Obesity Surgery (2019) 29:2886–2895
https://doi.org/10.1007/s11695-019-03909-1

ORIGINAL CONTRIBUTIONS

Bone Turnover Markers After Standard and Distal Roux-en-Y Gastric Bypass: Results from a Randomized Controlled Trial

Marius Svanevik[1,2,3] · Hilde Risstad[4] · Dag Hofsø[1] · Ingvild K Blom-Høgestøl[2,4] · Jon A. Kristinsson[5] · Rune Sandbu[1,3] · Milada Cvancarova Småstuen[1,6] · Per Medbøe Thorsby[7] · Tom Mala[5,8] · Jøran Hjelmesæth[1,2]

Published online: 8 May 2019

Abstract

Background Roux-en-Y gastric bypass is associated with increased risk of bone fractures. Malabsorptive procedures may be associated with secondary hyperparathyroidism and detrimental effects on bone health. We aimed to compare the effects of standard and distal gastric bypass on bone turnover markers 2 years after surgery.

Methods Patients with body mass index (BMI) 50–60 kg/m^2 ($n = 113$) were randomized to standard or distal gastric bypass, 105 patients (95%) completed 2-year follow-up. Serum C-terminal telopeptide of type I collagen (CTX-1), procollagen type I N-propeptide (PINP), and bone-derived alkaline phosphatase (BALP) was measured at baseline and up to 2 years after surgery. ANCOVA and linear mixed models were used to compare groups.

Results The levels of bone turnover markers increased significantly in both groups, with no statistically significant difference between groups. Two years after standard and distal gastric bypass mean (SD) CTX-1 were 0.81 (0.32) and 0.83 (0.31) μg/L ($p = 0.38$), mean PINP was 77.6 (23.2) and 77.7 (29.3) μg/L ($p = 0.42$), and BALP 47.9 (21.9) vs. 50.7 (19.6) μg/L ($p = 0.38$), respectively. Multiple linear regression analyses showed that PINP and BALP correlated positively ($p = 0.01$ and $p < 0.001$) with PTH, but only BALP was significantly higher in patients with secondary hyperparathyroidism ($p = 0.001$). Type of surgery, vitamin D serum concentrations, and 2-year BMI were all independently associated with PTH levels.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11695-019-03909-1) contains supplementary material, which is available to authorized users.

✉ Marius Svanevik
marius.svanevik@siv.no

Hilde Risstad
hiriss@outlook.com

Dag Hofsø
Dag.Hofso@siv.no

Ingvild K Blom-Høgestøl
inkhoe@ous-hf.no

Jon A. Kristinsson
joakri@ous-hf.no

Rune Sandbu
rune.sandbu@siv.no

Milada Cvancarova Småstuen
milasm@oslomet.no

Per Medbøe Thorsby
pertho@ous-hf.no

Tom Mala
tommal@ous-hf.no

Jøran Hjelmesæth
joran.hjelmeseth@siv.no

1 Morbid Obesity Center, Vestfold Hospital Trust, Tønsberg, Norway

2 Department of Endocrinology, Morbid Obesity and Preventive Medicine, Institute of Clinical Medicine, University of Oslo, Oslo, Norway

3 Department of Gastrointestinal Surgery, Vestfold Hospital Trust, Tønsberg, Norway

4 Department of Endocrinology, Morbid Obesity and Preventive Medicine, Oslo University Hospital, Oslo, Norway

5 Department of Morbid Obesity and Bariatric Surgery, Oslo University Hospital, Oslo, Norway

6 Oslo Metropolitan University, Oslo, Norway

7 Hormone Laboratory, Department of Medical Biochemistry, Oslo University Hospital, Oslo, Norway

8 Department of Gastrointestinal Surgery, Oslo University Hospital, Oslo, Norway

Conclusion A comparable increase in bone turnover markers 2 years after standard and distal gastric bypass was observed. There was a higher prevalence of secondary hyperparathyroidism after distal gastric bypass, but this did not impact bone turnover markers.

Trial Registration Clinical Trials.gov number NCT00821197.

Keywords Bariatric surgery · Gastric bypass · Malabsorptive · Bone

Introduction

Roux-en-Y gastric bypass (RYGB) has been the gold standard of surgical treatment of morbid obesity due to low morbidity and mortality rates and sustained weight loss and benefits on (or to) health-related quality of life and comorbidities [1].

RYGB seems, however, to be associated with an increased risk of fractures. The negative impact on bone health appears to be more prominent after malabsorptive bariatric procedures [2–5]. The mechanism of the increased fracture risk is unknown but is probably multifactorial. Reduced mechanical skeletal loading following weight loss induces loss of bone mass, but bone mass also seems to decline after weight stabilization [6]. Disturbed calcium homeostasis and vitamin D deficiency are associated with changes in bone mass and bone quality [7, 8]. Bone turnover is affected by hormonal changes in parathyroid and gastrointestinal hormones [9].

Estimation of bone mass density (BMD) by dual-energy absorptiometry is the gold standard for evaluation of bone quality [10], although low BMD is only a modest risk factor for fractures [11]. BMD, bone architecture, and bone material properties act in symphony to define bone quality and thus skeletal resistance to fracture. Bone quality is affected by bone turnover [12], the process of constant bone resorption and formation, and can be quantified by biochemical markers of bone health also used for the monitoring of treatments [13].

