseline and serial timepoints up to 24 weeks. Individual results are shown for each participant in the ZOL (black circles) and control groups (gray triangles).

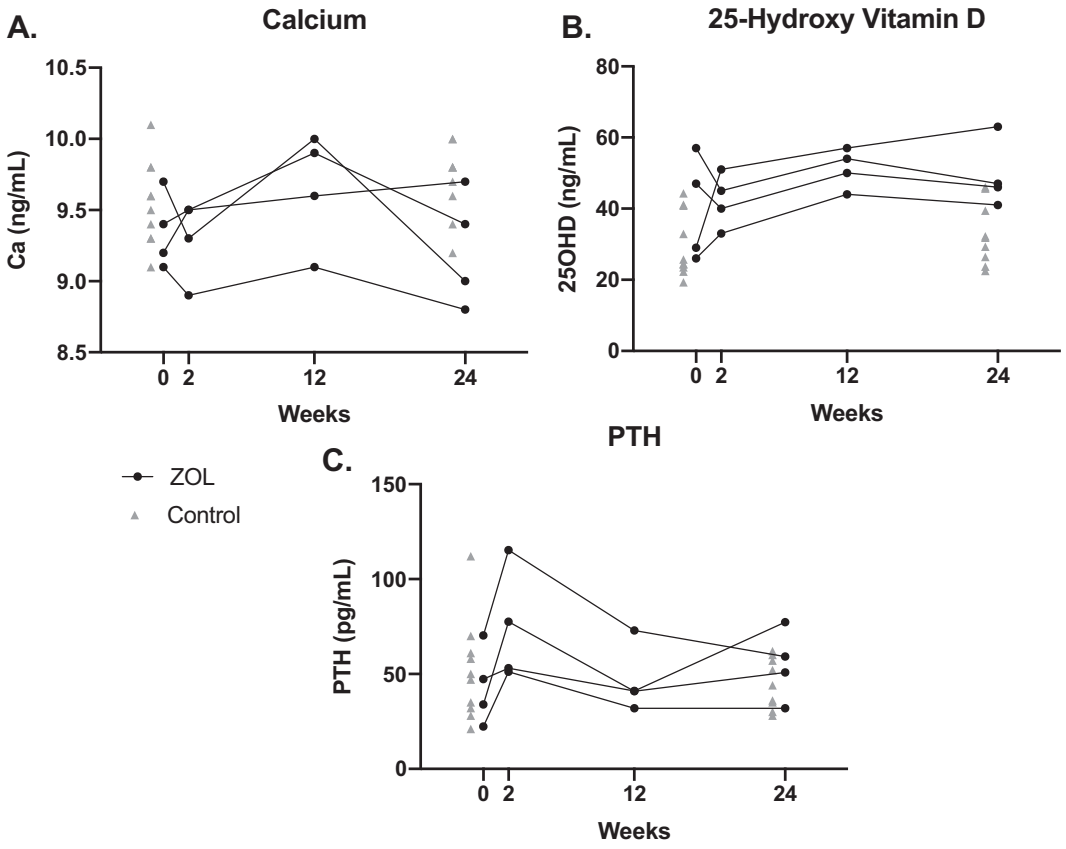

Fig. 2. Laboratory parameters in the 24 weeks after RYGB in zoledronic acid (ZOL) and control groups. Panels show serum calcium (A), 25-hydroxyvitamin D (B), and PTH (C) at pre-operative baseline and serial timepoints up to 24 weeks. Individual results are shown for each participant in the ZOL (black circles) and control groups (gray triangles).

decline in bone density at the total hip in the 24 weeks after RYGB that was of similar magnitude in both groups. In the ZOL group, there was no evidence of hypocalcemia and no significant adverse events were reported.

