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ORIGINAL CONTRIBUTIONS

Changes in Bone Metabolism After Sleeve Gastrectomy Versus Gastric Bypass: a Meta-Analysis

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Abstract

Background Gastric bypass (GB) and sleeve gastrectomy (SG) are two common types of bariatric surgery that carry many potential complications. Among these complications, bone metabolism-related diseases have attracted substantial attention; however, no meta-analysis of them has been performed to date.

Methods We searched PubMed, Web of Science, The Cochrane Library, and Embase to identify relevant studies published before January 2019. The following indicators were evaluated: serum parathyroid hormone (PTH), calcium, phosphorus and 25-hydroxyvitamin D levels, body mass index (BMI), and bone mineral density (BMD).

Results Thirteen studies met our inclusion criteria. Overall results showed that patients undergoing GB had lower levels of 25-hydroxyvitamin D (MD = − 1.85, 95% CI (− 3.32, − 0.39) $P = 0.01$) and calcium (MD = − 0.15, 95% CI (− 0.24, − 0.07) $P = 0.0006$) as well as higher levels of PTH (MD = 3.58, 95% CI (0.61, 7.09) $P = 0.02$) and phosphorus (MD = 0.22, 95% CI (0.10, 0.35) $P = 0.0005$). The results of BMI and BMD were comparable in each group.

Conclusion Our meta-analysis suggested that obese patients undergoing GB had lower levels of serum calcium and 25-hydroxyvitamin D as well as higher levels of serum phosphorus and PTH. To prevent postoperative bone metabolism-related diseases, appropriate postoperative interventions should be undertaken for particular surgical procedures.

Keywords Gastric bypass · Sleeve gastrectomy · Bone mineral density · Bone metabolism · Meta-analysis

Introduction

Most recent estimates suggest that more than 1/3 of world population is overweight. Obesity is becoming an even more serious problem with the increasing incidence of obesity-related diseases. Overweight and obesity are closely associated with many severe health problems, including type 2 diabetes, hypertension, cancer, sleep apnea, cardiovascular disease, hyperlipidemia, and stroke [1, 2].

Bariatric surgery is an established treatment for obesity and its complications. Nevertheless, a growing body of evidence indicates that bariatric surgery might lead to severe bone metabolism disorders: acceleration of bone remodeling, significantly elevated bone turnover, and decreased bone mineral density (BMD) [3]. Following these pathological changes is the markedly increased incidence of fractures [4, 5], osteoporosis [6], osteomalacia [7], and other bone-related diseases. Gastric bypass (GB) is currently one of the most popular bariatric procedures [8]. Sleeve gastrectomy (SG), which maintains the integrity of pylorus and bowel, is another commonly used approach to weight loss [9]. Extensive systematic reviews and meta-analyses have compared these two operations from many perspectives, including efficiency of weight loss [10, 11], curative effects on type 2 diabetes [12, 13], and other obesity-related comorbidities [14, 15]. Nevertheless, to date,

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no meta-analysis has been performed to demonstrate which procedure is superior with respect to bone-related complications.

Because concern is growing regarding bone-related complications induced by bariatric surgeries, a further literature review is needed to assess the latest scientific evidence comparing these two bariatric surgeries. Despite the fact that patients receive timely vitamin D and mineral supplementation after bariatric surgery, some patients nevertheless suffered osteomalacia, osteopenia, and osteoporosis [16]. This suggests that some deficiency might exist in the current supplementation strategies in terms of the defense against unbalanced bone metabolism. The bariatric procedure with more severe influence on endogenous bone metabolism requires higher quantities of relevant micronutrient supplementation. Therefore, the aim of our study was to identify the safer of two bariatric surgeries with respect to bone-related complications and to provide a theoretical basis for the establishment of clinical guidance for bone-related disease prevention after bariatric surgery.

Materials and Methods

This meta-analysis was based on the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines [17] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [18].

Data Sources and Searches

Databases searched included PubMed, Web of Science, the Cochrane Library, and Embase. The final search was carried out on 9 January 2019. Our full search strategy in PubMed was presented in supplementary materials.

Study Selection

Inclusion criteria were as follows: (i) original comparative reports with ≥ 5 patients; (ii) written in English; (iii) conducted on human subjects; (iv) observation of related indices of bone metabolism after SG and GB.