The optimal limb lengths in RYGB are not established, and few randomized studies have addressed varying intestinal limb lengths after RYGB [14–17]. The distal RYGB used in this study had a short common channel (distance from the entero-entero anastomoses to the ileocecal valve). We have previously shown that this variant of distal RYGB was associated with a higher prevalence of secondary hyperparathyroidism than standard RYGB [18]. To our knowledge, the effects of distal RYGB on bone turnover markers have not been reported.

The primary aim of this sub-study of the Vestfold and Aker Randomized long-limb versus distal Gastric bypass study (VARG study) was to compare bone turnover markers 2 years after standard and distal RYGB. Our hypothesis was that distal RYGB would lead to higher levels of bone turnover markers, as a result of the increased prevalence of secondary hyperparathyroidism.

Material and Methods

Trial Design and Participants

The design and methodology in this double-blind randomized controlled clinical trial have previously been described [19]. Briefly, all referred patients aged 18 to 60 years with a body mass index (BMI) of 50 to 60 were assessed for inclusion at two tertiary care centers for bariatric surgery in Norway between May 2011 and April 2013.

The study is approved by the Regional Ethics Committees for Medical and Health Research (S-08466d) and registered at clinicaltrials.gov (NCT00821197). All patients provided written and informed consent.

Interventions and Follow-Up

A low-calorie diet (approximately 1000 kcal/day) 3 weeks prior to surgery was advised to all patients. An antegastric antecolic Roux-en-Y configuration with a gastric pouch of about 25 mL and a biliopancreatic limb of 50 cm was constructed during both procedures. The standard RYGB included an alimentary limb of 150 cm, whereas the distal RYGB had a common channel of 150 cm. Identical vitamin and mineral supplementations were prescribed and consisted of daily supplementation with one tablet multivitamin (including 400 IU vitamin D_3), 1000 mg calcium carbonate/800-IU vitamin D_3, iron, and vitamin B_{12}. Baseline examination was performed prior to the low-calorie diet, and follow-up at 6 weeks, 6 months, 1 year, and 2 years after surgery.

Prespecified Outcomes

The primary outcome of this study was levels of bone turnover markers 2 years after surgery. Secondary outcomes were associations with bone turnover markers, and weight loss, dietary supplementation, and biochemical analytes. Exploratory outcomes included differences between patients with or without secondary hyperparathyroidism at 2 years. Secondary hyperparathyroidism was defined as PTH ≥ 7.1 pmol/L and the absence of hypercalcemia.

Bone Turnover Markers

Markers of bone turnover in blood reflect the metabolic activity of bone. Procollagen type I N propeptide (PINP) is a peptide at the end of type I collagen cleaved during bone matrix formation and released into the circulation by osteoblasts. Bone-specific alkaline phosphatase (BALP) is synthesized by osteoblast during bone formation and is presumed to be involved in the calcification of bone matrix. Bone resorption markers are degradation products of type I collagen, and serum collagen type 1 c-telopeptide (CTX-1) is a cross-linking telopeptide released into serum by osteoclasts during bone resorption.

Laboratory Analysis

Venous blood samples were obtained after an overnight fast. Serum CTX-1, BALP, PINP, parathyroid hormone (PTH), 25(OH) vitamin D (vitamin D), and ionized calcium were analyzed at the Hormone Laboratory, Oslo University Hospital. See Supplementary Table 1 for variation coefficients and reference ranges.

Serum CTX-1 and PINP were measured using electrochemical luminescence immunoassay (ECLIA) on a Roche Diagnostics Modular E170 or Cobas e601 automated analyzer. The reported values of serum BALP until February 2014 were analyzed with enzyme immunoassay (EIA) (Metra Biosystems Inc., Mountain View, CA, USA); measurements from March 2014 were analyzed with ECLIA (Dia-Sorin, Stillwater, MN, USA) and transformed to corresponding values using a validated regression algorithm (not shown).

Serum vitamin D was analyzed by radioimmunoassay (Dia-Sorin, Stillwater, MN, USA), until October 2012 and thereafter with liquid chromatography-mass spectrometry. The measurements of the two analytic methods were standardized according to the vitamin D standardization program [20].

Serum PTH was analyzed by a chemiluminoimmunometric assay (Immulite 2000 XPI, Siemens Healthcare Diagnostics, CA, USA).

Serum ionized calcium was analyzed with a Rapidlab 348 analyzer (Instru-Med Inc., GA, USA), until January 2012, thereafter a Cobas b221 (Roche Diagnostics GmbH, Germany). Values of ionized calcium from Rapidlab 348 measurements were transformed to corresponding values of Cobas b221 using a validated regression algorithm (not shown).

Serum levels of albumin, total protein, C-reactive protein, potassium, phosphate, magnesium, and total alkaline phosphatase (ALP) were analyzed at both Oslo University Hospital and Vestfold Hospital Trust.

Sample Size

The trial sample size was determined to detect a difference in change in BMI of 3.0 kg/m^2 or more at 2 years. We estimated that 88 patients would give a power of more than 80% to detect such a BMI difference as statistically significant at 2 years ($\alpha = 0.05$). To allow for possible dropouts, a total of 113 patients were included.

Statistical Analyses

Continuous variables are presented as mean and standard deviation (SD), categorical variables with counts (n), and percentages. Point estimates from the mixed model analysis are presented as means with 95% confidence intervals (CIs).