The finding that CTX was only transiently suppressed after zoledronic acid infusion in RYGB patients was unexpected and suggests a potential clinical challenge in managing bone loss in these patients. Zoledronic acid is a potent anti-resorptive agent and leads to suppression of bone resorption in many other high-turnover bone disorders. For instance, Paget's disease is characterized by accelerated bone turnover and marked elevations in indices of bone resorption. Prior studies have shown a single infusion of ZOL in Paget's disease produces sustained reductions of more than 80% in bone turnover markers for up to 6.5 years (Reid et al., 2011). Similarly, in prostate cancer patients at risk of hypogonadal bone loss in the setting of gonadotropin-releasing hormone agonists, a single dose of ZOL preserved bone density and achieved durable suppression of serum N-telopeptide levels by 17% for 12 months (Michaelson et al., 2007). A study of men with HIV revealed annual doses of ZOL for 2 years suppressed bone turnover by 41–52% for at least 5 years (Bolland et al., 2012). A single dose 5 mg of ZOL increased bone density and reduced bone turnover markers by approximately 45% for at least 5 years in postmenopausal women with osteopenia (Grey et al., 2012b). Finally, in a post hoc analysis of men and women with osteoporosis, a single dose of zoledronic acid lowered serum P1NP by 27% at 3-year follow up and appeared to decrease fracture risk by 32% (Reid et al., 2013).

Despite these studies demonstrating the potency of ZOL to durably suppress bone turnover and prevent bone loss in various metabolic bone conditions, our small study suggests that ZOL has a fairly short-lived effect on bone turnover in RYGB patients. CTX and P1NP were transiently suppressed by 41% and 35%, respectively, in the ZOL group at 2 weeks after RYGB, but by 24 weeks P1NP had already returned to baseline and CTX had risen to greater than preoperative levels. Although these 24-week changes in indices of bone resorption were lower than that observed in untreated controls, this pattern suggests that ZOL led to incomplete suppression of bone turnover in our RYGB patients. This clinical situation may be akin to the skeletal state observed after discontinuation of long-term denosumab, during which some studies have shown recurrent high bone turnover and large magnitude bone loss despite ZOL treatment (Sølling et al., 2020). It should be noted that we administered ZOL in the pre-operative period, prior to the onset of high-turnover bone loss. It remains unclear whether baseline bone turnover predicts bisphosphonate efficacy (Seibel, 2006), but one possibility is that ZOL was incompletely incorporated into the bone matrix during this state of lower bone turnover (Cremers et al., 2003), and that post-operative administration would have been more effective. Furthermore, the fast offset of ZOL in our study suggests that more frequent use of ZOL may be required to suppress high bone turnover after RYGB.

ZOL did not appear to prevent femoral bone loss at 24 weeks after RYGB, with both ZOL and control groups showing declines of 4–5% in total hip bone density. We did not find any significant change of lumbar spine bone density by DXA in either group. It's possible that the lack of change at the spine may reflect (1) a lesser effect of RYGB at the spine, which has been documented in many prior studies (Bredella et al., 2017; Yu et al., 2015; Vilarrasa et al., 2011; Schafer et al., 2018); (2) the relatively short duration of this 24-week proof of concept study; and/or (3) possible imaging artifact from weight loss. Using QCT, which may have greater discriminatory ability than DXA in the setting of soft tissue artifact, we did detect a trend toward increased trabecular spine volumetric bone density in the ZOL group, such that average vBMD was 5%