Exclusion criteria were as follows: (i) studies with unreliable design or substantial statistical errors; (ii) only one type of bariatric surgery included; and (iii) patients with stomach, kidney, liver, or any bone disease that might affect bone metabolism.

Data Extraction and Quality Assessment

Both included studies and data extraction were evaluated independently by two investigators (Tian and Fan) using a standardized tool. If there were discrepancies, they were resolved through discussion or resolution by a third investigator. We extracted the data measured at the end point of every study and we selected the most complete and recent data if several articles were derived from the same population. The information collected was as follows: first author, publication year, country, study design, age, BMI, BMD, serum calcium, phosphorus, parathyroid hormone, and 25-hydroxyvitamin D levels before and after the surgery.

The Newcastle-Ottawa Scale (NOS) was employed to judge the quality of included cohort studies and case-control studies [19]. A score of 0–9 stars was used to assess their quality. We considered a study as high quality when the score reached greater than six stars, and other studies were regarded as moderate. The Cochrane methodology was used to evaluate the quality of the included RCTs. Each criterion was judged as low, unknown, or high-risk bias. A risk of bias summary was used to place the results of the assertion.

Statistical Analysis

Statistical analysis was performed using Review Manager (RevMan 5.3) statistical software and Stata 12.0. Continuous variables were analyzed using mean differences (MD) and 95% confidence intervals (CIs). We used Cochran's Q (chi-square) test to quantify the heterogeneity [20], and a random effect model was used to estimate pooled effect sizes [21]. $P < 0.05$ was defined as statistical significance. Subgroup analysis was performed according to time course, measurement method, study design, and operative technique. Potential publication bias was evaluated using Egger's test [22] and Begg's test [23].

Results

Literature Search

The detailed steps for the literature search are presented in Fig. 1. The initial literature search yielded 395 articles, and 116 from them were deleted because of duplication. Two reviewers then excluded 238 articles after screening titles and abstracts independently, and 41 articles were assessed for eligibility. Ultimately, 13 studies [24–36] were selected for inclusion.

Study Characteristics and Quality Assessment

The 13 included studies were published from 2010 to 2018. The GB group included 734 patients, while the SG group included 769 patients. The characteristics and quality assessment of the studies are presented in Table 1 and Supplement materials. Nine studies [26–29, 31, 33–36] focused on laparoscopic surgery, and the remaining four [24, 25, 30, 32] dealt

