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ORIGINAL CONTRIBUTION

Secondary Hyperparathyroidism in Patients with Biliopancreatic Diversion After 10 Years of Follow-up, and Relationship with Vitamin D and Serum Calcium

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Abstract

Background Secondary hyperparathyroidism (SHPT) is a matter of concern after biliopancreatic diversion (BPD). The aim of this study was to investigate the relationship between SHPT, 25(OH)D, and calcium after BPD.

Design A retrospective analysis in obese patients after BPD performed between 1998 and 2016.

Methods Patients with at least 1 year of follow-up were included. SHPT was considered when PTH > 65 pg/mL in the absence of an elevated corrected calcium. 25(OH)D (ng/mL) status was defined as: deficiency < 20, insufficiency 20–29.9, and sufficiency ≥ 30.

Results In total, 321 patients were included (76.6% women), with mean age 43.0 (10.5) years. Median follow-up was 6.0 (IQR 3.0–9.0) years. Mean body mass index was 49.8 (7.0) kg/m^2. SHPT increased to a maximum of 81.9% in the ninth year of follow-up (95% CI: 1.5–9.1). Two years after surgery, 33.9% of patients with 25(OH)D sufficiency had SHPT ($p = 0.001$). Corrected calcium levels were lower in patients with PTH > 65 pg/mL when compared with PTH < 65 pg/mL; 1 year: 8.96 vs 9.1 mg/dL and 5 years: 8.75 vs 9.12 mg/dL ($p < 0.01$). After surgery, patients with PTH > 65 pg/mL and 25(OH)D sufficiency had lower corrected calcium levels when compared with subjects with PTH and 25(OH)D in normal range. Two years: 9.0 vs 9.2 mg/dL ($p < 0.05$) and 4 years: 8.9 vs 9.2 mg/dL ($p < 0.01$).

Conclusions Once 25(OH)D is sufficient, the increase in PTH persists associated with a decrease in serum corrected calcium. It is important to ensure a sufficient calcium intake in these patients in order to avoid SHPT and osteomalacia in the future.

Keywords Bariatric surgery · Biliopancreatic diversion · Hyperparathyroidism · Serum calcium · Parathyroid hormone · Vitamin D

Introduction

Over the past decades, obesity has become a worldwide health issue, with an increase in its prevalence and impact [1–3]. Although bariatric surgery (BS) is an effective intervention for the treatment of obesity, it is not risk-free, as one of its complications is the alteration of phosphate-calcium metabolism, especially in the malabsorptive surgical techniques [4]. Within these alterations, we can find a high prevalence of secondary hyperparathyroidism (SHPT) and vitamin D deficiency [5].

Calcium and vitamin D malabsorption are common after mixed or malabsorptive BS, and it is persistent despite oral supplementation. This malabsorption leads to a maintained increase of parathyroid hormone (PTH), triggering a negative effect on bone metabolism [6–8]. Given the important role of vitamin D in calcium absorption, low levels can exacerbate calcium malabsorption and consequently instigate a reduction in serum ionic calcium with subsequent stimulation of PTH synthesis and release [9].

Newbury et al. [8] studied calcium and PTH evolution in 82 patients undergoing biliopancreatic diversion (BPD), noting that 25.9% of patients had hypocalcemia between the

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second and third year of follow-up, of whom 50% had low levels of vitamin D and 63.1% had high levels of PTH. In another study following gastric bypass and duodenal switch, a higher relationship with ionic calcium and SHPT was found when compared to vitamin D [10].

In the current study, we investigated the relationship of SHPT with serum concentrations of calcium and vitamin D in patients undergoing BPD in a 10-year follow-up series.