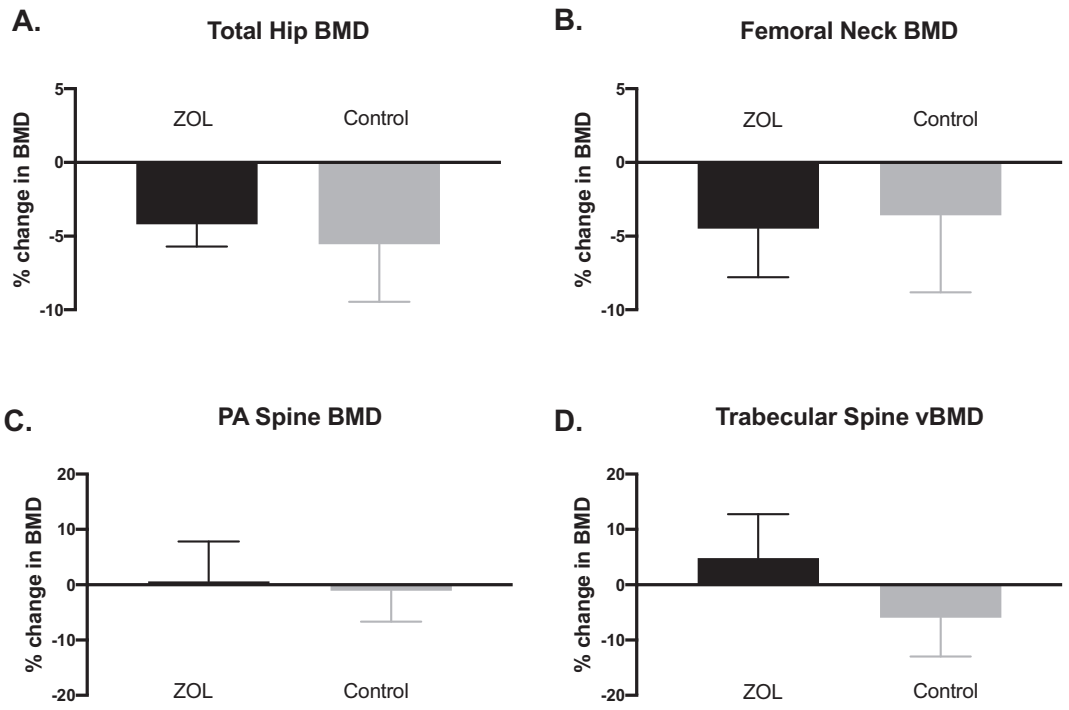

Fig. 3. Changes in bone density in the 24 weeks after RYGB in zoledronic acid (ZOL) and control groups. Percent change in bone mineral density (BMD) and volumetric BMD (vBMD) were assessed by DXA and QCT, and are shown at the total hip (A), femoral neck (B), posterior-anterior spine (C), and trabecular spine (D). Mean and standard deviation for each group are depicted with black bars (ZOL) and gray bars (controls). There were no statistically significant differences between groups at any skeletal site ($p > 0.05$).

higher than preoperative baseline, as compared to declining vBMD in the control group. While these observations were not statistically significant, given the small sample size it is possible that ZOL may provide some measure of protection at this trabecular site. These effects require evaluation in larger randomized controlled studies of more sustained duration.

We also examined preliminary safety outcomes. Calcium absorption has been shown to be lowered after RYGB (Schafer et al., 2015b; Riedt et al., 2006) and the incidence of postoperative hypocalcemia (<8.9 mg/dL) after RYGB has been cited to be 1–2%, particularly among patients with pre-existing renal failure (Yu et al., 2014; Shah et al., 2017; Diniz Mde et al., 2004). Given that ZOL may also infrequently lead to hypocalcemia (0.2% in the pivotal clinical trial of postmenopausal osteoporosis) (Black et al., 2007b), it is possible that RYGB patients may be more susceptible to developing hypocalcemia in response to ZOL. Although it is hard to extrapolate from our small sample size, we were reassured that we did not detect any decline in serum calcium after ZOL administration in our study, nor did we detect any difference of calcium between ZOL and control group in the setting of concurrent vitamin D and calcium supplementation. There was a transient increase in PTH at the 2-week postoperative timepoint, but PTH levels returned to baseline by 12 weeks. Furthermore, this phenomenon of transient PTH rise has also been described in RYGB patients in the absence of zoledronic acid treatment (Yu et al., 2016), and therefore it is difficult to assess whether this is an effect or surgery or treatment.

To date, our study is the first study to investigate pharmaceutical intervention to prevent bone loss in bariatric surgery patients. One previous study of gastric cancer patients undergoing gastrectomy revealed that a weekly dose of alendronate 70 mg reduced bone loss and durably suppressed bone resorption over the course of 12 months (Ha et al., 2020). Nevertheless, it is hard to extrapolate from these results to the bariatric population as surgical gastrectomy in these non-obese cancer patients may have different physiologic effects than RYGB. In addition, caution with oral bisphosphonates is generally advised in bariatric surgery patients due to concerns about the poor oral absorption of oral bisphosphonates in the setting of RYGB, and also the potential increased risk of gastrointestinal side effects (including surgical anastomotic ulcers). Another potent antiresorptive agent is denosumab, a RANK ligand antagonist that has demonstrated greater reduction in bone turnover markers and greater increase in BMD as compared to ZOL in postmenopausal women previously treated with oral bisphosphonates (Pittman et al., 2017). However, denosumab should be considered cautiously due to the potential of developing hypocalcemia in this population (Pittman et al., 2017), as well as the question of how to manage eventual denosumab discontinuation. Other treatment options might include PTH and PTHrP analogs such as teriparatide and abaloparatide, or the sclerostin antibody romosozumab, although it is unclear whether these therapies will address the underlying high bone turnover state induced by RYGB. None of these therapies have been rigorously studied in the bariatric population.