Repeated measurements were analyzed using linear mixed models with an unstructured covariance matrix, controlling for gender and age. Each model contained fixed effects for treatment, time (measured in weeks after surgery), treatment × time interaction, and a random intercept. Using these linear mixed models, we estimated mean treatment group values with 95% CIs.

Pairs of categorical variables were assessed using Fisher's exact test. Group comparison of patients with secondary hyperparathyroidism was performed using analysis of covariance (ANCOVA) controlling for baseline differences, Students t test for total weight loss and Fisher's exact test for categorical variables.

The relationship between PTH, CTX-1, PINP, and BALP as dependent variables and potential associative factors was analyzed using multiple linear regression analysis. First, all independent variables were analyzed using univariate regression. Second, a multiple regression model analysis with all independent variables and backward stepwise elimination ($p < 0.10$) was performed. Standardized beta (SB) is reported for comparison of effect sizes.

All tests were two-sided and p values < 0.05 were considered statistically significant. IBM SPSS Statistics for Windows, Version 23.0, was used for the statistical analyses.

Results

Participant Characteristics

One hundred eleven patients were included and 105 patients (95%) completed the 2-year follow-up (see Fig. 1 for details). Baseline and 2-year demographics, anthropometrics, and laboratory findings are listed in Table 1.

Primary Outcomes

There was no statistical difference in the level of bone turnover markers between groups 2 years after surgery (Table 1). Table 2 shows the percentage increase from baseline in mean values from linear mixed models of CTX-1, PINP, and BALP.

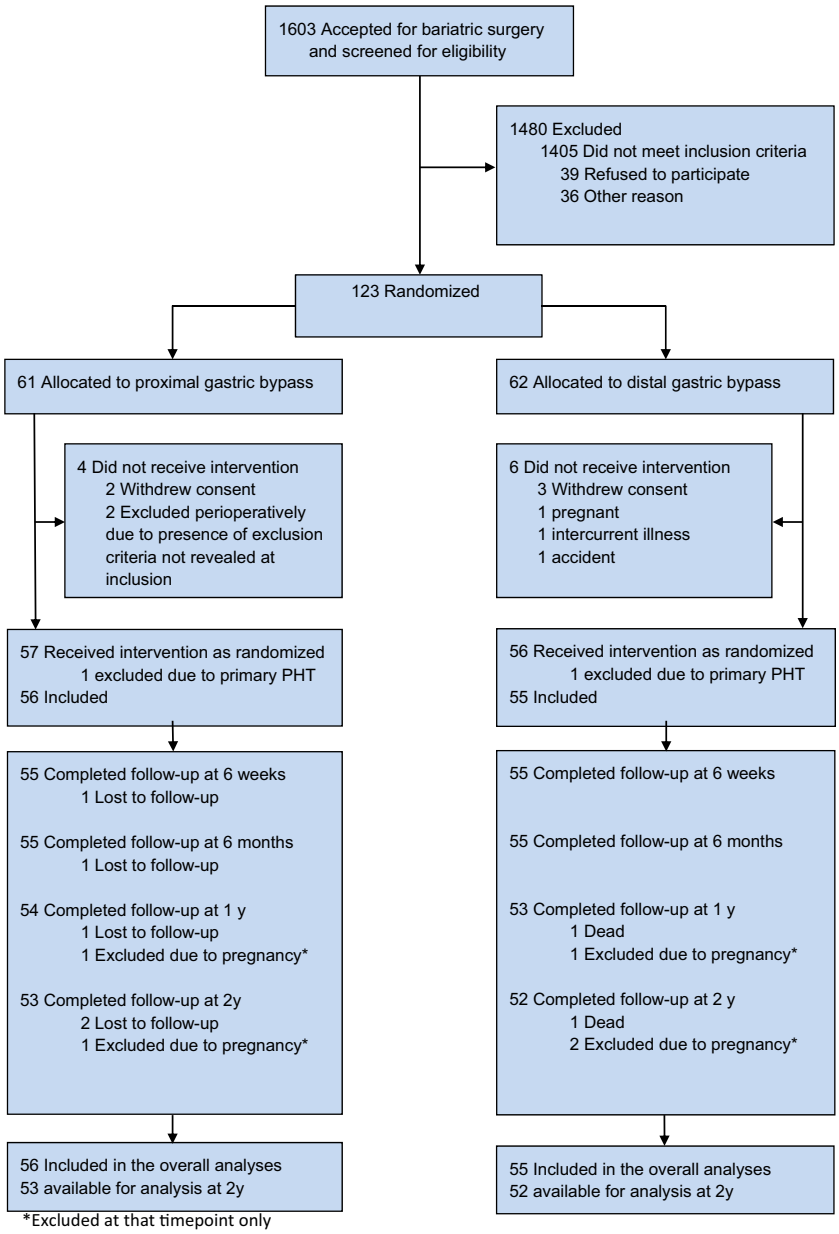

Fig. 1 Flow of patients through recruitment and follow-up

There were no significant differences between surgical groups at any time point.

Estimated mean values from mixed models for CTX-1, PINP, BALP, PTH, vitamin D, and ionized calcium over time are given in Fig. 2. The only notable difference between the procedures was the larger increase in PTH after distal RYGB and a lack of increase in vitamin D levels.

Secondary Outcomes

Multiple linear regressions demonstrated that the type of surgery was not correlated with CTX-1, PINP, or BALP (Supplementary Table 2a–c). Weight loss and adherence to calcium supplementation were independently correlated with CTX-1 and PINP, while serum levels of PTH correlated positively with BALP and PINP. Phosphate was independently correlated with CTX-1, but not with the other markers. Type of surgery, vitamin D levels, BMI at 2 years, and adherence to calcium supplementation were independently associated with PTH at 2 years (Table 3).