Methods

Patients and Study Design

A retrospective observational study was performed with morbidly obese patients who underwent BS at Complejo Asistencial Universitario de León (CAULE) during the period from January 1998 to December 2016. The criteria on which to perform BS comprised: age older than 18 years, body mass index (BMI) > 40 kg/m^2 without comorbidities or BMI 35–40 kg/m^2 with comorbidities. Patients were followed by a multidisciplinary team (endocrinologists, surgeons, and dietitian), and data were shown for each yearly visit. The inclusion criteria were the following: post-surgery follow-up compliance in the Clinical Nutrition and Dietetics Unit, a minimum follow-up of 1 year after surgery, and undergoing laboratory tests at our center. The BS technique performed was BPD, which involves the creation of a 300-cc gastric pouch by means of gastrectomy or gastric section and distal gastric preservation. The cross-section of the small bowel was performed at a distance of 250–310 cm from the ileocecal valve. An anastomosis was performed in the distal end of the ileum to the posterior wall of the gastric pouch (Roux-en-Y), and with an enteroenteric anastomosis 50–100 cm proximal to the ileocecal valve, forming three loops. Follow-up was performed: pre-surgery, post-surgery, every 3 months the first year, every 6 months the second year, and annually thereafter. Body weight was measured using an electric bioimpedance Tanita TBF-300A (TANITA Corporation, Japan), and height was measured using an analog stadiometer.

In total, 373 patients underwent surgery, of whom 321 were included in the study. Fifty-two patients were excluded, of whom 1 died due to postoperative complications, 22 did not complete 1 year of follow-up, and 31 underwent another BS technique. The study design was evaluated and approved by the Ethics Committee of CAULE. All data were collected using structured questionnaires and subsequently registered in a database. Being a retrospective study and given the difficulty of obtaining the informed consent of each patient, this was not performed.

Blood Tests

All analytical determinations were performed in the central laboratory of CAULE, using fresh serum collected while fasting (more than 8 h). Having attained the results, the Clinical Analysis specialist was responsible for validating them, comparing them with reference values by age and sex.

Calcium (mg/dL), phosphorus (mg/dL), alkaline phosphatase (U/L): After collection, samples were kept in a tube without anticoagulant. They were subsequently placed in analyzer equipment (Cobas 8000 Roche®), automatically calculating each of the parameters in each of the samples (Omega 3000 Roche®). Calcium was determined by direct colorimetry (Cresolphthalein complexone); phosphorus was determined by phosphomolybdate spectrophotometry at 340 nm, and alkaline phosphatase (ALP) was determined by enzymatic calorimetric measurement with 4-nitrophenyl phosphate substrate with AMP buffer (2-amino-2-methyl-1-propanol). Total serum calcium was corrected for serum albumin (corrected calcium) using the formula: corrected calcium = serum calcium + 0.8 × (4 mg/dl − albumin) [11].

Intact PTH (1–84), 25-Hydroxy Vitamin D (25(OH)D)

PTH (pg/mL) was analyzed in a plasma sample with EDTA by immunochemiluminescence (Cobas 8000 and Roche Omega 3000 program). 25(OH)D was determined using fresh serum collected while fasting and subsequently kept in a tube without anticoagulant. It was determined by the isocratic HPLC method (reverse phase) that provides accurate results for circulating levels of this vitamin. This method uses the values defined according to Standard Reference Material 972 of the National Institute of Standards and Technologies (NIST), an agency of the Department of Commerce of the United States. The normal ranges of each parameter are: corrected calcium (8.2–10.2 mg/dL), phosphorus (2.7–4.5 mg/dL), PTH (15–65 pg/mL), 25(OH)D (30–100 ng/mL), and ALP (80–260 U/L in men and 70–210 U/L in women).

For SHPT diagnosis, a serum PTH concentration above the reference range (> 65 pg/mL) was defined if serum calcium concentrations were normal. The levels of 25(OH)D were classified into three categories following the recommendations of the Endocrine Society [11]: sufficient ≥ 30 ng/mL, insufficient 20–29.9 ng/mL, and deficient < 20 ng/mL. Patients with vitamin D deficiency before surgery and all those undergoing BPD were supplemented with calcium and vitamin D according to the standard recommendations (2 g/day of calcium and calcifediol 0.266 mg weekly initially, and multivitamin (Multicentrum®), adjusting according to levels of 25(OH)D and depending on the needs of each patient). In addition, patients received information on the correct administration of the medicine; recommendations were made on food intake with the largest number of reports, and the importance of these supplements was emphasized.

Statistical Analysis

The statistical analysis was performed with SPSS v.20 for Windows 10 Pro. Kolmogorov-Smirnov tests were used to assess the adjustment to a normal distribution, and data are shown as mean (standard deviation) in this case or median (interquartile range, IQR). The significance value used was $p < 0.05$. Student's *t* test was used to compare the independent mean variables, ANOVA to compare means and chi-square for proportions. We also analyzed the association between PTH as a dependent variable and the factors of interest in the univariate and multivariate linear regressions.