There are data that non-pharmacologic interventions including calcium, vitamin D, and protein supplementation, as well as rigorous exercise interventions may be able to partially mitigate bone loss after RYGB (Schafer et al., 2015b; Riedt et al., 2006; Carlin et al., 2009). The joint guideline from the American Association of Clinical Endocrinologists, the Obesity Society, and the American Society for Metabolic and Bariatric Surgery suggests 1200 to 1500 g/d of calcium citrate and 3000 units/d of vitamin D intake for patients undergoing bariatric surgeries (Mechanick et al., 2013). Regarding exercise, three randomized controlled trials found that bone loss and increases in bone turnover markers were less pronounced among participants who received intensive supervised exercise training programs, along with calcium and/or vitamin D supplemention (Campanha-Versiani et al., 2017; Murai et al., 2019; Diniz-Sousa et al., 2020). These exercise studies focused on a younger population (average age ~ 40 years) and therefore it's unclear whether results can be extrapolated to older bariatric patients, who have more accelerated bone loss (Vilarrasa et al., 2011; Schafer et al., 2018). In addition, while bone loss was less dramatic than without intervention,

the exercise arms of these studies still experienced 4–6% bone loss at the femur at 1 year after RYGB. Therefore, appropriate nutritional supplementation and exercise should be counseled for all RYGB patients, and yet there may still be a role for pharmacologic treatment, particularly among older adults.

Our study had several limitations, the most important of which is the small sample size and short duration that may have lessened our power to detect statistically significant effects. Despite the small number of studied individuals, we were able to detect significant elevations of CTX and declines in total hip bone density from baseline in both groups, and differences in CTX rise between groups. Clearly, larger, randomized placebo controlled trials of bariatric surgery patients are needed to definitively evaluate skeletal endpoints in response to zoledronic acid. Another limitation of this study was the use of historical controls and the lack of follow-up at intervening timepoints (e.g. 2 weeks and 12 weeks) in the control group. However, we reported in a previous unrelated study that elevations in CTX among RYGB patients occurred as early as postoperative day 10 (Yu et al., 2016), which directly contrasts with the transient decline in CTX that we observed at 2 weeks among ZOL treated RYGB patients in the current study. As discussed earlier, our protocol studied a single dose of pre-operative ZOL. Future treatment regimens may need to consider postoperative administration of antiresorptive agents, and/or repeated treatments to achieve more durable suppression of bone turnover and to preserve bone density at femoral sites. Finally, our study only included patients receiving RYGB. Our results cannot be extrapolated to patients receiving other forms of bariatric surgery such as gastric banding or sleeve gastrectomy.

In summary, this proof of concept study suggests that a single dose of pre-operative zoledronic acid may mitigate but not fully prevent high bone turnover in the acute postoperative period. At 24 weeks after RYGB, our preliminary data suggest that ZOL may preserve bone density at the spine, but was not sufficient to prevent bone loss at the hip. Larger prospective randomized placebo controlled studies are needed to investigate strategies to prevent negative skeletal effects in the growing population of adults receiving bariatric surgery.

Transparency document

The Transparency document associated with this article can be found, in online version.

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Declaration of competing interest

Dr. Yu reports grants from NIH, Doris Duke Charitable Foundation, and Massachusetts General Hospital obtained during the conduct of the study; and investigator-initiated research grants from Amgen Inc. and Seres Therapeutics that are outside the submitted work. The other authors state that they have no conflicts of interest.

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CRediT authorship contribution statement

Study design: EWY. Study conduct: EWY, MC, MCC, KGL, CCR, and MMH. Data collection and analysis: YL, MC, MCC, and KGL. Data interpretation: YL and EWY. Drafting manuscript: YL and EWY. Revising and approving final version of manuscript: all authors. EWY takes responsibility for the integrity of the data analysis.

References

Angrisani, L., Santonicola, A., Iovino, P., Vitiello, A., Zundel, N., Buchwald, H., Scopinaro, N., 2017. Bariatric surgery and endoluminal procedures: IFSO worldwide survey 2014. Obes. Surg. 27 (9), 2279–2289.

Belavy, D.L., Baecker, N., Armbrecht, G., Beller, G., Buehlmeier, J., Frings-Meuthen, P., Rittweger, J., Roth, H.J., Heer, M., Felsenberg, D., 2016. Serum sclerostin and DKK1 in relation to exercise against bone loss in experimental bed rest. J. Bone Miner. Metab. 34 (3), 354–365.