Exploratory Outcomes

Patients with and without secondary hyperparathyroidism are presented in Table 4. Ionized calcium was lower among patients with secondary hyperparathyroidism, whereas vitamin D did not differ significantly between groups. Mean BALP, but not CTX-1 and PINP, was significantly higher in the group

Table 1 Observed baseline and 2-year data by treatment group

	Baseline				2 years				
	n	Standard gastric bypass	*n*	Distal gastric bypass	*n*	Standard gastric bypass	*n*	Distal gastric bypass	*p* value
Demographics									
Age, baseline, years(SD)	56	38.5 (9.3)	55	41.5 (8.4)		–		–	–
Gender, female, no. (%)	56	35 (63%)	55	37 (67%)		–		–	–
Ethnicity, caucasian, no. (%)	56	56 (100)	55	54 (98)		–		–	–
Anthropometrics									
Height, cm (SD)	56	173.3 (9.6)	55	170.8 (9.2)		–		–	–
Weight, kg (SD)	56	160.6 (19.9)	55	156.6 (16.4)	53	103.9 (19.8)	52	103.4 (13.5)	0.73[a]
BMI, kg/m^2 (SD)	56	53.3 (2.6)	55	53.6 (3.3)	53	34.8 (6.2)	52	35.6 (4.2)	0.41[a]
TWL, % (SD)		–		–	53	34.9 (10.8)	52	33.9 (7.8)	0.57[b]
Fasting laboratory values									
Vitamin D, nmol/L (SD)	56	46.8 (20.2)	54	46.4 (18.0)	52	57.3 (21.4)	51	48.5 (21.4)	0.02[a]
Calcium, ionized, mmol/L (SD)	54	1.20 (0.04)	51	1.21 (0.04)	50	1.20 (0.04)	48	1.19 (0.03)	0.18[a]
Magnesium, mmol/L (SD)	56	0.84 (0.06)	55	0.83 (0.07)	53	0.85 (0.06)	51	0.84 (0.05)	0.19[a]
Phosphate, mmol/L (SD)	56	1.04 (0.15)	55	1.04 (0.14)	53	1.12 (0.14)	51	1.10 (0.14)	0.88[a]
Albumin, g/L (SD)	56	43.5 (3.1)	55	43.0 (2.8)	53	43.0 (3.8)	51	41.4 (3.2)	0.02[a]
Total protein, g/L (SD)	56	72.7 (4.4)	54	71.6 (3.6)	53	68.7 (4.9)	51	66.4 (4.1)	0.01[a]
C-reactive protein, mg/L (SD)	56	12.8 (9.8)	55	15.2 (24.2)	53	2.0 (1.6)	51	2.2 (2.8)	0.95[a]
Alkaline phosphatase, U/L (SD)	56	82.9 (18.8)	55	80.2 (22.8)	53	85.0 (26.1)	51	85.5 (23.3)	0.83[a]
PTH, pmol/L (SD)	56	5.7 (3.4)	54	5.8 (4.0)	53	6.3 (3.1)	51	8.3 (3.6)	0.01[a]
CTX-1, μg/L (SD)	56	0.34 (0.16)	55	0.31 (0.17)	53	0.81 (0.32)	52	0.83 (0.31)	0.38[a]
PINP, μg/L (SD)	56	45.6 (15.8)	55	41.7 (13.1)	53	77.6 (23.2)	52	77.7 (29.3)	0.42[a]
BALP, μg/L (SD)	56	32.2 (7.1)	55	32.5 (9.1)	53	47.9 (21.9)	52	50.7 (19.6)	0.38[a]
Hyperparathyroidism									
Secondary, no. (%)	56	11 (20)	55	12 (22)	53	18 (34)	52	31 (60)	< 0.01[c]

[a] Mixed model analysis adjusted for age and gender (*p* values)

[b] ANOVA (*p* values)

[c] Fisher's Exact (*p* values)

BMI, body mass index; *TWL*, total weight loss; *PTH*, parathyroid hormone; *CTX-1*, collagen type 1 C-telopeptide; *PINP*, procollagen type 1 N-terminal propeptide; *BALP*, bone-derived alkaline phosphatase

with secondary hyperparathyroidism. There were 29 (51%) females with normal PTH, and 38 (78%) females with secondary hyperparathyroidism ($p < 0.01$). The mean percentage of total weight loss was lower in patients with secondary hyperparathyroidism ($p < 0.01$).

Discussion

In contrast with our primary hypothesis, the levels of bone turnover markers did not differ significantly between treatment groups 2 years after surgery. However, increasing weight loss and non-adherence to calcium supplementation were associated with higher levels of CTX-1 and PINP, and increased PTH was associated with increasing levels of BALP and PINP. Despite a significant increase in the prevalence of secondary hyperparathyroidism, this did not affect changes in bone turnover markers. Our exploratory analysis of bone turnover markers in patients with secondary hyperparathyroidism showed only increased BALP in this group, with no significant difference in levels of CTX-1 and PINP.