Results

The baseline patient characteristics are shown in Table 1. In total, 76.6% of patients were female. The median follow-up was 6.0 (IQR 3.0–9.0) years. Women had greater BMIs than men (50.10 vs 48.96 kg/m^2), and women also had higher levels of 25(OH)D (29.73 vs 23.28 ng/mL; $p = 0.020$) and ALP (156.69 vs 136.24 U/L; $p = 0.008$). The other parameters did not differ according to sex. Before surgery, 41.3% of patients had SHPT; regarding 25(OH)D, 44.3% of patients were deficient, 21.6% were insufficient, and 34.1% were sufficient.

One year after surgery, an increase in the percentage of patients with SHPT compared to baseline (56.3% vs 41.3%) was observed. This rose to 81.9% in the ninth year of follow-up. Regarding 25(OH)D ranges, in the first year after surgery, a decrease in the percentage of patients with 25(OH)D deficiency compared with baseline was observed (37.1% vs 44.3% (95% CI 0.6–1.0)). However, from the first year, the prevalence of patients with 25(OH)D deficiency rose to 50%, 6 years after surgery (95% CI 2.1–9.4). The full results are shown in Fig. 1 and Table 2. SHPT was significantly more prevalent in patients with 25(OH)D deficiency (< 20 ng/mL), constituting 48.5% of patients in the first year after surgery and reaching 61% after 8 years of follow-up when compared to other groups ($p = 0.002$ and $p < 0.001$, respectively). The significant prevalence of SHPT in patients with 25(OH)D sufficiency, this being 33.9% 2 years after surgery ($p = 0.001$), should be highlighted. When compared with the patients with 25(OH)D deficiency, the prevalence was similar (RR 0.73; 95% CI 0.53–1.01). Nevertheless, when compared with the patients with 25(OH)D insufficiency, the prevalence was higher (RR 1.69; 95% CI 1.08–2.64), as seen in Table 3.

Table 1 Patients' baseline characteristics

Variables (normal values)	Mean	SD
Age (years)	43.07	10.50
Weight (kg)	131.60	21.11
BMI (kg/m^2)	49.82	7.00
Corrected calcium (8.5–10.5 mg/dL)	9.12	0.5
Phosphorus (2.7–4.5 mg/dL)	3.42	0.53
ALP (70–260 U/L)	151.57	46.37
PTH (15–65 pg/mL)	66.95	34.14
25(OH)D (30–100 ng/mL)	27.82	21.02

BMI body mass index, *ALP* alkaline phosphatase, *25(OH)D* 25-hydroxy vitamin D, *PTH* parathyroid hormone

Serum corrected calcium levels revealed an inverse pattern compared with PTH, with a maximum association at the fourth year of follow-up for both PTH and SHPT (Pearson's correlation $r = -0.45$; $p = 0.0001$). Patients with PTH > 65 pg/mL showed significantly lower mean serum calcium levels (but within normal parameters) relative to patients without SHPT. This relationship persisted throughout the follow-up, as shown in Fig. 2a. Corrected calcium levels were lower in patients with deficiency and insufficiency of 25(OH)D when compared with patients with sufficiency during all of the follow-up: first year (8.8 vs 8.9 vs 9.1 mg/dL $p = 0.005$); after 5 years (8.5 vs 8.8 vs 8.9 mg/dL $p = 0.04$); and after 10 years (8.7 vs 8.9 vs 9.0 mg/dL $p = 0.04$), respectively.

Patients with PTH > 65 pg/mL and 25(OH)D ≥ 30 ng/mL showed lower levels of serum corrected calcium when compared to patients with PTH < 65 pg/mL, this being statistically lower during the first year after surgery (after 2 years 8.7 vs 9.0 mg/dL ($p < 0.01$) and after 4 years 8.7 vs 8.9 mg/dL ($p < 0.04$)). Among those in insufficient and deficient ranges for 25(OH)D, lower serum corrected calcium levels were also observed throughout the follow-up in subjects with PTH > 65 pg/mL; these differences were higher in the fourth year after surgery (8.4 vs 8.9 mg/dL $p < 0.001$) (Fig. 2 b–d).

