Vitamin D Metabolism in Bariatric Surgery

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KEYWORDS

• Vitamin D • Obesity • Bariatric surgery • RYGB • SG • Guidelines

KEY POINTS

- Vitamin D deficiency is common before and after bariatric surgery, and is more severe after roux-en-Y gastric bypass than after sleeve gastrectomy, because of decreased vitamin D absorption.
- The increase in serum 25-hydroxyvitamin D [25(OH)D] level (ng/100 IU) after vitamin D seems dose dependent and decreases at high doses.
- Based on limited evidence, vitamin D replacement doses of 3000 IU/d to 50,000 IU 1 to 3 times per week are recommended by various organizations.
- Dose-ranging randomized trials according to the type of surgery will help define the recommended daily allowance for vitamin D to achieve a serum 25(OH)D level greater than 20 ng/mL.
- The desirable 25(OH)D level to optimize musculoskeletal health in the bariatric population is unknown.

BACKGROUND

Obesity, defined as a body mass index (BMI) greater than or equal to 30 kg/m^2, is a major risk factor for cancer and noncommunicable diseases, and is associated with a 50% to 100% increase risk of premature death. The World Health Organization (WHO) projected that, by 2015, around 2.3 billion adults will be overweight (BMI $\geq$25 kg/m^2) and more than 700 million will be obese.[1] The US Centers for Disease Control and Prevention (CDC) estimates that 78 million Americans are obese,[2] and 24 million are severely or morbidly obese.[3] The prevalence of obesity in the United States tripled between 1960 and 2010,[4] and is still steadily increasing. The National Health

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and Nutrition Examination Survey (NHANES) study revealed that one-third of Americans adults were obese, 35.7% in 2009 to 2010, and 36.5% in 2011 to 2014.[5,6] This epidemic has not spared the youth. One-third of children and adolescents aged 6 to 19 years are considered overweight or obese, and more than 1 in 6 are obese.[7]

Hypovitaminosis D is prevalent worldwide, and across all age groups.[8–13] Skin is the major source of vitamin D and its synthesis requires ultraviolet B (UVB) rays, but small amounts (100–200 IU) are obtained from the diet.[13] Serum 25-hydroxyvitamin D [25(OH)D] concentration is the preferred indicator of vitamin D nutritional status, because of its fat solubility and long half-life. Obesity is a major risk factor for low 25(OH)D levels.[13–17] This association was also established in a meta-analysis of 23 studies, in adults/elderly as well as children and adolescents, and was independent of latitude, vitamin D cutoffs used, and human development index of the study location.[18] The cause for this association is not clear, but may in part be explained by decreased outdoor activities and poor dietary habits.[17–19] Other possibilities include decreased skin synthesis in response to a given UVB dose, decreased ability of the skin to release vitamin D into the circulation, alterations in the synthetic pathway in the liver from nonalcoholic fatty liver disease (NAFLD), enhanced degradation of 25(OH)D caused by increased cytochrome P (CYP) 24A1 activity, decreased synthesis of 1,25-dihydroxyvitamin D [$1,25(OH)_2$ D] caused by altered 1-alpha hydroxylase activity and negative feedback caused by increased parathyroid hormone (PTH) and calcitriol levels.[17,20] In addition, dilution caused by large body size, and decreased bioavailability and/or sequestration of 25(OH)D in fat, both visceral and subcutaneous, have been proposed.[14,16,17,21,22] This possibility was further examined in a study that directly measured vitamin D content in various adipose tissue compartments in 27 obese and 26 control subjects. Vitamin D total body stores were higher in the obese group, and serum 25(OH)D level was directly related to adipose tissue in both study groups.[16] However, the 2 groups did not differ in visceral or subcutaneous vitamin D stores, and the comparable mean serum 25(OH)D levels at entry were a major study limitation.[16]

Diet therapy and medical management have limited success in the treatment of morbid obesity, and bariatric surgery, therefore, prevails as the only effective long-term treatment option for weight reduction.[23] It results in substantial improvements or complete remission of associated comorbidities and reduced mortality.[24–26] A meta-analysis that included 22,904 patients showed that bariatric surgery resulted in a mean weight loss of 61%, with substantial improvement in diabetes, hyperlipidemia, hypertension, and obstructive sleep apnea,[27] and a reduction in the risk of premature death by 30% to 40%.[28,29] The Swedish Obese Subjects trial showed prevention of incident diabetes and cardiovascular events, and reduced mortality, on long-term follow-up.[28,30]

The estimated number of bariatric surgery procedures in the United States has increased from 158,000 in 2011 to 196,000 in 2015.[31] Although roux-en-Y gastric bypass (RYGB) was the commonest procedure worldwide,[32] it is fast being replaced by sleeve gastrectomy (SG) because of a good efficacy and a lower complication rate. Gastric banding (GB) is the least effective, with inferior efficacy that further decreases on long-term follow-up. To-date, these procedures are almost exclusively performed through a laparoscopic approach, and the most recent estimates from the American Society of Metabolic and Bariatric Surgery (ASMBS) reveal that 54% of these procedures are laparoscopic SG, 23% are laparoscopic RYGB, 14% are revisions, and 6.7% are laparoscopic GB.[33] Although GB (**Fig. 1**C) is a purely restrictive procedure that reduces the amount of food (thus energy consumed), SG (see **Fig. 1**A) and RYGB (see **Fig. 1**B) have additional components incurred from alterations in the secretion of gut