Possible Mechanisms and Explanations

Although there was no difference in bone turnover markers between the two procedures, there were significant differences in the levels of PTH and the prevalence of secondary hyperparathyroidism. Vitamin D and calcium supplementation are recommended after RYGB to reduce the risk of secondary hyperparathyroidism [21]. We observed an increase in the

Table 2 Percentage increase from baseline of bone turnover markers from mixed model analysis at all time points

	Percentage increase from baseline at			
	6 weeks	6 months	1 year	2 years
CTX-1, μg/L				
Standard	111	189	171	129
(95% CI)	94–129	162–211	146–197	106–151
Distal	121	197	203	158
(95% CI)	103–139	172–224	176–230	133–185
p value	n.s.	n.s.	n.s.	n.s.
PINP, μg/L				
Standard	33	81	97	67
(95% CI)	21–45	67–95	79–115	52–83
Distal	45	76	100	85
(95% CI)	32–58	61–90	81–120	69–101
p value				
BALP, μg/L				
Standard	10	28	27	50
(95% CI)	2–18	17–38	14–39	32–67
Distal	3	20	36	57
(95% CI)	− 6–11	10–31	23–48	40–74
p value	n.s.	n.s.	n.s.	n.s.

Percentage calculated from estimated means from mixed model adjusting for age and gender

CTX-1, collagen type 1 C-telopeptide; *PINP*, procollagen type 1 N-terminal propeptide; *BALP*, bone-derived alkaline phosphatase

mean levels of vitamin D after a standard but not after distal RYGB, indicating that the recommended level of supplementation may be too low for these patients [22, 23]. Low adherence to calcium supplementation was associated with increased serum levels of CTX-1, PINP, and PTH. Seasonal variations in sun exposure can affect vitamin D levels but are unlikely to impact the between-group findings of our study due to the randomized controlled design.

Both procedures bypass the duodenum and proximal jejunum, the predominant site of active vitamin D-mediated calcium uptake. The length of small bowel exposed to nutrients is similar after both procedures; however, the long alimentary limb without digestive enzymes after distal RYGB could reduce the bioavailability of calcium. Calcium is secreted with bile, most of which is reabsorbed. After distal RYGB, the small bowel exposed to bile is shortened significantly, possibly resulting in less reabsorption. This intestinal loss of calcium could lead to upregulation of PTH and secondary hyperparathyroidism. Other studies have shown left-shifted calcium distribution, corresponding to a state of relative calcium insufficiency [24]. The two procedures could induce different dietary habits. Without standardized evaluation of dietary intake, however, this remains unknown.

The levels of bone turnover markers were comparable in both groups despite the difference in PTH. The reason for this remains unclear, but both groups had similar weight loss, and the length of the biliopancreatic limb was identical. Although levels of vitamin D were lower after distal RYGB, they are probably over the threshold causing detrimental effects on bone turnover. Potential negative effects of PTH on bone health after distal gastric bypass might be offset by other mechanisms such as gut hormones or changes in bile acids protecting the bone. Glucagon-like peptide 1 (GLP-1) and peptide tyrosine tyrosine (PYY) have been shown to have direct effects on bone metabolism, where GLP-1 has an insulin-independent anabolic effect on bone, and PYY direct effects inhibiting osteoblasts [9]. Distal gastric bypass leads to lower glucose, HbA1c, and LDL cholesterol despite similar weight loss, potentially indicating different effects on bile acids or gut hormones [18], but further studies are needed to investigate this.

The findings of low levels of vitamin D, and increased PTH, indicate that a certain level of malabsorption exists after distal gastric bypass compared to a standard gastric bypass. We therefore recommend that patients should follow-up more closely after distal gastric bypass.

Comparison with Other Reports

Studies indicate an increased fracture risk after bariatric surgery, especially after malabsorptive procedures [2–4]. Most studies on bone turnover markers after bariatric surgery have