In the linear regression analysis, gender, serum calcium, and 25(OH)D were independently associated with PTH 2 years after surgery. However, 5 years after surgery, only the serum corrected calcium maintained this association. No statistically significant differences were found with age, sex, and BMI. The results are shown in Table 4.

Discussion

This study showed a high prevalence of SHPT related to low levels of 25(OH)D throughout the follow-up after BPD. However, a high percentage of patients with SHPT had levels of 25(OH)D in the normal range; in this group, levels of calcium were significantly lower compared to those without SHPT. Lower levels of calcium might explain the high prevalence of SHPT after BS, creating uncertainty regarding the long-term bone health of these patients.

These data are similar to other published studies [8, 10, 12, 13, 15]. PTH was independently related to 25(OH)D and calcium after 2 years of follow-up, but only calcium levels remained significant predictors of PTH levels after 5 years. It is possible

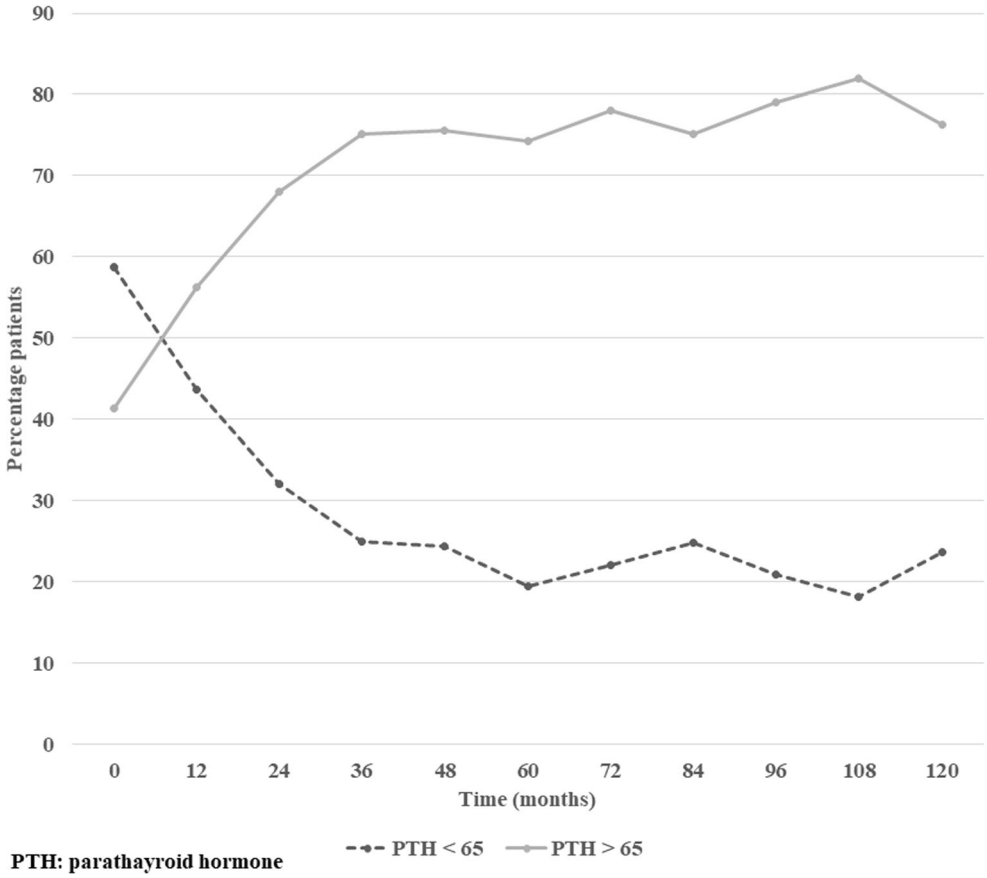

Fig. 1 Percentage of patients according to ranges of PTH

that this difference is related to the fact that long-term adherence to calcium supplementation is harder to maintain than vitamin D supplementation, but one of the limitations of this study is that adherence to the supplementation was not collected. SHPT prevalence is around 50% in patients with morbid obesity, and it increases after BS [14, 15], enhancing bone mass loss, osteopenia risk, and osteoporosis in the long term [16]. Most existing studies concerning bone metabolism and SHPT after BS have been based in patients who underwent gastric bypass and sleeve gastrectomy, with very few based on BPD. Furthermore, they have tended to have a short-term follow-up, with the exception of a few studies with published results at 10 years [5, 10, 13, 15, 17–27]. In this study, SHPT prevalence after BPD was seen in 56–81% of patients throughout the follow-up, consistent with the results of other publications.