D.M. Black, P.D. Delmas, R. Eastell, I.R. Reid, S. Boonen, J.A. Cauley, F. Cosman, P.t. Lakatos, P.C. Leung, Z. Man, C. Mautalen, P. Mesenbrink, H. Hu, J. Caminis, K. Tong, T. Rosario-Jansen, J. Krasnow, T.F. Hue, D. Sellmeyer, E.F. Eriksen, S.R. Cummings Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis, New England Journal of Medicine 356(18) (2007a) 1809–1822.

Black, D.M., Delmas, P.D., Eastell, R., Reid, I.R., Boonen, S., Cauley, J.A., Cosman, F., Lakatos, P., Leung, P.C., Man, Z., Mautalen, C., Mesenbrink, P., Hu, H., Caminis, J., Tong, K., Rosario-Jansen, T., Krasnow, J., Hue, T.F., Sellmeyer, D., Eriksen, E.F., Cummings, S.R., 2007b. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N. Engl. J. Med. 356 (18), 1809–1822.

Blom-Hogestol, I.K., Hewitt, S., Chahal-Kummen, M., Brunborg, C., Gulseth, H.L., Kristinsson, J.A., Eriksen, E.F., Mala, T., 2019. Bone metabolism, bone mineral density and low-energy fractures 10years after Roux-en-Y gastric bypass. Bone 127, 436–445.

Bolland, M.J., Grey, A., Horne, A.M., Briggs, S.E., Thomas, M.G., Ellis-Pegler, R.B., Gamble, G.D., Reid, I.R., 2012. Effects of intravenous zoledronate on bone turnover and bone density persist for at least five years in HIV-infected men. J. Clin. Endocrinol. Metab. 97 (6), 1922–1928.

Bredella, M.A., Greenblatt, L.B., Eajazi, A., Torriani, M., Yu, E.W., 2017. Effects of Roux-en-Y gastric bypass and sleeve gastrectomy on bone mineral density and marrow adipose tissue. Bone 95, 85–90.

A.M. Brufsky, W.G. Harker, J.T. Beck, L. Bosserman, C. Vogel, C. Seidler, L. Jin, G. Warsi, E. Argonza-Aviles, J. Hohneker, S.G. Ericson, E.A. Perez, Final 5-year results of Z-FAST trial: adjuvant zoledronic acid maintains bone mass in postmenopausal breast cancer patients receiving letrozole, Cancer 118(5) 1192–201.

Campanha-Versiani, L., Pereira, D.A.G., Ribeiro-Samora, G.A., Ramos, A.V., de Sander Diniz, M.F.H., De Marco, L.A., Soares, M.M.S., 2017. The effect of a muscle weight-bearing and aerobic exercise program on the body composition. muscular strength, biochemical markers, and bone mass of obese patients who have undergone gastric bypass surgery, Obes Surg 27 (8), 2129–2137.

Carlin, A.M., Rao, D.S., Yager, K.M., Parikh, N.J., Kapke, A., 2009. Treatment of vitamin D depletion after Roux-en-Y gastric bypass: a randomized prospective clinical trial. Surg. Obes. Relat. Dis. 5 (4), 444–449.

Chang, S.H., Stoll, C.R., Song, J., Varela, J.E., Eagon, C.J., Colditz, G.A., 2014. The effectiveness and risks of bariatric surgery: an updated systematic review and meta-analysis, 2003-2012. JAMA Surg 149 (3), 275–287.

Craig, C.L., Marshall, A.L., Sjostrom, M., Bauman, A.E., Booth, M.L., Ainsworth, B.E., Pratt, M., Ekelund, U., Yngve, A., Sallis, J.F., Oja, P., 2003. International physical activity questionnaire: 12-country reliability and validity. Med. Sci. Sports Exerc. 35 (8), 1381–1395.

Crawford, B.A., Kam, C., Pavlovic, J., Byth, K., Handelsman, D.J., Angus, P.W., McCaughan, G.W., 2006. Zoledronic acid prevents bone loss after liver transplantation: a randomized, double-blind, placebo-controlled trial. Ann. Intern. Med. 144 (4), 239–248.

Cremers, S.C., Eekhoff, M.E., Den Hartigh, J., Hamdy, N.A., Vermeij, P., Papapoulos, S.E., 2003. Relationships between pharmacokinetics and rate of bone turnover after intravenous bisphosphonate (olpadronate) in patients with Paget's disease of bone. J. Bone Miner. Res. 18 (5), 868–875.