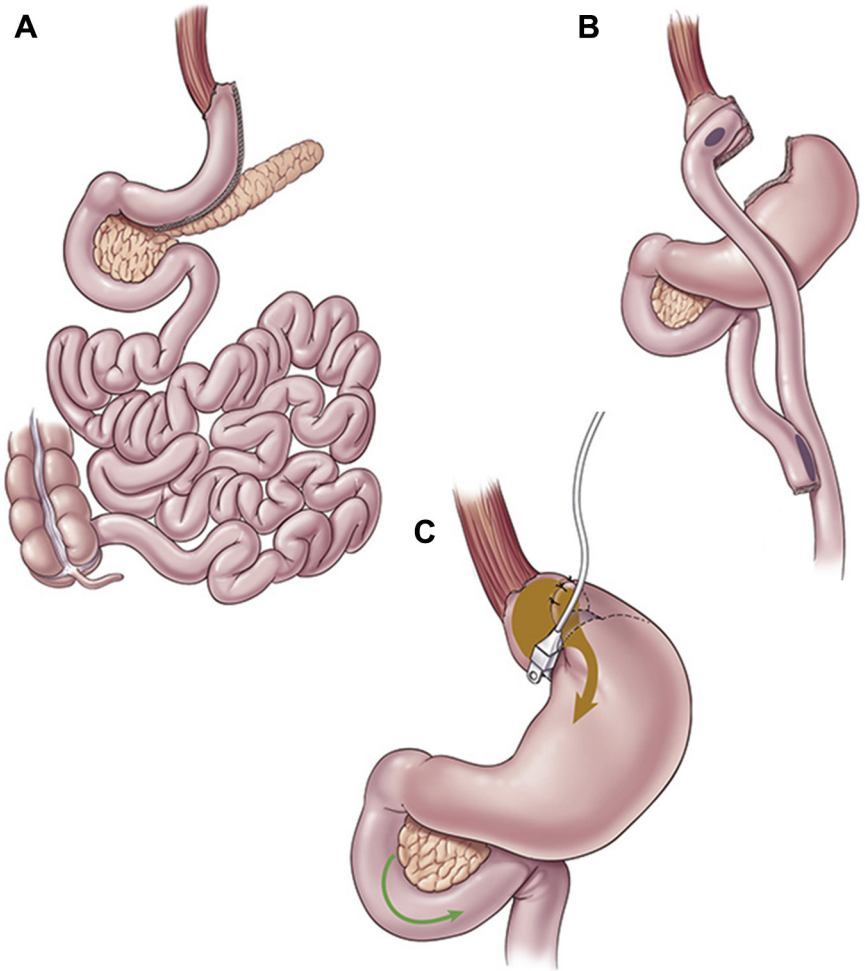

Fig. 1. Anatomy of the stomach and bowel loops with 3 common bariatric procedures. For additional details regarding the procedures please see the Web site of the American Society of Metabolic and Bariatric Surgery page https://asmbs.org/patients/bariatric-surgery-procedures. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2006 to 2017 All rights reserved. (*A*) SG: more than three-quarters of the stomach are removed, and the remaining tubular pouch holds a considerably smaller volume, and thus less food and fewer calories are consumed, compared with the normal stomach. The greater impact on weight loss seems to be the effect this surgery has on gut hormones that affect hunger, satiety, and glycemic control. (*B*) RYGB: a small stomach pouch, approximately 30 mL (1 fluid ounce), is created by dividing the top of the stomach from the rest of the stomach, the bottom end of the divided small intestine is brought up and connected to this pouch, and its top portion is connected further down the intestine, to allow the bypassed stomach acids and digestive enzymes to eventually mix with the food. The mechanism of action for weight loss is similar to SG and in addition results from a malabsorptive element resulting from the bypassed small intestine (75–150 cm). (*C*) GB: an inflatable band is placed around the upper portion of the stomach, creating a small stomach pouch above the band, and the rest of the stomach below the band. The feeling of fullness depends on the size of the opening between the pouch and the remainder of the stomach. The size of the opening is adjustable by filling the band with sterile saline, injected through a port placed under the skin.

and satiety hormones. RYGB also bypasses large portions (75–150 cm) of the small intestine, causing delays and reduction in the timing allowed for the mixing of food with gastric and pancreatic juices, and thus further reductions in energy absorption. This anatomic change is also seen in SG with duodenal switch and biliopancreatic diversion, procedures that cause the most malabsorption.[32,34–36]

Despite its substantial advantages, bariatric surgery is accompanied by several complications, such as leaks (0.5%), bleeds (1%), pulmonary embolism (0.5%), strictures (3%–4%),[37] and deficiencies in various macronutrients and micronutrients, including water-soluble nutrients and the fat-soluble vitamins A and D, iron, vitamin B_{12}, and folate in 20% to 50% of patients.[36,38–41] Vitamin D plays a key role in mineral and musculoskeletal metabolism across the lifecycle.[13,42–45] In obese patients undergoing bariatric surgery, vitamin D is also implicated in bone and mineral metabolism.[32,35,46,47]

This article reviews studies describing vitamin D nutritional status before and after surgery, vitamin D replacement (including observational studies and randomized trials), and vitamin D guidelines issued by several organizations, in adult patients undergoing bariatric surgery. Studies that investigate the impact of vitamin D on skeletal and nonskeletal outcomes in patients undergoing bariatric surgery are beyond the scope of this article, and therefore are only briefly discussed.

SEARCH METHODOLOGY

Vitamin D Randomized Controlled Trials in Bariatric Surgery

The authors conducted a literature search for an ongoing systematic review of randomized controlled trials (RCTs) on the topic for the Cochrane Library in 5 databases (Medline, Cochrane, PubMed, Embase, LILACS), updated in March 2017, through automatic Ovid alerts. The search strategy was designed as described previously.[48] The authors used MeSH (Medical Subject Headings) terms and keywords relevant to vitamin D, bariatric surgery, and RCTs, with different combinations, to ensure a comprehensive search methodology.

Vitamin D Replacement Guidelines in Bariatric Surgery

The authors conducted a systematic literature search to identify guidelines on vitamin D replacement following bariatric surgery in Medline, PubMed, Embase, and the National Guideline Clearinghouse, updated in March 2017, through automatic Ovid alerts. MeSH terms and keywords relevant to vitamin D, bariatric surgery, and guidelines were used. Details of the original search methodology are published elsewhere.[49]

We also conducted a PubMed search using MeSH terms and keywords relevant to vitamin D and bariatric surgery from 2015 to March 2017, and screened the reference list of the relevant retrieved articles and of articles available in the authors' library. For the identification of ongoing prospective studies and randomized trials, we searched the ClinicalTrials.gov (https://clinicaltrials.gov/) and the WHO International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/), in March 2017, using MeSH terms and keywords relevant to vitamin D and bariatric surgery.

HYPOVITAMINOSIS D IN BARIATRIC SURGERY AND ASSOCIATIONS WITH OUTCOMES

The cause of vitamin D deficiency after bariatric surgery is multifactorial. In addition to altered vitamin D metabolism preoperatively and low sun exposure, there is poor adherence to dietary and supplement recommendations. Bypass of the duodenum and proximal ileum, which are sites of vitamin D absorption, further reduce the dietary vitamin D intake from diet.