Given the known inverse relationship between PTH and 25(OH)D, most previous studies have focused on this parameter in order to justify the high prevalence of SHPT and the loss of bone mass after surgery. In this study, SHPT was present in 48–61% of the patients with 25(OH)D deficiency (< 20 ng/mL) and 11–24% of the patients with 25(OH)D insufficiency (20–29.9 ng/mL) throughout 10 years of follow-up. However, it should be noted that a significant percentage of patients had SHPT even though they retained sufficient levels of 25(OH)D (28.2% in the first year, 33.9% at 2 years, and 37.8% at 5 years after surgery), stimulating us to seek other causes of SHPT in these patients. These data are similar to those published by Hewitt et al. [10] in 2012, who concluded that there was no inverse relationship between SHPT and vitamin D.

Table 2 Percentage of patients according to ranges of 25(OH)D

Time (months)		0	12	24	36	48	60	72	84	96	108	120
N		185	202	179	168	151	148	124	108	83	71	63
25(OH)D (%)	< 20	44.3	37.1	37.4	38.7	43.0	48.6	50.8	50.0	50.6	46.5	34.9
	20–29	21.6	25.7	17.9	13.1	15.2	14.2	16.9	22.2	14.5	19.7	20.6
	> 30	34.1	37.1	44.7	48.2	42.7	37.2	32.3	27.8	34.9	33.8	44.4

25(OH)D 25-hydroxy vitamin D

Table 3 Percentage of patients with secondary hyperparathyroidism and PTH levels as a function of 25(OH)D

Time (months)		0	12	24	36	48	60	72	84	96	108	120
N		176	103	115	109	102	111	90	70	60	56	42
	SHPT (%)											
25(OH)D (ng/mL)	< 20	51.4	48.5	46.1	39.4	51.0	50.5	57.8	61.4	56.7	53.6	38.1
	20–29	20.8	23.3	20.0	13.8	16.7	11.7	21.1	24.3	16.7	21.4	23.8
	> 30	27.8	28.2	33.9	46.8	32.4	37.8	21.1	14.3	26.7	25.0	38.1
p		0.3	0.002	0.001	0.4	0.001	0.15	0.0001	0.0001	0.014	0.0001	0.013

SHPT secondary hyperparathyroidism, *25(OH)D* 25-hydroxy vitamin D, *PTH* parathyroid hormone

The anatomic changes suffered after BPD will influence the gastrointestinal absorption of nutrients, potentially altering the absorption of calcium and vitamin D in these patients [5, 16, 28], and of significance when discussing SHPT in patients undergoing BPD. Due to the maintenance of SHPT in patients with sufficient levels of 25(OH)D, other mechanisms have been proposed as justification, with several publications expressing support for the importance of a decrease in the levels of serum and ionic calcium [8, 10, 19, 26, 29, 30]. In this study, patients within the sufficiency range for 25(OH)D and with PTH > 65 pg/mL had lower levels of serum calcium. This was statistically significant in the first year, although during the follow-up, the differences generally disappeared, most likely due to the adjustment of malabsorption. This relationship might be justified by the tight regulation of serum calcium by PTH, as low or relatively low levels cause an increase in PTH at the expense of bone calcium mobilization [28]. During the follow-up of the patients in this study, levels at