Diniz Mde, F., Diniz, M.T., Sanches, S.R., Salgado, P.P., Valadao, M.M., Araujo, F.C., Martins, D.S., Rocha, A.L., 2004. Elevated serum parathormone after Roux-en-Y gastric bypass. Obes. Surg. 14 (9), 1222–1226.

Diniz-Sousa, F., Veras, L., Boppre, G., Sa-Couto, P., Devezas, V., Santos-Sousa, H., Preto, J., Vilas-Boas, J.P., Machado, L., Oliveira, J., Fonseca, H., 2020. The effect of an exercise intervention program on bone health after bariatric surgery: a randomized controlled trial. J. Bone Miner. Res. Epub Published online December 9, 2020.

Gagnon, C., Schafer, A.L., 2018. Bone health after bariatric surgery. JBMR Plus 2 (3), 121–133.

Gebhart, A., Young, M.T., Nguyen, N.T., 2015. Bariatric surgery in the elderly: 2009-2013. Surg. Obes. Relat. Dis. 11 (2), 393–398.

Grey, A., Bolland, M.J., Horne, A., Wattie, D., House, M., Gamble, G., Reid, I.R., 2012a. Five years of anti-resorptive activity after a single dose of zoledronate—results from a randomized double-blind placebo-controlled trial. Bone 50 (6), 1389–1393.

Grey, A., Bolland, M.J., Horne, A., Wattie, D., House, M., Gamble, G., Reid, I.R., 2012b. Five years of anti-resorptive activity after a single dose of zoledronate—results from a randomized double-blind placebo-controlled trial. Bone 50 (6), 1389–1393.

Ha, J., Lee, J.M., Lim, Y., Kim, M.K., Kwon, H.S., Song, K.H., Jeon, H.M., Kang, M.I., Baek, K.H., 2020. Effect of bisphosphonate on the prevention of bone loss in patients with gastric cancer after gastrectomy: a randomized controlled trial. Bone 130, 115138.

Haskins, I.N., Ju, T., Whitlock, A.E., Rivas, L., Amdur, R.L., Lin, P.P., Vaziri, K., 2018. Older age confers a higher risk of 30-day morbidity and mortality following laparoscopic bariatric surgery: an analysis of the metabolic and bariatric surgery quality improvement program. Obes. Surg. 28 (9), 2745–2752.

Khan, A.A., Bilezikian, J.P., Kung, A.W., Ahmed, M.M., Dubois, S.J., Ho, A.Y., Schussheim, D., Rubin, M.R., Shaikh, A.M., Silverberg, S.J., Standish, T.I., Syed, Z., Syed, Z.A., 2004. Alendronate in primary hyperparathyroidism: a double-blind, randomized, placebo-controlled trial. J. Clin. Endocrinol. Metab. 89 (7), 3319–3325.

Lang, T.F., Li, J., Harris, S.T., Genant, H.K., 1999. Assessment of vertebral bone mineral density using volumetric quantitative CT. J. Comput. Assist. Tomogr. 23 (1), 130–137.

Lindeman, K.G., Greenblatt, L.B., Rourke, C., Bouxsein, M.L., Finkelstein, J.S., Yu, E.W., 2018. Longitudinal 5-year evaluation of bone density and microarchitecture after Roux-en-Y gastric bypass surgery. J. Clin. Endocrinol. Metab. 103 (11), 4104–4112.

Lindeman, K.G., Rushin, C.C., Cheney, M.C., Bouxsein, M.L., Hutter, M.M., Yu, E.W., 2020. Bone density and trabecular morphology at least 10 years after gastric bypass and gastric banding. J. Bone Miner. Res. 35 (11), 2132–2142.

J.I. Mechanick, A. Youdim, D.B. Jones, W.T. Garvey, D.L. Hurley, M.M. McMahon, L.J. Heinberg, R. Kushner, T.D. Adams, S. Shikora, J.B. Dixon, S. Brethauer, E. American Association of Clinical, S. Obesity, M. American Society for, S. Bariatric, Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient—2013 update: cosponsored by American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery, Obesity (Silver Spring) 21 Suppl 1 (2013) S1–27.

Michaelson, M.D., Kaufman, D.S., Lee, H., McGovern, F.J., Kantoff, P.W., Fallon, M.A., Finkelstein, J.S., Smith, M.R., 2007. Randomized controlled trial of annual zoledronic acid to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer. J. Clin. Oncol. 25 (9), 1038–1042.