Generalized absorption problems occur from vomiting, the reduced time available for food digestion, and bacterial overgrowth.[36,38,40,41,50] The RYGB procedure circumvents the duodenum and proximal jejunum, thus bypassing the transport pathways for iron, calcium, and the fat-soluble vitamins A and D.[18] The reported prevalence of low vitamin D levels depends on factors discussed earlier, the definition of vitamin D deficiency, and the type of surgery performed. It is most extensively reported and characterized in RYGB, the commonest procedure until recently, and one that incurs significant malabsorption. Both osteomalacia and osteitis fibrosa cystica have been described in patients post-RYGB.[32] Concomitant vitamin D deficiency and increased PTH levels are associated with increased bone remodeling and bone loss. These abnormalities in calciotropic hormones persist or could even be exacerbated by the malabsorptive state and nutritional deficiencies that often ensue from bariatric surgery. In addition, although high BMI has long been considered a protective factor against osteoporosis, concerns regarding an increased risk, incurred from the inflammatory state and increased marrow adiposity commonly seen in obesity, have emerged.[51,52]

Mineral and Skeletal Metabolism

A recent systematic review of 14 observational studies reported on findings from 2688 patients following RYGB, all followed for 24 months and half of whom received calcium and/or vitamin D, at doses of up to 1100 IU/d.[53] Hypovitaminosis D and secondary hyperparathyroidism were common up to 5 years after bypass. The weighted mean serum 25(OH)D level initially increased from 18.3 (3.6) ng/mL to 24.7 (2.3) ng/mL at 2 years, then decreased to 20.5 (4.4) ng/mL and 20.8 (3.8) ng/mL at 2 to 5 years and 5 years postoperatively.[53] The adjusted mean PTH level increased progressively from 53.7 (11.3) pg/mL preoperatively to 60.3 (7.5) pg/mL at 2 years, 71.7 (6.6) pg/mL at 2 to 5 years, and 78.3 (13.2) pg/mL at more than 5 years.[53] Two studies have compared vitamin D status and hyperparathyroidism rate before and after laparoscopic SG and laparoscopic RYGB, using the same supplementation regimen in both groups.[54,55] The first did not present baseline mineral parameters but showed a significantly higher prevalence of hypovitaminosis D and secondary hyperparathyroidism at 3 to 36 months postoperatively in the laparoscopic RYGB group, compared with the laparoscopic SG group.[54] The other study reported comparable 25(OH)D and PTH levels in laparoscopic RYGB and laparoscopic SG groups, before and 1 and 2 years postoperatively.[55]

Hypovitaminosis D was inversely correlated with PTH levels postoperatively both in prospective and retrospective studies, and was associated with osteoporosis.[56–58] Serum 25(OH)D level was one of the significant predictors of bone density following weight loss surgery.[47,59–61] However, a causative effect of vitamin D on bone loss has been put into question in light of studies performed in patients post-RYGB who showed an increase in bone remodeling[62] and a decrease in dual-energy x-ray absorptiometry (DXA) bone mineral density (BMD) at multiple skeletal sites, not related to changes in serum 25(OH)D and PTH levels.[62,63] Increased bone remodeling may be related to the concomitant calcium malabsorption, rather than to vitamin D.[20] DXA-derived bone density measurements are limited by logistic and technical considerations. These considerations include artifacts from overlying soft tissue for axial sites (spine and hip), in addition to accuracy errors caused by changes in body composition, secondary to drastic weight loss following bypass procedures, panniculus fat pad overlying the hip region, and so forth.[32,35] However, post–bariatric surgery true bone loss has been validated by concomitant volumetric bone density assessment using quantitative computed

tomography at the lumbar spine,[64] and ultrasonography measurements of the peripheral skeleton.[62]

In addition to secondary hyperparathyroidism after RYGB surgery, other mechanisms contribute to alterations in bone metabolism.[32,35,46] These mechanisms include decreased mechanical loading, an increase in adiponectin level, a decrease in leptin level, and changes in the levels of gut-derived hormones, all of which favor bone loss, with the exception of serotonin and glucagonlike peptide-1.[46] In addition, there is a decrease in gonadal steroid levels.[46]

Fracture risk following bariatric surgery is a matter of debate. Results were inconsistent between several observational studies, secondary to the heterogeneity in study design; data collection methods; and, importantly, type of surgical procedure.[65–69] However, there may be a more consistent increase in fracture risk following malabsorptive procedures, such as RYGB and the less commonly used biliopancreatic diversion (BPD).[67,70,71] In the last 3 studies, fracture risk increased by 40% to 200%, depending on the fracture site, the surgical procedure, and the comparator group (community population, obese control patients, or obese patients undergoing a restrictive procedure).[67,70,71] In the most recent study, by Yu and colleagues,[70] analysis of claims from a US health care plan, with 12,482 RYGB and 8922 GB patients, there was a significant increase in fracture risk of hip (relative risk [RR] = 1.54) and radius (RR = 1.45) in patients post-RYGB compared with GB, that occurred 2.3 (1.9) years postoperatively (propensity matched analyses). None of the studies provided 25(OH)D levels and therefore the contribution of vitamin D to fracture risk is unclear. However, reported vitamin D deficiency in one retrospective study was identified as a significant risk factor, and it was associated with a doubled risk of fracture, after adjustment for age and type of surgery.[67]

For detailed reviews on bone disease following bariatric surgery, please refer to dedicated reviews and systematic reviews on the topic.[32,35,47,72,73]

Nonskeletal Outcomes

A serum 25(OH)D level less than 30 ng/mL was linked to a 3-fold increase in the risk of infections, after controlling for several covariates, demographics, and comorbidities, in a study of 770 obese patients (70% female), with a mean baseline BMI of 46 to 48 kg/m^2 undergoing RYGB.[74] In a retrospective study from France that enrolled 258 obese patients, 87% female, with a mean baseline BMI of 40.90 kg/m^2, there was no association between vitamin D deficiency and complication rate post-RYGB.[75] In unadjusted analyses from the same study, subjects who were vitamin D replete at baseline (serum 25(OH)D level >30 ng/mL) had a 10% higher excess weight loss at 2 years postsurgery, compared with those with vitamin D insufficiency or deficiency.[75] However, RCTs have not shown an effect of vitamin D on weight loss post–bariatric surgery (discussed later). Serum 25(OH)D level was also associated with resolution of hypertension 1 year post-RYGB in 196 obese patients, with a baseline BMI of 32 to 33 kg/m^2. In an unadjusted analysis, hypertension resolution rate was significantly lower in patients with serum 25(OH)D less than or equal to 20 ng/mL (42%) compared with patients with serum 25(OH)D level greater than 20 ng/mL (61%).[76] The association between vitamin D and cardiovascular morbidity and mortality, and all-cause mortality, post–bariatric surgery, has not been evaluated.