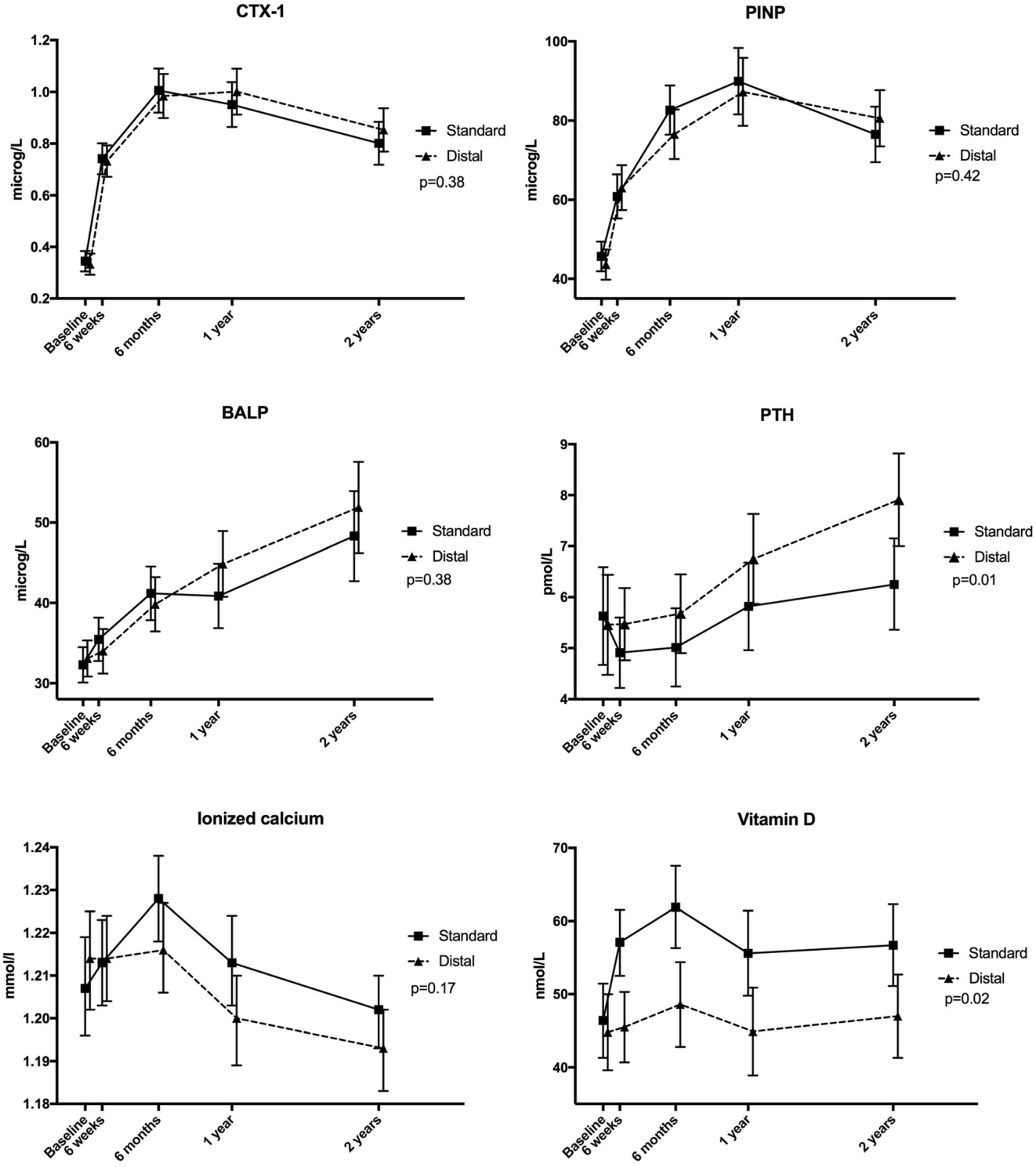

fig. 2 Modeled mean (95%CI) changes over time of serum levels of parathyroid hormone (PTH), vitamin D, ionized calcium, CTX-1, PINP, and BALP after standard ($n = 56$) and distal ($n = 55$) gastric bypass

compared RYGB with sleeve gastrectomy, and no direct comparative studies with distal RYGB exist. Previously reported increases in CTX-1 and PINP after RYGB are comparable with our observations. [25, 26]. A study comparing RYGB and intensive lifestyle intervention showed that the increase in bone turnover markers was independently associated with

Table 3 Associations with PTH (dependent) and independent variables 2 years after surgical treatment

Variable	Univariate analysis			Multivariate analysis			
	B	95% CI	*p* value	*B*	95% CI	SCB	*p* value
Distal gastric bypass	1.95	0.65, 3.25	< 0.01	1.37	0.49, 2.26	0.20	< 0.01
Age	0.05	− 0.02, 0.13	0.16	–	–		–
Gender	− 1.21	− 2.60, 0.18	0.09	–	–		–
BMI	0.22	0.09, 0.34	0.001	0.12	0.04, 0.20	0.18	0.01
Weight loss 2 years	− 0.06	− 0.09, − 0.02	< 0.01	–	–		–
Ionized calcium	− 28.10	− 45.93, − 10.28	< 0.01	–	–		–
Vitamin D	− 0.04	− 0.07, − 0.01	0.01	− 0.03	− 0.05, − 0.01	− 0.17	0.01
Magnesium	5.90	− 6.44, 18.24	0.34	–	–		–
Phosphate	− 5.51	− 10.17, -0.84	0.02	–	–		–
Albumin	− 0.11	− 0.31, 0.08	0.24	–	–		–
Calcium supplement	− 0.97	− 2.49, 0.55	0.21	− 1.04	− 2.03, − 0.04	− 0.13	0.04
PTH baseline	0.66	0.53, 0.79	< 0.001	0.63	0.51, 0.75	0.67	< 0.001

B, beta; *CI*, confidence interval; *SCB*, standardized coefficient beta; *PTH*, parathyroid hormone

both weight loss and surgery [5], indicating that bone turnover is not solely a physiologic adaptation to weight loss. Importantly, increased bone turnover has also been shown to increase bone fragility [27, 28].

The weight loss after RYGB usually plateaus after 1 to 1 years. A recent study reported that osteocalcin and CTX-1 remained elevated 5 years after RYGB, indicating long-term disturbances [29]. We found a drop in levels of PINP and CTX-1 between 1 and 2 years, while BALP continued to increase. While BALP is dependent on bone mineralization, CTX-1 and PINP are markers of bone collagen metabolism. This difference might indicate that bone remodeling due to weight loss plateaus, but changes in bone mineralization continue due to inadequate calcium levels. Long-term studies

Table 4 Observed 2-year data for patients with normal PTH and with secondary hyperparathyroidism