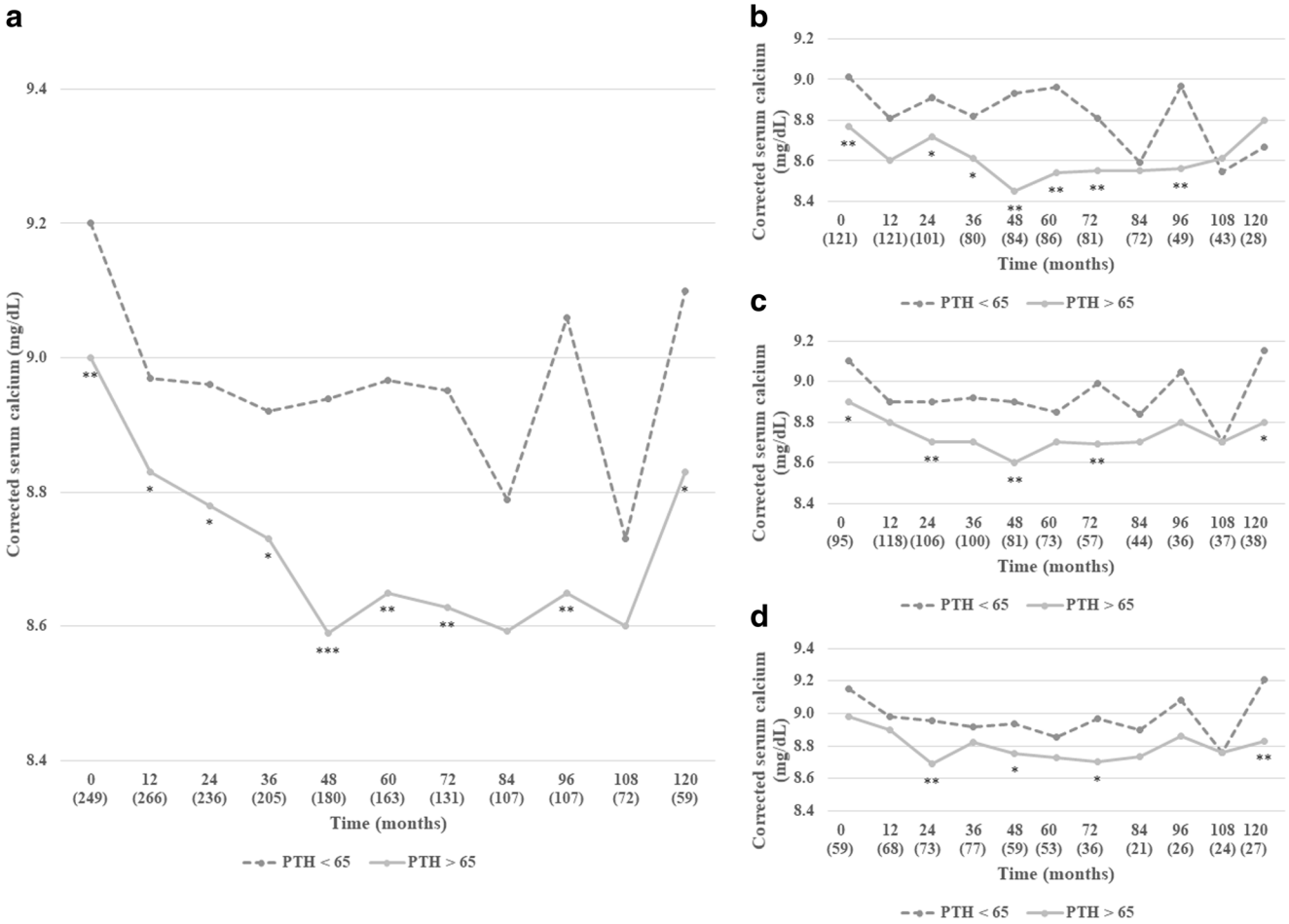

Fig. 2 Hyperparathyroidism secondary to serum calcium and vitamin D Data expressed in mean and standard deviation. 25(OH)D 25-hydroxy vitamin D, PTH parathyroid hormone. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. **a** Serum calcium levels according to PTH. **b–d** Serum calcium levels as a function of the PTH ranges in subjects with 25(OH)D < 30 ng/ml, 25(OH)D ≥ 20 ng/ml, and 25(OH)D ≥ 30 ng/ml

Table 4 Multivariate linear regression analysis of PTH with probable modulating factors 2 and 5 years after surgery