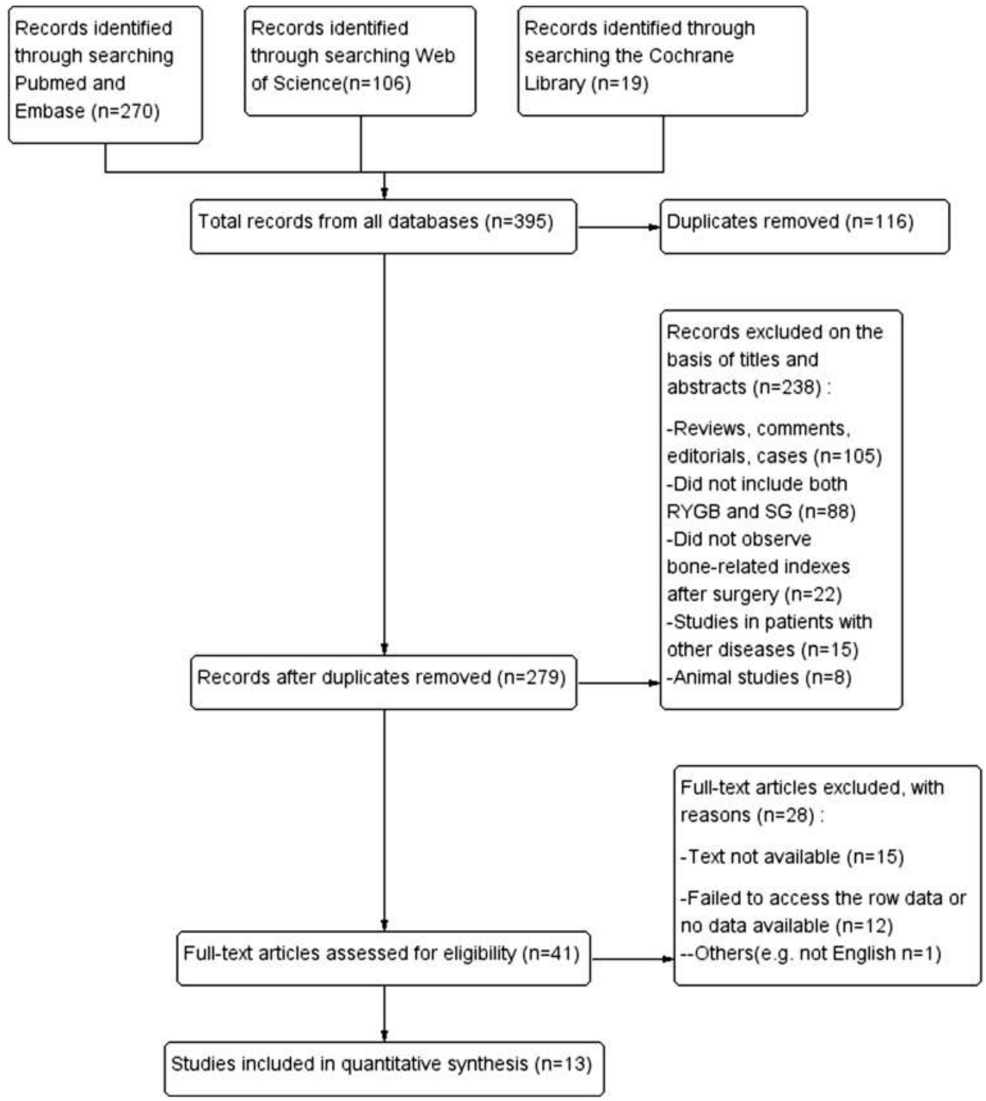

Fig. 1 The flow chart of literature search

with unknown surgery. Circulating calcium, phosphorus, parathyroid hormone, and 25-hydroxyvitamin D levels in all included studies were examined after overnight fasting except for one study [24] in which there was no detailed explanation. Blood samples were obtained from serum except two studies where they were obtained from plasma [30, 35]. Bone mineral density was measured using dual-energy X-ray absorptiometry (DEXA) in all related studies. Three authors independently reviewed and cross-checked the articles, and all agreed that the relevant studies were qualified.

Overall Analysis

BMI After GB Versus SG

As shown in Supplement Fig. 2, no significant difference was detected in terms of BMI (MD = − 0.05, 95% CI (− 0.78, 0.69) $P = 0.90$) after GB versus SG.

Calcium, Phosphorus, Parathyroid Hormone, and 25-Hydroxyvitamin D Levels After GB Versus SG

The results of meta-analysis revealed a more significant deficiency of 25-hydroxyvitamin D (MD = − 1.85, 95% CI (− 3.32, − 0.39) $P = 0.01$, Fig. 2) in the GB group. The circulating levels of parathyroid hormone were similar in patients undergoing SG and GB surgery (Supplement Fig. 3). Patients in the GB group had lower levels of calcium (MD = − 0.15, 95% CI (− 0.24, − 0.07) $P = 0.0006$, Fig. 3) and higher levels of phosphorus (MD = 0.22, 95% CI (0.10, 0.35) $P = 0.0005$, Fig. 3) than did the SG group.

Bone Density Changes

No significant difference was detected in BMD between the groups, regardless of location tested: femoral neck, lumbar spine, total hip, or total body (Fig. 4).