Findings from these observational studies remain limited by the retrospective study design, the small sample size, and confounders that were only adjusted for in 1 study.[74]

VITAMIN D STATUS AND REPLACEMENT IN PATIENTS UNDERGOING BARIATRIC SURGERY

A vitamin D intake that is body weight specific may be needed to achieve target 25(OH)D levels in obese individuals. A systematic review of 144 cohorts reported in 94 independent studies that included 11,566 subjects who received 200 to 10,000 IU/d of vitamin D, and 9766 controls, reported that baseline BMI is a strong predictor of response to vitamin D supplementation in obese individuals.[77] Other predictors included age, calcium intake from diet or supplements, baseline 25(OH)D level,[77] and possibly polymorphisms in the vitamin D receptor, vitamin D binding protein, and CYP enzymes.[17] Weight loss is accompanied by increments in serum 25(OH)D levels caused by mobilization of vitamin D from fat stores,[78–80] and patients who lose more weight experience a greater increase in serum 25(OH)D level.[81]

Special considerations when interpreting serum 25(OH)D levels in patients after bypass gastric surgery include the type of surgery incurred and the regimen prescribed, whether a loading dose for a certain period preoperatively or postoperatively was administered, and patient adherence. A 25% decrease in the absorption of cholecalciferol was shown in 14 morbidly obese premenopausal women 4 weeks after RYGB.[82] All of these covariates explain the wide variability in 25(OH)D levels achieved, at varying time points, in response to varying vitamin D regimens post–gastric bypass.

Observational Studies

Before bariatric surgery

The prevalence of hypovitaminosis D in obese patients undergoing bariatric surgery was reported to vary widely between studies conducted in Western populations, ranging from 13% to 92%.[83] Similarly, a single-center study from the Middle East (N = 257) showed that 91% of the obese patients presenting for bariatric surgery had a 25(OH)D level less than 30 ng/mL, and 69% were vitamin D deficient [25(OH)D level <20 ng/mL].[84] In a recent systematic review of observational studies, the authors identified 51 studies, each with at least 50 participants, describing vitamin D status before and/or after bariatric surgery.[85] All studies were conducted in Western populations, 7 studies were cross-sectional and 44 longitudinal, with retrospective or prospective designs. Thirty-eight studies were conducted in patients undergoing malabsorptive/combination procedures, 5 studies were conducted in laparoscopic SG patients, and 8 studies included both types of procedures.[85] The mean serum 25(OH)D level was less than 30 ng/mL preoperatively in 29 studies and less than 20 ng/mL in more than half of them (N = 17 studies).[85] Serum 25(OH)D levels did not differ between the BMI categories with weighted means (standard deviations [SDs]) of 43.6 (8.2), 47.6 (15.5), and 52.8 (9.9) kg/m^2.[85] Similar results were described in a 2017 systematic review of 15 observational studies conducted in patients undergoing SG, in Europe and the United States.[60] All studies reported a mean serum 25(OH)D level less than 30 ng/mL, and 8 studies a mean 25(OH)D level less than 20 ng/mL.[60] Ethnic differences in vitamin D levels, similar to those reported in the general population, were observed in a study from the United States. White people had the highest mean 25(OH)D level, with a mean of 25.5 ng/mL, compared with 12.9 ng/mL in African Americans, and 14.9 ng/mL in Hispanic people.[86] Therefore, the prevalence of hypovitaminosis D in Western and non-Western countries is comparable, if the ranges reported in individual studies are considered.[53,83,84] Systematic reviews that report mean serum 25(OH) levels also consistently yield comparable but more conservative estimates.[60,85]

After bariatric surgery

Despite various vitamin D supplementation regimens, our systematic review of observational studies revealed that only 13% of the included studies reported a mean post-replacement 25(OH)D level greater than 30 ng/mL, measured 3 months to 10 years postoperatively.[85] Several studies administering a low dose of vitamin D, 200 to 800 IU/d, showed no change or a decrease in 25(OH)D level.[85] In vitamin D–deficient patients, a significant increase in 25(OH)D level, of 9 to 13 ng/mL, was shown only in studies that used loading doses of vitamin D (1100–7100 IU/d) followed by a maintenance dose (400–2000 IU/d).[85] However, these increments in 25(OH)D level remained lower than increments observed with similar doses in the general nonobese population.[87,88] These indirect comparisons suggest that higher doses of vitamin D are needed to correct vitamin D deficiency in obese patients undergoing bariatric surgery. The proportion of patients reaching a 25(OH)D level greater than or equal to 20 ng/mL, the target set by the Institute of Medicine (IOM) for a normal population,[89] increased from 25% to 55% at baseline to 70% to 93% at follow-up, depending on the replacement dose and type of surgery.[85] Another systematic review and meta-analysis of prospective studies in patients undergoing gastric bypass, of at least 6 months' duration, revealed no significant change in serum 25(OH)D level with vitamin D doses less than or equal to 1200 IU/d.[90] The mean difference in serum 25(OH)D level was 1.35 (−1.12; 3.83, unit not provided; $P = .28$), and the high heterogeneity (I^2 84%) could be explained by the wide range of vitamin D doses used (from none to 1200 IU/d), follow-up duration (6–36 months), and baseline BMI.[90]

It is noteworthy that the few studies that did not include any supplementation following laparoscopic SG showed a significant improvement in serum 25(OH)D level at early (6 months)[91] and late (1–2 years) follow-up.[92,93] In one study, 25(OH)D level increased from 23.6 (14.2) to 32.2 (16.5) ng/mL, at 6 months postoperatively.[91] In 2 studies, 25(OH)D levels at baseline were 13.5 (8.1) and 17.4 (8) ng/mL, and increased to 26.3(7.6) and 42.1(10.2), at 1 year after surgery, respectively[92,93] and 1 of them reported a 25(OH)D level of 49.4 (14.4) at 2 years.[93] The increase in serum 25(OH)D in the early postoperative period could be explained by the lack of a malabsorptive element in this type of procedure, coupled with vitamin D mobilization from adipose tissue,[94] whereas the long-term improvement may be related to lifestyle changes, sun exposure, and other factors.