2 years after BS	B	SD	95% CI	β	p
Age (years)	0.415	0.456	− 0.486; 1.317	0.072	0.364
Gender	20.74	9.821	1.341; 40.143	0.163	0.036
BMI (kg/m^2)	1.430	0.788	− 0.127; 2.986	0.138	0.072
25(OH)D (ng/ml)	− 0.714	0.193	− 1.096; − 0.333	− 0.277	0.000
Corrected calcium (mg/dl)	− 41.835	10.618	− 62.812; − 20.858	− 0.301	0.000
5 years after BS					
Age (years)	− 0.532	0.593	− 1.705; 0.642	− 0.075	0.372
Gender	27.47	17.90	− 11.793; 50.114	0.132	0.128
BMI (kg/m^2)	0.321	1.240	− 2.138; 2.780	0.022	0.796
25(OH)D (ng/ml)	− 0.380	0.216	− 1.004; − 0.037	− 0.146	0.081
Calcium (mg/dl)	− 59.810	13.140	− 85.825; − 33.796	− 0.389	0.000

B regression coefficient, *SD* standard deviation, *CI* confidence interval, β standard coefficient of the regression, *BMI* body mass index, *25(OH)D* 25-hydroxy vitamin D, *PTH* parathyroid hormone

the low end of the normal range of serum corrected calcium were observed in patients with PTH > 65 pg/mL when compared with patients with PTH in the normal range (1 year: 8.8 vs 9.0 mg/dL; 2 years: 8.8 vs 9.0 mg/dL; and 5 years 8.6 vs 9.1 mg/dL after surgery, respectively), being statistically significant in all visits. In 1996, Chapin [26] proposed this relationship in patients undergoing BPD, but few studies have since been published. These data suggest that a constant increase in PTH from the first year after surgery is probably largely related to calcium malabsorption, as well as potentially poor adherence to the prescribed supplementation, rather than suboptimal levels of vitamin D. The evidence of calcium malabsorption could be detected by a 24-h urine calcium test, although this was not used in our study.

There are numerous causes of bone fragility after BS, of which malabsorption is the most likely after BPD [31, 32]. This procedure leads to calcium malabsorption with low calcium levels being the main stimulator of PTH secretion. In accordance with the findings of our study, we might state that a relatively low level of calcium has been given little importance with regard to vitamin D deficiency. Phosphorus has not been related to SHPT in other published series of BS, and in our findings, only an inverse relationship between phosphorus and PTH was observed. Another probable cause of SHPT is poor adherence to treatment or inadequate calcium and vitamin D administration after BS [5, 16, 27]. Although patients in our study were on calcium supplementation depending on their individual needs, a persistence of SHPT was found, which might suggest a requirement for higher supplementation or inadequate adherence to treatment. Again, it should be noted that one of this study's limitations is the lack of information regarding the adherence to supplementation, as it is a retrospective study.

Another issue for consideration is the high prevalence of vitamin D deficiency in patients with morbid obesity prior to BS, which can lead to SHPT [5, 30, 33–35]. In this study, the prevalence of SHPT before BS was 41.3%, while 65.9% of the patients showed levels of 25(OH)D < 30 ng/mL. Although more studies on PTH and morbid obesity are certainly required, we found that patients with SHPT had a higher BMI (data not shown) in the first 2 years after surgery. However, linear regression analysis did not find a relationship between these parameters, and so it may act as a confounding factor.

Whether bone loss after BS owes to an adaptation to weight loss or if there are additional mechanisms related to surgery (such as malabsorption and hormonal changes) contributing to this process still needs to be explained. The increased ALP data in our study would tip the balance towards a higher rate of bone turnover in patients with elevated PTH. In addition, further studies on bone fracture after BS are necessary.

A strength of this study is that we describe a large cohort in a single center undergoing a malabsorptive surgery technique, a procedure that may create significant bone metabolism issues. In addition, the evolution of PTH, 25(OH)D, and long-term serum calcium parameters (10 years of follow-up) after BS are described, with few series with long-term follow-up currently existing in the literature. All patients underwent the same procedure, and the blood analyses were performed in the same center. In terms of the limitations of the study, the retrospective study design is significant, as well as the absence of data on 1,25-dihydroxy vitamin D and urinary calcium concentrations.

Based on the findings of this study and in accordance with other series reviewed in the literature, there is a need to optimize calcium levels after BS, requiring more intervention studies to improve strategies of supplementation doses, and thus prevent SHPT and the long-term loss of bone mass. In addition, given the greater prevalence of this complication in patients undergoing BPD, its supplementation should be planned from the preoperative period and maintained throughout the post-surgery follow-up. A multidisciplinary approach is necessary to achieve the best possible results, especially when malabsorption procedures are undertaken.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Informed Consent No informed consent was needed in this study.

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