	Normal PTH* $n = 56$	Secondary HPT* $n = 49$	*p* value
Anthropometrics			
Gender, female no.(%)	29 (51)	38 (78)	< 0.01[a]
BMI, kg/m^2 (SD)	33.6 (4.9)	37.0 (5.1)	0.001[b]
Total weight loss, % (SD)	62.3 (24.6)	47.7 (18.4)	< 0.01[c]
Age, years (SD)	41.3 (9.7)	42.8 (8.0)	0.39[c]
Fasting laboratory values			
Vitamin D, nmol/L (SD)	55.2 (20.8)	50.3 (22.7)	0.33[b]
Calcium, ionized, mmol/L (SD)	1.21 (0.03)	1.18 (0.04)	0.001[b]
Magnesium, mmol/L (SD)	0.85 (0.05)	0.85 (0.06)	0.45[b]
Phosphate, mmol/L (SD)	1.12 (0.14)	1.09 (0.15)	0.42[b]
CTX-1, μg/L (SD)	0.80 (0.31)	0.84 (0.31)	0.22[b]
PINP, μg/L (SD)	73.7 (23.4)	82.1(28.7)	0.10[b]
BALP, μg/L (SD)	43.7 (12.5)	55.8 (26.0)	0.001[b]
PTH, pmol/L (SD)	5.0 (1.4)	10.0 (3.3)	< 0.001[b]

[a] Fischers Exact (*p* values)

[b] ANCOVA (*p* values)

[c] *t* test (*p* values)

*Normal PTH defined as PTH ≤ 7.0 pmol/L, secondary hyperparathyroidism as PTH ≥ 7.1 mol/L

PTH, parathyroid hormone; *CTX-1*, collagen type 1 C-telopeptide; *PINP*, procollagen type 1 N-terminal propeptide; *BALP*, bone-derived alkaline phosphatase

focusing on fracture risk and changes in bone mineral density are needed to further explore this.

High prevalence of secondary hyperparathyroidism after RYGB, and even higher after malabsorptive procedures, has been reported [24, 30, 31]. In our study, only BALP was increased in patients with secondary hyperparathyroidism compared with patients with normal PTH at 2 years, while multivariate analysis also showed correlation with PINP. Previous studies have shown a correlation between CTX-1 and PTH after RYGB but not after sleeve gastrectomy [29].

Patients with secondary hyperparathyroidism had lower weight loss than patients with normal PTH. Hyperparathyroidism has previously been associated with metabolic syndrome and increased risk of cardio-metabolic disease [32], and this combined with a less favorable weight loss outcome could reflect a high-risk population.

Strengths and Limitations

Strengths include the randomized controlled design, standardized surgical procedures, and the high rate of follow-up. The comparable weight loss in both groups provides an opportunity to investigate the effects of the surgery not impacted by weight loss.

This study was not specifically powered to detect differences in bone turnover markers although this was a prespecified secondary endpoint. The follow-up was limited to 2 years, but bone remodeling could continue. Bone turnover markers are surrogate markers of bone health and dual energy absorptiometry was not performed. We have no information on the menstrual status and limited information about medication. Systematic data on potential fractures during follow-up was not retrieved, and standardized questionnaires on dietary intake were not used.

Changes in laboratory analytic methods during the study could have introduced some bias; however, ionized calcium concentrations and BALP were analyzed at the same laboratory and values were compared using validated algorithms.

Conclusion

A comparable increase in bone turnover markers 2 years after standard and distal gastric bypass was observed. There was a higher prevalence of secondary hyperparathyroidism after distal gastric bypass, but this did not impact bone turnover markers.

Acknowledgments We thank Linda Mathisen (Vestfold Hospital Trust) and Marianne Sæther (Oslo University Hospital), for general project support, and finally, we thank all the patients for participating in the study.

Funding Marius Svanevik has received a research grant from the south-eastern Norway Regional Health Authority.

Compliance with Ethical Standards

The study is approved by the Regional Ethics Committees for Medical and Health Research (S-08466d).

Conflict of Interest Marius Svanevik reports grants from Southern and Eastern Norway Health Authority, during the conduct of the study. All other authors declare that they have no conflict of interest.

Statement of Informed Consent Informed consent was obtained from all individual participants included in the study.

Statement of Human and Animal Rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References

1. Angrisani L, Santonicola A, Iovino P, et al. Bariatric surgery worldwide 2013. Obes Surg. 2015;25:1822–32.
2. Rousseau C, Jean S, Gamache P, et al. Change in fracture risk and fracture pattern after bariatric surgery: nested case-control study. BMJ. 2016:3794–12.
3. Lu C-W, Chang Y-K, Chang H-H, et al. Fracture risk after bariatric surgery. Medicine. 2015;94:2087–7.
4. Nakamura KM, Haglind EGC, Clowes JA, et al. Fracture risk following bariatric surgery: a population-based study. Osteoporos Int. 2013;25:151–8.
5. Hofsø D, Bollerslev J, Sandbu R, et al. Bone resorption following weight loss surgery is associated with treatment procedure and changes in secreted Wnt antagonists. Endocrine. Springer US. 2016;53:313–21.
6. Raoof M, Näslund I, Rask E, et al. Effect of gastric bypass on bone mineral density, parathyroid hormone and vitamin D: 5 years follow-up. Obes Surg. Springer US. 2016;26:1141–5.
7. Switzer NJ, Marcil G, Prasad S, et al. Long-term hypovitaminosis D and secondary hyperparathyroidism outcomes of the Roux-en-Y gastric bypass: a systematic review. Obes Rev. 2017;18:560–6.
8. Schafer AL, Weaver CM, Black DM, et al. Intestinal calcium absorption decreases dramatically after gastric bypass surgery despite optimization of vitamin D status. J Bone Miner Res. 2015;30:1377–85.
9. Brzozowska MM, Sainsbury A, Eisman JA, et al. Bariatric surgery, bone loss, obesity and possible mechanisms. Obes Rev. 2012;14:52–67.
10. Genant HK, Cooper C, Poor G, et al. Interim report and recommendations of the World Health Organization Task-Force for Osteoporosis. Osteoporos Int. 1999;10:259–64.
11. Siris ES, Chen Y-T, Abbott TA, et al. Bone mineral density thresholds for pharmacological intervention to prevent fractures. Arch Intern Med American Medical Association. 2004;164:1108–12.
12. Bouxsein ML. Bone quality: where do we go from here? Osteoporos Int. 2003;14 Suppl(5):118–27.
13. Garnero P, Hausherr E, Chapuy MC, et al. Markers of bone resorption predict hip fracture in elderly women: the EPIDOS prospective study. J Bone Miner Res Wiley-Blackwell. 1996;11:1531–8.