Such differences by type of surgery were not readily detectable in our systematic review.[85] We identified 5 studies that included more than 50 participants per arm, each comparing RYGB with SG (N = 2) or GB (N = 3), and only 2 studies showed that subjects undergoing RYGB procedures may require a higher dose of vitamin D, compared with those having SG or GB procedures, in unadjusted analyses.[85]

There was a large variability in the 25(OH)D assays used, which by itself may account for differences between studies,[13,95] and time points at which vitamin D status was assessed in the studies discussed earlier.[85] Furthermore, the type of vitamin D used, duration of supplementation, and compliance rates were poorly reported. These limitations explain the wide heterogeneity of results obtained and underscore the need for high-quality randomized trials to define the vitamin D dose response in this specific population.

Randomized Controlled Trials

Eight trials investigated vitamin D replacement in obese patients undergoing bariatric surgery, all from Western countries (**Table 1**).[96–103] The number of participants was fewer than 50 per arm in all but 2 studies (Dogan and colleagues[102] [n = 75/arm], Muschitz and colleagues[103] [n = 110/arm]). With 1 exception,[99] all were conducted

Table 1
Randomized controlled trials and controlled clinical trials of vitamin D replacement in bariatric surgery

Author, Year Country	Intervention Equivalent Daily Dose	N Randomized	N Completers	Gender % Women	Age (y) Mean (SD)	BMI Baseline (kg/m^2) Mean (SD)	BMI Follow-up (kg/m^2) Mean (SD)	Type of Surgery	Vitamin D Assay	Duration (mo)	Cointervention Ca (mg/d)	Baseline 25(OH)D Level (ng/mL) Mean (SD)	Postintervention 25(OH)D Level (ng/mL) Mean (SD)	Change in 25(OH)D Level (ng/mL) Mean (SD)	Comorbidities (%)	Adverse Events
Intervention ≤ 3 months:																
Stein et al,[96] 2009 United States[a]	D_3 1143 IU/d	12	12	75.0	39	47.5	NR	NR	LCMS Rochester, MN	2	NR	15.1 (6.9)	23.6 (6.9)	NR	NR	None
	D_2 7143 IU/d	13	13	75.0								13.6 (4.3)	31.3 (7.2)			
Sundbom et al,[99] 2016 Sweden[d]	UVB (for 4 wk) +D_3 600 IU/d	31	NR	70	40.5 (5.7)	42.7 (5.2)	31.3 (5.4)	RYGB	HPLC	3	NR	27.3 (11.9)	28.7 (9.9)	NR	NR	NR
	D_3 600.000 IU IM once + 600 IU/d	21		75	38.2 (5.3)	42.7 (5)	30.2 (5.9)					22.3 (7.2)	31.2 (6.3)			
	Control + D_3 600 IU/d	27		65.0	40.6 (6.3)	42.4 (4.3)	29.9 (4.6)					20.2 (6.7)	19.5 (6.3)			
Wolf et al,[98] 2016 Germany[c]	Placebo + D_3 200 IU/d	47	41	61.7	43 (11)	50 (46.3; 58.8)	NR	SG	ELISA kit IDS, Frankfurt/ Main, Germany	3	NR	23.2 (10.3)	NR	0	HTN: 66 DM: 29.8 Arthrosis: 6.4 Depression: 8.5 OSA: 40.4 Degenerative alteration 59.6	NR
	D_3 3200 IU/d + 200 IU/d	47	38	66.0	43 (10)	46.7 (44.6; 57.4)						24 (7.4)	NR	Estimated change 12.8	HTN: 61.7 DM: 25.5 Arthrosis: 6.4 Depression: 14.9 OSA 31.9 Degenerative alteration: 57.4	

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Table 1
(continued)

Author, Year Country	Intervention Equivalent Daily Dose	N Randomized	N Completers	Gender % Women	Age (y) Mean (SD)	BMI Baseline (kg/m^2) Mean (SD)	BMI Follow-up (kg/m^2) Mean (SD)	Type of Surgery	Vitamin D Assay	Duration (mo)	Cointervention Ca (mg/d)	Baseline 25(OH)D Level (ng/mL) Mean (SD)	Postintervention 25(OH)D Level (ng/mL) Mean (SD)	Change in 25(OH)D Level (ng/mL) Mean (SD)	Comorbidities (%)	Adverse Events
Luger et al,[97] 2017 Austria[b]	D_3 100,000 IU every 2 wk for 3 doses then 3420 IU/d	25	21	80.0	43 (12.6)	44.6 (4.2)	33.1 (3.9)	Omega loop gastric bypass	NR	6	NR	15.5 (5.7)	27	NR	Liver fibrosis: 36	In the whole study Myocardial infarct (n = 1)
	Placebo (3 doses) then D_3 3420 IU/d	25	22	80.0	41.8 (13)	42.9 (4.3)	31.1 (3.5)					15.7 (5.9)	21		Liver fibrosis: 20	Liver hepatoma (n = 1)
Intervention ≥ 12 months:																
Carlin et al,[100] 2009 United States[e]	Control + D 800 IU/d	30	29	100	42.9 (11.3)	50.9 (6.6)	32.7 (4.6)	RYGB	CLIA Liaison Platform DiaSorin, Stillwater, MN	12	Ca 1500	19.7 (8.5)	NR	−4.4 (11.4)	NR	Death (n = 1) in the high dose group
	D 7143 + 800 IU/d	30	24	100	43.0 (11.9)	50.3 (4.9)	32.5 (5.1)				Ca 1500	18.5 (9.4)		16.3 (15.7)		
Goldner et al,[101] 2009 United States[f]	D_3 800 IU/d	13	9	NR	48.2 (11.8)	52.5 (9)	Change in weight (kg) −52.2 (18)	RYGB	CLIA Salt Lake City, UT	12	Ca 2000	19.1 (9.9)	NR	11 (12.4)	NR	Hypercalciuria (n = 1) in the high dose group
	D_3 2000 IU/d	13	9		48.3 (6.6)	60.4 (14.2)	−41.7 (19)				Ca 2000	15 (9.3)		24.1 (15)		
	D_3 5000 IU/d	15	10		44.6 (10.9)	56.2 (10.3)	−45.7 (13)				Ca 2000	22.9 (10.3)		26.4 (16.9)		
Dogan et al,[102] 2014 Holland[g]	D 160 + 1200 IU/d	75	74	68.0	43.4 (10)	44.8 (4.8)	Weight at follow-up (kg) 90.6 (17.4)	RYGB	NR	12	Ca 1500	17 (7.2)	30.7 (9.8)	13.2 (10.9)	DM: 32 HTN: 44 DL: 13.3 OSA: 14.7	No adverse events related to intervention
	D 500 + 1200 IU/d	75	74	71.0	45.3 (10.2)	44.8 (6.4)	93.8 (16.9)				Ca 1500	17.7 (8.2)	28.2 (10.2)	10 (10.8)	DM: 33.3 HTN: 37.3 DL: 26.7 OSA: 18.7	