Murai, I.H., Roschel, H., Dantas, W.S., Gil, S., Merege-Filho, C., de Cleva, R., de Sa-Pinto, A.L., Lima, F., Santo, M.A., Benatti, F.B., Kirwan, J.P., Pereira, R.M., Gualano, B., 2019. Exercise mitigates bone loss in women with severe obesity after Roux-en-Y gastric bypass: a randomized controlled trial. J. Clin. Endocrinol. Metab. 104 (10), 4639–4650.

N.C.D.R.F. Collaboration, Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults, Lancet 390(10113) (2017) 2627–2642.

Nakamura, K.M., Haglind, E.G., Clowes, J.A., Achenbach, S.J., Atkinson, E.J., Melton III, L.J., Kennel, K.A., 2014. Fracture risk following bariatric surgery: a population-based study. Osteoporos. Int. 25 (1), 151–158.

Petrick, A.T., Kuhn, J.E., Parker, D.M., Prasad, J., Still, C., Wood, G.C., 2019. Bariatric surgery is safe and effective in Medicare patients regardless of age: an analysis of primary gastric bypass and sleeve gastrectomy outcomes. Surg. Obes. Relat. Dis. 15 (10), 1704–1711.

Pittman, K., Antill, Y.C., Goldrick, A., Goh, J., de Boer, R.H., 2017. Denosumab: prevention and management of hypocalcemia, osteonecrosis of the jaw and atypical fractures. Asia Pac J Clin Oncol 13 (4), 266–276.

Reid, I.R., Miller, P., Lyles, K., Fraser, W., Brown, J.P., Saidi, Y., Mesenbrink, P., Su, G., Pak, J., Zelenakas, K., Luchi, M., Richardson, P., Hosking, D., 2005. Comparison of a single infusion of zoledronic acid with risedronate for Paget's disease. N. Engl. J. Med. 353 (9), 898–908.

Reid, D.M., Devogelaer, J.P., Saag, K., Roux, C., Lau, C.S., Reginster, J.Y., Papanastasiou, P., Ferreira, A., Hartl, F., Fashola, T., Mesenbrink, P., Sambrook, P. N., H. Investigators, 2009. Zoledronic acid and risedronate in the prevention and treatment of glucocorticoid-induced osteoporosis (HORIZON): a multicentre, double-blind, double-dummy, randomised controlled trial. Lancet 373 (9671), 1253–1263.

Reid, I.R., Lyles, K., Su, G., Brown, J.P., Walsh, J.P., del Pino-Montes, J., Miller, P.D., Fraser, W.D., Cafoncelli, S., Bucci-Rechtweg, C., Hosking, D.J, 2011. A single infusion of zoledronic acid produces sustained remissions in Paget disease: data to 6.5 years. J Bone Mineral Res 26 (9), 2261–2270.

Reid, I.R., Black, D.M., Eastell, R., Bucci-Rechtweg, C., Su, G., Hue, T.F., Mesenbrink, P., Lyles, K.W., Boonen, S., H.P.F. Trial, H.R.F.T.S. Committees, 2013. Reduction in the risk of clinical fractures after a single dose of zoledronic acid 5 milligrams. J. Clin. Endocrinol. Metab. 98 (2), 557–653.

Riedt, C.S., Brolin, R.E., Sherrell, R.M., Field, M.P., Shapses, S.A., 2006. True fractional calcium absorption is decreased after Roux-en-Y gastric bypass surgery. Obesity (Silver Spring) 14 (11), 1940–1948.

Rosen, C.J., Brown, S., 2003. Severe hypocalcemia after intravenous bisphosphonate therapy in occult vitamin D deficiency. N. Engl. J. Med. 348 (15), 1503–1504.

Schafer, A.L., Li, X., Schwartz, A.V., Tufts, L.S., Wheeler, A.L., Grunfeld, C., Stewart, L., Rogers, S.J., Carter, J.T., Posselt, A.M., Black, D.M., Shoback, D.M., 2015a. Changes in vertebral bone marrow fat and bone mass after gastric bypass surgery: a pilot study. Bone 74, 140–145.

Schafer, A.L., Weaver, C.M., Black, D.M., Wheeler, A.L., Chang, H., Szefc, G.V., Stewart, L., Rogers, S.J., Carter, J.T., Posselt, A.M., Shoback, D.M., Sellmeyer, D.E., 2015b. Intestinal calcium absorption decreases dramatically after gastric bypass surgery despite optimization of vitamin D status. J. Bone Miner. Res. 30 (8), 1377–1385.