Table 1 Characteristics of the included studies

Study	Region	Study type	Surgical (M/F)	Follow (month)	Age (years)	Initial BMI (kg/m^2)	Initial calcium (mg/dl)	Initial phosphorus (ng/ml)	Initial 25-hydroxyvitamin D (ng/ml)	Initial parathyroid (pg/ml)
						Normal range	9–11	3–5	> 30	10–65
Muriel Coupaye 2013	France	Cohort	LGB (12/31)	12	45 ± 11	48.5 ± 9.6	9.82 ± 0.36	3.503 ± 0.527	14.8 ± 10.7	52.1 ± 28.5
			LSG (12/31)		44 ± 9	48.6 ± 7.8	9.14 ± 0.4	3.41 ± 0.527	15.2 ± 8.7	52 ± 28
Nuria Vilarrasa 2013	Spain	Cohort	RYGB (0/33)	12	49.7 ± 8.4	46.87 ± 4.8	9.34 ± 0.6	3.78 ± 0.9	20.16 ± 8.02	42.36 ± 17.63
			SG (0/33)		45.8 ± 12	49.06 ± 7.2	9.26 ± 0.4	3.66 ± 0.68	17.66 ± 8.02	49.91 ± 24.82
Michel Vix 2013	France	RCT	LRYGB (6/39)	12	35.23 ± 9.37	47.0 ± 5.64	–	–	–	50.1 ± 16.39
			LSG (12/43)		35.13 ± 9.7	45.5 ± 4.79	–	–	–	52.5 ± 17.34
Fernando Carrasco 2014	Chile	Cohort	GB (0/23)	12	36.9 ± 8.4	42.0 ± 3.8	–	–	20.5 ± 9.2	–
			SG (0/20)		33.5 ± 8.6	37.4 ± 2.9	–	–	26.2 ± 12.7	–
Enrique Lanzarini 2015	Spain	Cohort	LRYGB (68)	24	42.5 ± 8.5	44.9 ± 2.8	–	–	14.8 ± 2.8	51.3 ± 25.6
			LSG (96)		45.7 ± 8.9	43 ± 5.5	–	–	15.2 ± 7	54.4 ± 24.5
Hong Chang Tan 2015	Singapore	Cohort	LRYGB (5/5)	12	45.6 ± 9.1	36.7 ± 4.4	–	–	–	–
			LSG (4/8)		36.3 ± 8	40.5 ± 6.6	–	–	–	–
Ming-Che Hsin, M.D. 2015	Taiwan	Case control	LRYGB (13/27)	12	29.9 ± 4.8	39.8 ± 3.4	–	–	–	–
			LSG (13/27)		30.0 ± 6.4	39.5 ± 3.1	–	–	–	–
Miriam A. Bredella 2016	United States	Cohort	RYGB (2/9)	12	48.6 ± 8.9	44.1 ± 5.1	9.5 ± 0.5	–	25.5 ± 5.7	51.1 ± 16.1
			SG (1/9)		49.6 ± 13.6	43.7 ± 5.9	9.6 ± 0.5	–	31.2 ± 12.7	62.9 ± 33.9
Andoni Lancha 2014	Spain	Cohort	LRYGB (8/32)	15	38.7 ± 13.5	45.2 ± 7.9	9.07 ± 0.42	3.41 ± 0.55	10.1 ± 4.6	85.4 ± 33.3
			LSG (4/7)		44.3 ± 10.5	40.4 ± 6.1	8.4 ± 0.5	3.24 ± 0.53	13.5 ± 8.1	117.4 ± 66.3
Jih-Hua Wei 2014	Taiwan	Retrospective review	LRYGB (88/234)	12	35.8 ± 10.5	38.9 ± 7.5	9.1 ± 0.6	–	13.5 ± 6	50.9 ± 26.8
			LSG (109/251)		34.8 ± 9.9	38.5 ± 7.4	9.1 ± 0.6	–	9.5 ± 5.3	53.6 ± 29.8
Megan R. Crawford, DO 2017	American	RCT	RYGB (21/16)	60	47.4 ± 8.8	37.3 ± 3.2	9.7 ± 0.52	–	21.6 ± 10	39.6 ± 17.1
			SG (25/8)		47.8 ± 7.7	35.9 ± 4.1	9.5 ± 0.56	–	26.3 ± 15	44.4 ± 25.8
Muriel Coupaye 2012	France	Cohort	LRYGB (8/22)	6	45.6 ± 7.9	49.8 ± 8.4	8.98 ± 0.36	3.5 ± 0.56	14 ± 9.6	47.6 ± 25.6
			LSG (8/22)		47.7 ± 9.7	49.6 ± 10.4	9.18 ± 0.44	3.4 ± 0.56	15.2 ± 9.5	54.9 ± 31.3
Fernando Carrasco 2018	Chile	Cohort	RYGB (32)	24	–	42.0 ± 4.2	8.82 ± 0.49	3.83 ± 0.52	20.9 ± 10.2	–
			SG (26)		–	37.3 ± 3.2	9.13 ± 0.61	3.92 ± 0.49	26.8 ± 12.8	–

Data presented as means ± SD. *RCT*, randomized controlled trial; *GB*, gastric bypass; *SG*, sleeve gastrectomy; *RYGB*, Roux-en-Y gastric bypass; *L*, laparoscopic; *Subject M/F*, subject male/female