Muschitz et al,[103] 2016 Austria[h]	D_3 4000 IU/d for 8 wk then 2286 IU/d + D 200 IU/d	110	94	60.0	41 (34–45)	44.3 (41.1; 47.9)	Change in BMI (kg/m^2) −5.5 (−9.4; −3.2)	RYGB and SG	Chemiluminescence on the IDS-iSYS System, Boldon, United Kingdom	24	Calcium and lifestyle changes	17.4 (13.4; 22.6)	44.6 (34.9;52.8)	NR	NR	NR
	Control + D 200 IU/d	110	97	55.5	40 (35–45.8)	44.2 (40.7; 47.7)	−7.3 (−9.4; −1.7)				NR	17.7 (13; 21.9)	18 (15; 22.1)			

Abbreviations: CLIA, chemiluminescent immunoassay; DL, dyslipidemia; DM, diabetes mellitus; ELISA, enzyme-linked immunosorbent assay; HPLC, high-pressure liquid chromatography; HTN, hypertension; IDS, Iduronate-2-Sulfatase; LCMS, liquid chromatography mass spectrometry; NR, not reported; OSA, obstructive sleep apnea.

[a] Longitudinal pilot study: intervention was D_2 50,000 IU weekly versus D_3 8000 IU weekly for 8 weeks; participants with vitamin D deficiency in the cross-sectional study were included in the trial; baseline characteristics for the pilot study were same as for the cross-sectional study; results on demographics included here are for all the participants in the cross-sectional study.

[b] Intervention was given as a loading dose of 100,000 IU at 0, 2 weeks, and 4 weeks, but the study duration was 6 months.

[c] Study compared 3200 IU/d versus placebo; two-thirds of all participants received an additional 200 IU/d and one-third of participants received an additional 10 to 20 IU/d. Medians (range) of BMI at baseline are provided.

[d] Study was conducted at 4.1 (1.1) years after bariatric surgery; as per the authors, "although no hypercalcemia or other toxic symptoms, for example, poor appetite and constipation to severe thirst and failure, were seen in the kidney present study, the risk cannot be ignored." All participants received 600 IU/d.

[e] Open-label study comparing 50,000 IU weekly versus no vitamin D; all participants received 800 IU/d; one of the limitations of the trial was noncompliance, but further details were not provided.

[f] The investigators describe that they had difficulty in compliance, but no further details were provided. Data on 6, 12, and 24 months are available.

[g] All participants received vitamin D 1200 IU/d and Ca 1500 mg/d; all participants received other multivitamins and minerals, in 2 different doses. These vitamins and minerals were: biotin, calcium, chloride, chrome, copper, folic acid, iodine, iron, manganese, magnesium, molybdenum, selenium, vitamins (A, B_1, B_2, B_3, B_5, B_6, B_{12}, C, D, E, K_1), and zinc. No significant difference in 25(OH)D level was detected between the 2 arms. Vitamin D deficiency before surgery was corrected with a mean loading dose of 226,087 (±60,442) IU with a maintenance dose of 25,000 IU/mo, and stopped 2 months before surgery.

[h] The intervention group received 28,000 IU cholecalciferol per week for 8 weeks before bariatric surgery, 16,000 IU/wk after surgery, the control group did not receive any loading nor maintenance vitamin D; in addition to vitamin D, the intervention consisted of 1000 mg of calcium monocitrate per day, daily BMI-adjusted protein supplementation, and physical exercise. All participants received vitamin D 200 IU/d.

in the immediate postoperative phase. The surgical procedures were RYGB,[99–102] omega loop bypass,[97] SG,[98] or one of the 2 procedures, RYGB or SG,[103] and not specified in 1 study.[96] Vitamin D supplementation was given for a period greater than or equal to 12 months in 4 studies,[100–103] 3 months in 1 study,[98] and less than 3 months in the other 3 studies.[96,97,99] We did not identify any study in which supplementation was started immediately postsurgery and given for a duration of between 3 and 12 months postsurgery, a period during which the most rapid weight loss occurs, and during which vitamin D levels may increase because of mobilization from fat. The vitamin D doses were given daily (3 studies),[98,101,102] weekly (3 studies),[96,100,103] or biweekly (1 study),[97] and consisted of D_3 in a liquid form,[97,98] a sublingual tablet,[103] or as a single intramuscular (IM) high dose of vitamin D compared with UVB (and no supplementation).[99] The daily equivalent vitamin D doses varied from 200 to 7940 IU/d. Five studies gave, in addition to the intervention, vitamin D as part of multivitamins for all participants, at a dose of 200 to 1200 IU/d.[98–100,102,103] All studies had a preponderance of women, in their 40s, with a mean BMI at the start of the intervention less than or equal to 50 kg/m^2 in 6 studies,[96–99,102,103] and between 50 and 60 kg/m^2 in 2 studies.[100,101] Only 2 studies used high-pressure liquid chromatography[99] and liquid chromatography mass spectrometry[96] to measure serum 25(OH)D levels, which is an important consideration in studies that may have used use D_2 instead of D_3, and platform assays that do not detect 100% of this D_2 metabolite.[104] Baseline 25(OH)D levels ranged between 15 and 20 ng/mL in 6 studies,[96,97,100–103] and 20 and 30 ng/mL in 2 studies.[98,99] Three studies gave concomitant calcium supplementation, at a dose of 1500 to 2000 mg daily, to all treatment arms,[100–102] and cointervention differed between arms in 2 studies.[102,103] In 1 of them, the intervention consisted of vitamin D_3 in addition to exercise and high-protein diet versus no intervention.[103] In the other, cointervention included calcium, iron, and other vitamins and minerals, at different doses between arms.[102] Comorbidities such as diabetes mellitus, hypertension, obstructive sleep apnea, and dyslipidemia were discussed in only 2 studies[98,102] (see **Table 1** for details). Adherence with supplementation was reported in only 2 studies and exceeded 80% in both.[96,98]