Schafer, A.L., Kazakia, G.J., Vittinghoff, E., Stewart, L., Rogers, S.J., Kim, T.Y., Carter, J. T., Posselt, A.M., Pasco, C., Shoback, D.M., Black, D.M., 2018. Effects of gastric bypass surgery on bone mass and microarchitecture occur early and particularly impact postmenopausal women. J. Bone Miner. Res. 33 (6), 975–986.

Seibel, M.J., 2006. Biochemical markers of bone turnover part II: clinical applications in the management of osteoporosis. Clin. Biochem. Rev. 27 (3), 123–138.

Shah, M., Sharma, A., Wermers, R.A., Kennel, K.A., Kellogg, T.A., Mundi, M.S., 2017. Hypocalcemia after bariatric surgery: prevalence and associated risk factors. Obes. Surg. 27 (11), 2905–2911.

Smith, M.R., Eastham, J., Gleason, D.M., Shasha, D., Tchekmedyian, S., Zinner, N., 2003. Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer. J. Urol. 169 (6), 2008–2012.

Sølling, A.S., Harsløf, T., Langdahl, B., 2020. Treatment with zoledronate subsequent to denosumab in osteoporosis: a randomized trial. J. Bone Miner. Res. 35 (10), 1858–1870.

Sowers, M.R., Zheng, H., Greendale, G.A., Neer, R.M., Cauley, J.A., Ellis, J., Johnson, S., Finkelstein, J.S., 2013. Changes in bone resorption across the menopause transition: effects of reproductive hormones, body size, and ethnicity. J. Clin. Endocrinol. Metab. 98 (7), 2854–2863.

van Staveren, W.A., de Boer, J.O., Burema, J., 1985. Validity and reproducibility of a dietary history method estimating the usual food intake during one month. Am. J. Clin. Nutr. 42 (3), 554–559.

Vilarrasa, N., San Jose, P., Garcia, I., Gomez-Vaquero, C., Miras, P.M., de Gordejuela, A. G., Masdevall, C., Pujol, J., Soler, J., Gomez, J.M., 2011. Evaluation of bone mineral density loss in morbidly obese women after gastric bypass: 3-year follow-up. Obes. Surg. 21 (4), 465–472.

Yu, E.W., 2014. Bone metabolism after bariatric surgery. J. Bone Miner. Res. 29 (7), 1507–1518.

Yu, E.W., Bouxsein, M.L., Roy, A.E., Baldwin, C., Cange, A., Neer, R.M., Kaplan, L.M., Finkelstein, J.S., 2014. Bone loss after bariatric surgery: discordant results between DXA and QCT bone density. J. Bone Miner. Res. 29 (3), 542–550.

Yu, E.W., Bouxsein, M.L., Putman, M.S., Monis, E.L., Roy, A.E., Pratt, J.S., Butsch, W.S., Finkelstein, J.S., 2015. Two-year changes in bone density after Roux-en-Y gastric bypass surgery. J. Clin. Endocrinol. Metab. 100 (4), 1452–1459.

Yu, E.W., Wewalka, M., Ding, S.A., Simonson, D.C., Foster, K., Holst, J.J., Vernon, A., Goldfine, A.B., Halperin, F., 2016. Effects of gastric bypass and gastric banding on bone remodeling in obese patients with type 2 diabetes. J. Clin. Endocrinol. Metab. 101 (2), 714–722.

Yu, E.W., Lee, M.P., Landon, J.E., Lindeman, K.G., Kim, S.C., 2017. Fracture risk after bariatric surgery: Roux-en-Y gastric bypass versus adjustable gastric banding. J. Bone Miner. Res. 32 (6), 1229–1236.

Zibellini, J., Seimon, R.V., Lee, C.M., Gibson, A.A., Hsu, M.S., Shapses, S.A., Nguyen, T. V., Sainsbury, A., 2015. Does diet-induced weight loss Lead to bone loss in overweight or obese adults? A systematic review and meta-analysis of clinical trials, J Bone Miner Res 30 (12), 2168–2178.

Zulkifli, S.N., Yu, S.M., 1992. The food frequency method for dietary assessment. J. Am. Diet. Assoc. 92 (6), 681–685.