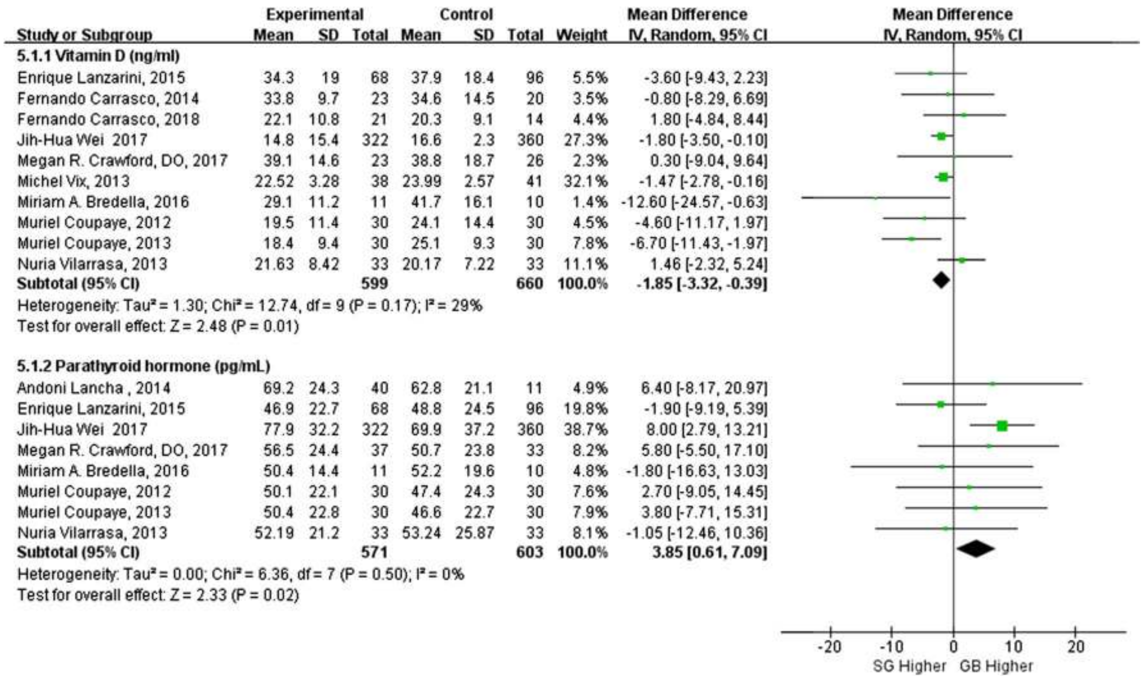

Fig. 2 Meta-analysis comparing postoperative 25-hydroxyvitamin D and parathyroid hormone levels after GB with SG

Subgroup Analysis

Because of high heterogeneity of PTH index in the overall analysis, we conducted a subgroup analysis to explore the source of heterogeneity. In subgroup analysis, study type (RCT or non-RCT), blood sample (plasma or serum), measuring method (ELISA or (E)CLIA), operative technique (laparoscopic, open/unknown), and follow-up time (short-term or long-term) were considered when we investigated the results of PTH. As illustrated in Table 2, the outcomes were of either high heterogeneity or no significance based on the presented evidence. We then performed an influence analysis (Supplement Fig. 4) and found that the article from Vix et al. [27] was the main source of heterogeneity. On the basis of the results of the influence analysis and the medium quality of this article, we doubted the credibility of their data and excluded this article when analyzing PTH. We found that the heterogeneity was completely eliminated and the PTH levels of the GB group were significantly higher than that of the SG group (MD = 3.58, 95% CI (0.61, 7.09) $P = 0.02$, Fig. 2).