Effect of Vitamin D Supplementation for at Least 12 Months

Four RCTs[100–103] administered vitamin D as D_3 in 2 studies,[101,103] whereas no details were provided in the other 2 (**Fig. 2**, see **Table 1**).[100,102] The same cointervention was used in all study arms in 2 studies.[100,101] The first study compared a vitamin D (type not specified) dose of 50,000 IU/wk with controls in an open-label study design in 60 women who had RYGB. However, all participants received multivitamins postoperatively.[100] Therefore, the equivalent vitamin D doses were 7943 IU/d versus 800 IU/d.[100] The baseline 25(OH)D level was 18 to 19 ng/mL, decreased by 4.4 (11.4) ng/mL in the control arm, but increased by 16.3 (15.7) ng/mL in the high-dose arm at 12 months.[100] The authors calculated an increase in serum 25(OH)D of 0.2 ng/mL per 100 IU of vitamin D.[100] The second was a pilot study, comparing 3 different cholecalciferol doses in patients undergoing RYGB: 800 IU/d (n = 13), 2000 IU/d (n = 13), and 5000 IU/d (n = 15). Despite the imbalance in the baseline characteristics between treatment arms, including serum 25(OH)D level (see **Table 1**), the absolute increase in serum 25(OH)D was 24 ng/mL on the intermediate dose, 26 ng/mL on the high dose, and 11 ng/mL on the low dose.[101] The increase in serum 25(OH)D per 100 IU vitamin D was calculated to be 1.4 ng/mL in the low dose, 1.2 ng/mL in the intermediate dose, and 0.5 ng/mL in the high dose.

In 2 other studies, the cointervention differed between study arms.[102,103] In the largest trial, from Austria, there was a significant increase in mean serum 25(OH)D level

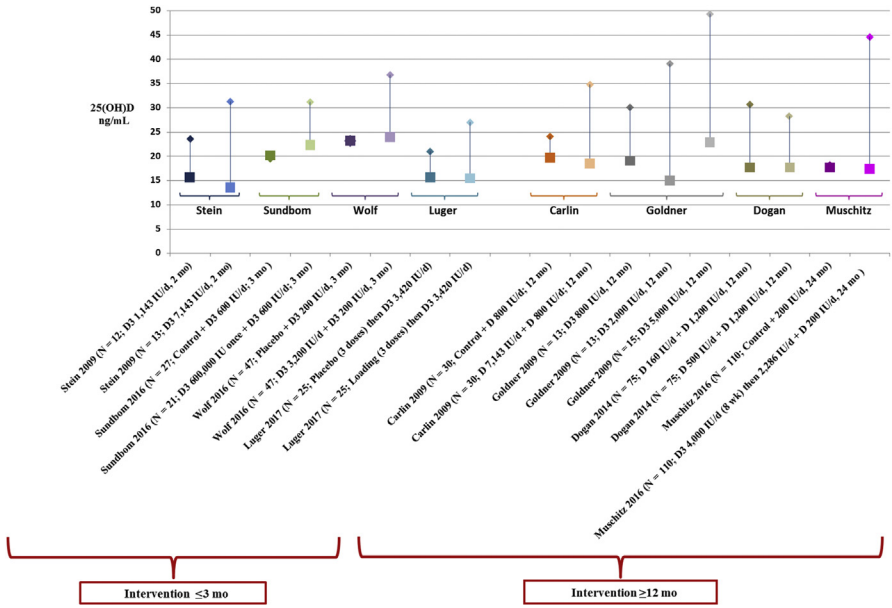

Fig. 2. Mean serum 25(OH)D level in RCTs, by intervention duration. Mean serum 25(OH)D levels in studies grouped by the duration of the intervention (≤3 months and ≥12 months) before and after vitamin D supplementation, in patients undergoing RYGB,[97,99–102] SG,[98] SG or RYGB.[103] One study did not specify the surgical procedure type.[96] Each color represents 1 study; dark colors represent low dose or controls, and light colors represent high dose. (*Data from* Refs.[97–103])

from 17.4 ng/mL to 44.6 ng/mL in response to vitamin D_3 doses of 4000 IU/d for 8 weeks followed by 2286 IU/d (n = 110), and no change in the control arm (n = 110) in patients undergoing RYGB or SG.[103] However, cointervention with 200 IU/d, high-protein diet, and other lifestyle changes could have affected the response to vitamin D supplementation.[103] Another trial compared 2 doses of vitamin D [160 IU/d (n = 75) versus 500 IU/d (n = 75)] in 2 supplements, containing differing concentrations of calcium, iron, and other minerals and vitamins (see footnote to **Table 1**).[102] There was no significant difference in serum 25(OH)D level 12 months post-RYGB; these findings could be explained by the small difference in the vitamin D dose between the 2 arms, the 1200 IU in the cointervention, and/or nutrient interference in vitamin D absorption, specifically calcium and iron supplementation.[102]