14. Brolin RE, Kenler HA, Gorman JH, et al. Long-limb gastric bypass in the superobese. A prospective randomized study. Ann Surg. 1992;215:387–95.
15. Choban PS, Flancbaum L. The effect of Roux limb lengths on outcome after Roux-en-Y gastric bypass: a prospective, randomized clinical trial. Obes Surg. 2002;12:540–5.
16. Inabnet WB, Quinn T, Gagner M, et al. Laparoscopic Roux-en-Y gastric bypass in patients with BMI <50: a prospective randomized trial comparing short and long limb lengths. Obes Surg. 2005;15:51–7.
17. Pinheiro JS, Schiavon CA, Pereira PB, et al. Long-long limb Roux-en-Y gastric bypass is more efficacious in treatment of type 2 diabetes and lipid disorders in super-obese patients. Surg Obes Relat Dis. 2008;4:521–5.
18. Risstad H, Svanevik M, Kristinsson JA, et al. Standard vs distal Roux-en-Y gastric bypass in patients with body mass index 50 to 60. JAMA Surg. 2016;151:1146–10.
19. Svanevik M, Risstad H, Hofsø D, et al. Perioperative outcomes of proximal and distal gastric bypass in patients with BMI ranged 50 −60 kg/m(2)–a double-blind, Randomized Controlled Trial. Obes Surg. 2015;25:1788–95.
20. Cashman KD, Dowling KG, Škrabáková Z, et al. Standardizing serum 25-hydroxyvitamin D data from four Nordic population samples using the vitamin D standardization Programprotocols: shedding new light on vitamin D status in Nordic individuals. Scand J Clin Lab Invest. 2015;75:549–61.
21. Parrott J, Frank L, Rabena R, et al. American Society for Metabolic and Bariatric Surgery Integrated Health Nutritional Guidelines for the sSurgical Weight Loss Patient 2016 Update_ Micronutrients. SOARD. Elsevier Inc. 2017;13:727–41.
22. Muschitz C, Kocijan R, Haschka J, et al. The impact of vitamin D, calcium, protein supplementation, and physical exercise on bone metabolism after bariatric surgery: the BABS study. J Bone Miner Res. 2015;31:672–82.
23. Bischoff-Ferrari HA, Dawson-Hughes B, Orav EJ, et al. Monthly high-dose vitamin D treatment for the prevention of functional decline. JAMA Intern Med. 2016;176:175–9.
24. Hewitt S, Søvik TT, Aasheim ET, et al. Secondary hyperparathyroidism, vitamin D sufficiency, and serum calcium 5 years after gastric bypass and duodenal switch. Obes Surg. Springer-Verlag. 2012;23:384–90.
25. Bredella MA, Greenblatt LB, Eajazi A, et al. Effects of Roux-en-Y gastric bypass and sleeve gastrectomy on bone mineral density and marrow adipose tissue. Bone. 2017;95:85–90.
26. Ivaska KK, Huovinen V, Soinio M, et al. Changes in bone metabolism after bariatric surgery by gastric bypass or sleeve gastrectomy. Bone Elsevier Inc. 2017;95:47–54.
27. Bowen J, Noakes M, Clifton PM. A high dairy protein, high-calcium diet minimizes bone turnover in overweight adults during weight loss. J Nutr. 2004;134:568–73.
28. Seeman E, Delmas PD. Bone quality–the material and structural basis of bone strength and fragility. N Engl J Med. 2006;354:2250–61.
29. Crawford MR, Pham N, Khan L, et al. Increased bone turnover in type 2 diabetes patients randomized to bariatric surgery versus medical therapy at 5 years. Endocr Pract. American Association of Clinical Endocrinologists Corporation, INC. 2018;24:256–64.
30. Wei JH, Lee WJ, Chong K, et al. High Incidence of Secondary Hyperparathyroidism in Bariatric Patients: Comparing Different Procedures. Obes Surg. 2018;28(3):798–804.
31. Nergaard BJ, Leifsson BG, Hedenbro J, et al. Gastric bypass with long alimentary limb or long pancreato-biliary limb—long-term results on weight loss, resolution of co-morbidities and metabolic parameters. Obes Surg Springer US, 2014;24:1595–602.
32. Røislien J, Van Calster B, Hjelmesaeth J Parathyroid hormone is a plausible mediator for the metabolic syndrome in the morbidly obese: a cross-sectional study. Cardiovasc Diabetol. BioMed Central Ltd; 2011;10:17.