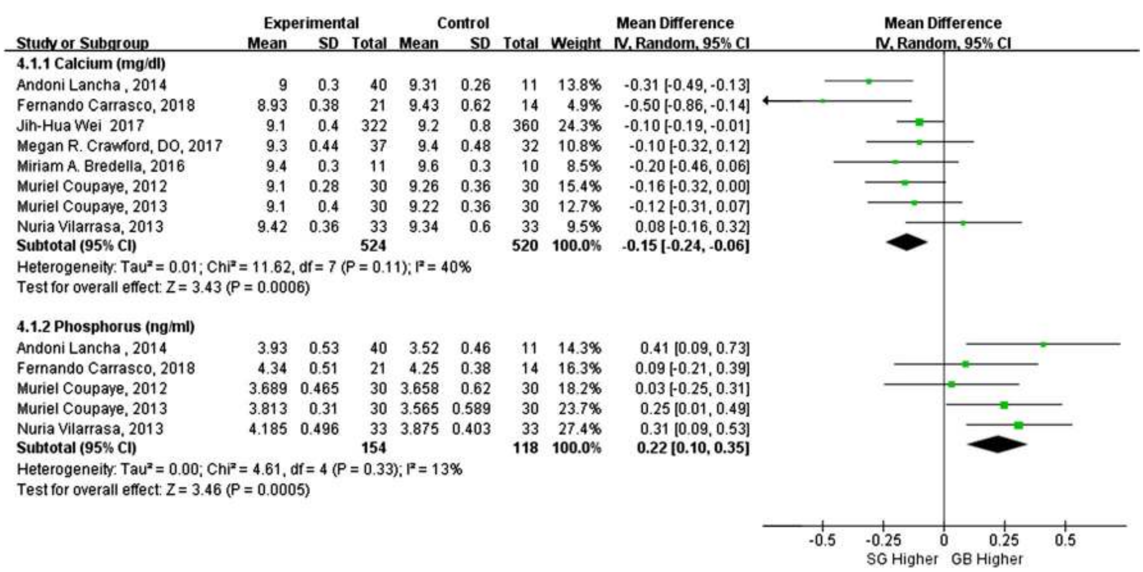

Fig. 3 Meta-analysis comparing postoperative calcium and phosphorus levels after GB with SG

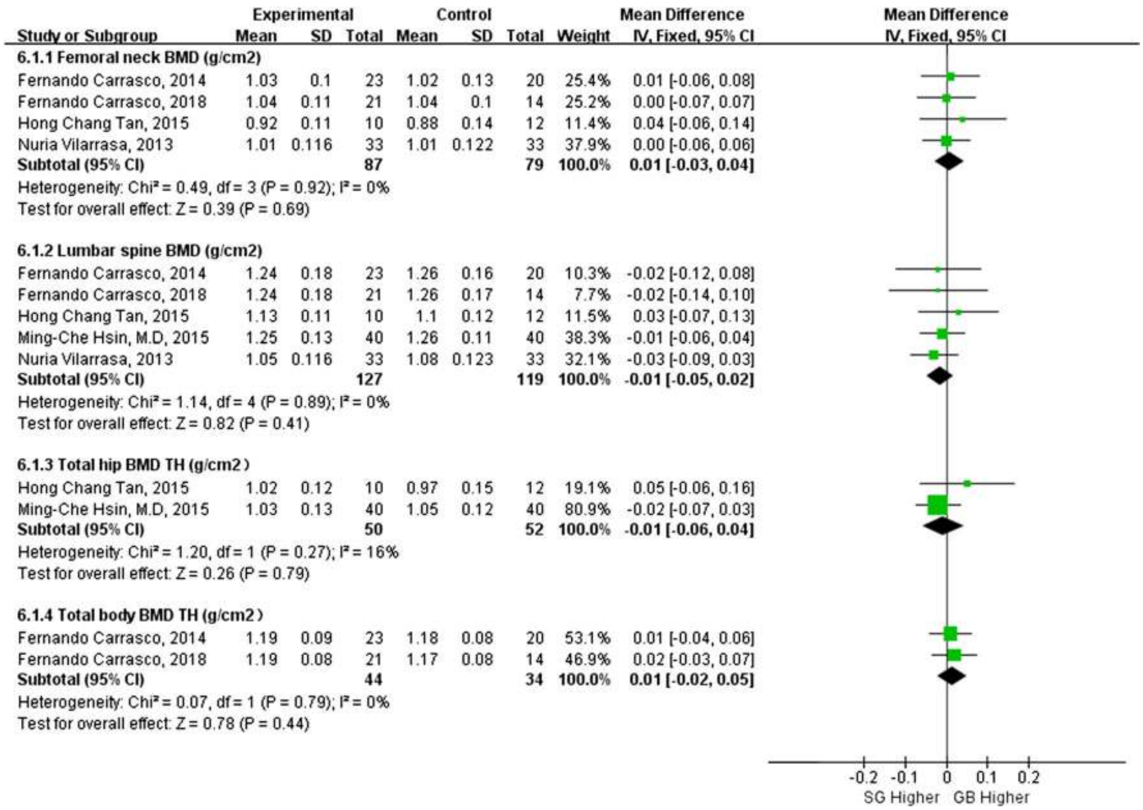

Fig. 4 Meta-analysis comparing postoperative bone mineral density after GB with SG

Publication Bias

Publication bias was measured using Egger's test ($T = 1.36$, $P = 0.194 > 0.1$) and Begg's test ($Z = 0.16$, $P = 0.876 > 0.1$). No publication bias was detected among the included articles.

Discussion

The skeleton plays crucial roles in supporting body weight, movement, maintaining blood calcium levels, phosphorus balance, and hematopoiesis. As bariatric surgery has become increasingly popular for weight loss and glucose control [37], postoperative changes in bone mineral metabolism have raised widespread concerns in recent years [38]. GB and SG are two of the most common bariatric procedures [39, 40]. Previous studies concluded that they had comparable effects on weight loss and type 2 diabetes remission [10, 13] while Osland et al. found that fewer early minor and major complications were associated with SG than with GB. In the context of these concerns and controversies, no meta-analysis regarding bone metabolism-related syndromes had been published previously. Therefore, we explored the differences between these two surgical procedures in terms of bone metabolism-related indices.

As early as the 1980s, Krolner et al. demonstrated that bariatric surgery could lead to osteoporosis, suggesting that osteoporosis was associated with weight loss [41]. However, the mechanism of osteoporosis after weight loss surgery remains unidentified. There are several hypotheses: (1) reduction in mechanical loads on bone followed by a decrease in bone mass resulted from weight loss [42]; (2) postoperative changes in hormones such as leptin, adiponectin, insulin, GLP-1, and ghrelin [43–47]; and (3) surgical changes in the gastrointestinal tract leading to deficiencies in vitamin D and calcium [48].

PTH and vitamin D are two primary regulators of bone metabolism. In the kidney, PTH is the main stimulator of vitamin D synthesis, while vitamin D exerts negative feedback on PTH secretion. PTH and vitamin D are crucial to maintenance of phosphate and calcium balance. The former elevates calcium levels and suppresses phosphate metabolism. By contrast, vitamin D stimulates both calcium and phosphate metabolism, to provide sufficient mineral for bone formation [49]. In this meta-analysis, we reviewed these relevant indices of bone metabolism in two classical bariatric procedures. Eight of thirteen included studies reported the serum calcium level of postoperative patients undergoing SG or GB. Except for two studies [35, 36], the remaining six showed similar calcium levels between patients after SG and GB [24, 26, 29, 30, 32, 34]. In our overall analysis, we found that patients

Table 2 Summary risk estimates of parathyroid levels after GB versus SG

	Number of studies	Number of participants (GB and SG)	Random effects SMD (95% CI)	I^2 (%)	*P* value
Overall	9	609,644	5.41 [− 1.12, 11.95]	79	0.1
Subgroup analysis					
Blood sample					
Serum	7	536,600	6.09 [− 1.47, 13.64]	83	0.11
Plasma	2	73,44	1.78 [− 7.20, 10.77]	0	0.7
Measuring method					
ELISA	4	458,527	7.87 [− 2.72, 18.47]	90	0.15
(E)CLIA	5	151,117	2.72 [− 2.84, 8.29]	0	0.34
Operative technique					
Laparoscopic	6	528,568	7.13 [− 1.09, 15.36]	85	0.09
Unknown/open	3	81,76	1.45 [− 5.61, 8.52]	0	0.69
Follow-up time					
Short-term	5	142,144	5.71 [− 5.61, 17.03]	84	0.32
Long-term	4	467,500	4.46 [− 0.91, 9.82]	37	0.1
Study type					
RCT	2	75,74	3.54 [0.03, 7.05]	83	0.06
Non-RCT	7	534,570	14.27 [− 0.50, 29.03]	4	0.05

SMD, standard mean difference; *CI*, confidence interval; *ELISA*, enzyme-linked immune sorbent assay; *(E)CLIA*, (electro) chemiluminescent immunoassay; *RCT*, randomized controlled trial

treated with GB had lower levels of calcium than did patients undergoing SG. Four studies found that levels of circulative phosphorus were similar [26, 29, 30, 34]. Only Lancha et al. reported the quantitative value of phosphorus in postoperative patients without making a comparison [35]. We observed higher phosphorus levels in patients undergoing GB, contrary to the results for calcium. Two of the included articles showed that vitamin D deficiency was more likely to occur 1 year after GB [29, 31], while other articles found that vitamin D levels were similar [24, 26, 28, 30, 32, 34]. Only one study [31] demonstrated that hyperparathyroidism was more likely to occur after GB, while the remaining studies showed that GB and SG were comparable with respect to the level of serum PTH [24, 26, 28–30, 32, 34]. Nevertheless, after analysis, we concluded that obese patients were more likely to suffer from secondary hyperparathyroidism after GB than after SG, although this issue requires more high-quality clinical studies for further confirmation. Carrasco et al. concluded that femoral neck (FN) BMD decreased more profoundly after GB (follow-up of 24 months) [34], while other related studies reported similar results in terms of FN BMD between two groups (follow-up of 12 months) [25, 33]. The inconformity of this result might be due to the different follow-up time. As for the lumbar spine (LS) BMD, all studies found comparable results between GB and SG groups [25, 27, 33–35]. Though we found no significant difference in BMD with the presence of differences in other indicators mentioned above, we believe this result could be explained. Only one study that measured BMD [34] had follow-up time reaching 2 years, while the other studies only followed up for 1 year. Only five studies measured BMD; therefore, it is possible that the insignificant difference of BMD is attributable to the insufficiency of follow-up time and lack of included studies.

Our results might raise new concerns regarding current recommendations for vitamin D and calcium supplementation after surgery. Despite universal recommendations for vitamin and mineral supplements, deficiencies in micronutrients remain common after bariatric surgery [50, 51]. Several studies reported that the association between GB and bone loss was partly caused by malabsorption of calcium, phosphate, and vitamin D [52, 53]. Given that SG is a restrictive technique instead of a malabsorptive procedure [51], this could be the main reason for the difference between SG and GB groups regarding calcium, phosphate, and PTH levels. The Endocrine Society proposed that daily intake of vitamin D3 and basic calcium should be 1000 IU and 1200–2000 mg, respectively, for patients undergoing bariatric surgery [54], while other medical societies recommend taking 800 IU vitamin D and at least 1200 mg of basic calcium [55]. We found that the levels of calcium and vitamin D in patients undergoing GB were significantly lower than those of patients undergoing SG; this was followed by a higher probability of suffering from secondary hyperparathyroidism (this result was also reflected in our study). Both SG and GB patients in this study were deficient in vitamin D, and GB patients even had greater degrees of deficiency. GB patients were shown to have significantly lower calcium levels, though calcium levels in both groups were on the edge of the normal range. Therefore, we argue that larger doses of vitamin D should be considered for the daily supplementation of GB patients, and that circulating levels of calcium, 25-hydroxyvitamin D should be monitored more frequently, especially when patients are suffering from vitamin D deficiency or secondary hyperparathyroidism.

Our meta-analysis also has some limitations. First, regarding medical ethics, only two of the trials were randomized controlled trials, and the sample sizes in some studies were comparably limited. The second limitation is that, because of the limited number of included studies, we could not perform adequate combinatorial analysis when performing subgroup analysis, and analyses on many other parameters that might reflect bone metabolism (e.g., alkaline phosphatase, CRP, some hormones like ghrelin and adiponectin, fracture incidence, and *T* scores) were not considered in the final results. Finally, despite every effort to conduct a comprehensive search, the analysis was still restricted by the quality of individual studies and other important factors could not be further analyzed, including menstrual cycle, eating habits, and ethnic differences, all of which might affect bone metabolism. Considering the limitations of our meta-analysis, further large-scale research with long-term follow-up and comparative nonsurgical controls are still needed in order to suggest improved strategies for the selection of particular surgical procedures, as well as to suggest postoperative nutritional supplements to prevent bone loss and osteoporosis in patients undergoing bariatric procedures.

In summary, the overall analysis suggested that obese patients undergoing GB had lower levels of serum calcium and 25-hydroxyvitamin D as well as higher levels of serum phosphorus. Our results also indicated that GB and SG had similar effects on postoperative BMI, PTH, and BMD. In subgroup analysis, we found individuals in the GB group were more likely to develop hyperparathyroidism. Because the majority of the included studies presented only 12-month data, our results showed the beginning of a trend. The data suggest that longer-term analyses may reveal further separation of levels to the degree of clinical significance. This study is expected to raise our level of attention regarding the selection of surgical procedures, as well as supporting strategies of vitamin D and other supplements for the prevention of bone-related metabolism diseases.

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Compliance with Ethical Standards

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

Ethical Approval For this type of study, formal consent is not required.

Informed Consent Does not apply.

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