Effect of Vitamin D Supplementation for Less Than or Equal to 3 Months

The authors identified 4 studies administering vitamin D for a duration of 3 months or less (see **Fig. 2**, see **Table 1**). The effect of a cholecalciferol dose of 3200 IU/d (n = 47), was compared with placebo (n = 47) in patients undergoing SG, with baseline serum 25(OH)D level of 23 to 24 ng/mL, and all participants received 200 IU/d, as part of postoperative multivitamins.[98] Although there was no change in serum 25(OH)D level in the placebo group, an estimated increase of 12.8 ng/mL was reported with the high dose.[98] The authors calculate the increase in 25(OH)D level to be 0.4 ng/mL/100 IU of vitamin D. A study that extended over 6 months compared the effect of a loading vitamin D dose, cholecalciferol 100,000 IU for 3 doses, at 0, 2, and 4 weeks, followed by a maintenance dose (3420 IU/d) (n = 25), with placebo loading followed by the

same maintenance dose (3420 IU/d) (n = 25)[97] in omega loop gastric bypass (includes 200 cm of jejunal bypass).[97] The mean serum 25(OH)D level increased from a baseline of 15 ng/mL to 27 ng/mL in the group receiving a loading/maintenance dose and to 21 ng/mL in the maintenance arm.[97] However, the study results cannot be generalized because a subset of patients had liver fibrosis.[97] In addition, 1 study compared parenteral vitamin D supplementation (single IM dose of 600,000 IU once) versus placebo or UVB in patients undergoing RYGB.[99] All subjects received cholecalciferol 600 IU/d as part of a multivitamin.[99] There was a significant increase in serum 25(OH)D level, from 22.3 (7.2) to 31.2 (6.3) ng/mL, only in the intervention arm, 3 months postintervention.[99] However, a single high loading dose of vitamin D may not be sufficient to maintain a steady state in the long term, both in normal-weight and obese patients.[105] Similarly, treatment with vitamin D for a period of less than 2 to 3 months may not be sufficient to reach a steady state in vitamin D levels.[87] Therefore, with the exception of Wolf and colleagues,[98] the effect of vitamin D supplementation cannot be accurately evaluated in these studies, secondary to the short study duration.

Based on the studies of at least 3 months' duration, with the same cointervention across study arms, the absolute serum 25(OH)D levels achieved were higher in response to higher vitamin D doses. The increments, expressed in ng/mL per 100 IU daily equivalent of vitamin D, were inversely proportional to the vitamin D doses administered. They are similar to changes in the general population but lower in magnitude for comparable vitamin D doses.[88,106,107]

Despite the use of high-vitamin-D doses, the mean 25(OH)D level achieved in the studies described earlier remained less than 40 ng/mL (see **Table 1**), with the exception of 2 studies, both of which lasted 12 months (see **Fig. 2**, see **Table 1**). One used a loading dose of 4000 IU/d for 8 weeks followed by a maintenance dose of 2286 IU/d, and the mean 25(OH)D level reached was 44.6 ng/mL.[103] The study that used a high dose of 5000 IU/d led to an estimated 25(OH)D level of 49 ng/mL.[101] In that study, baseline 25(OH)D levels differed, but the mean change in 25(OH)D was comparable for the 2000 IU/d and the 5000 IU/d doses, an observation worthy of follow-up in larger blinded randomized trials. The findings in 3 randomized trials are limited by the low quality of the studies, related to the lack of description of allocation concealment (3 studies),[98,100,101] the high attrition rate and lack of blinding (2 studies),[100,101] the imbalance in baseline characteristics (1 study),[101] in addition to the small sample size. None of the studies reported an increase in 25(OH)D level to a toxic level, toxicity being defined as a 25(OH)D level greater than 100 to 150 ng/mL in association with hypercalcemia.[13] The reporting of adverse events in the individual studies was poor (see **Table 1**). Notoriously, information regarding kidney stones was lacking, which is an important consideration in view of the increased risk of kidney stones post-RYGB.[108,109]

Effect of Vitamin D Supplementation on Other Bone and Mineral Parameters

Serum and urine calcium level

None of the studies reported a significant change in mean serum calcium level in the intervention arms, and hypercalcemia was not reported. There were no data on 24-hour urine calcium excretion.

Parathyroid hormone level

All the identified studies evaluated the effect of vitamin D supplementation on PTH level. In 1 study, PTH levels were significantly different at baseline, 88.1 (42.0), 106.4 (51.6), and 70.8 (63.3) pg/mL in the 800 IU/d, the 2000 IU/d, and the 5000 IU/d arms, respectively (P = .03). At 12 months, PTH level decreased by 17.0

(42.6) pg/mL, 32.4 (62.3) pg/mL, and 25.3 (82.1) pg/mL, in the low, intermediate, and high doses, respectively (P = nonsignificant).[101] Two other studies with an intervention for less than 3 months showed significant decreases in PTH levels (17%–21%) only in the intervention arms, whereas they remained increased in the controls.[97,103]

In a pilot study comparing vitamin D_2 50,000 IU weekly with vitamin D_3 8000 IU weekly over 8 weeks, the mean PTH level decreased from 91 (10) pg/mL to 76 (6) ng/mL in the cholecalciferol group, and from 77 (10) to 72 (6) pg/mL in the ergocalciferol group (P>.05).[96] These findings raise questions as to whether D_3 is more potent than D_2 in suppressing PTH levels,[96] as has been debated for normal individuals. The other trials did not report significant changes in PTH levels within or between arms throughout the study period. The variable findings with regard to PTH levels may be related to the small sample size, the differences in baseline 25(OH)D level, the variability in the vitamin D dose, and the 25(OH)D levels achieved in the individual studies.

Bone density, bone markers, and fracture

Two RCTs assessed the effect of vitamin D supplementation on BMD following bariatric surgery.[100,103] One study showed a nonsignificant decrease in bone density of spine and radius at 12 months post-RYGB but a significant change in hip BMD, in favor of a protective effect of the high vitamin D dose of 50,000 IU weekly (high dose, 0.08 (0.05) g/cm^2; low dose, 0.12 (0.06) g/cm^2; P = .043). This finding was paralleled by a significant increase in bone turnover markers in both study arms.[100] The serum 25(OH)D level achieved with the high dose was 34.8 ng/mL.[100] In the second study, which combined RYGB and SG, the intervention group received vitamin D_3 4000 IU/d for 8 weeks, followed by 2286 IU/d for a total of 24 months, and reached a mean serum 25(OH)D level of 44.6 ng/mL.[103] There was a significant decrease in total hip and total body BMD, but to a lesser extent in the intervention group compared with the control group.[103] In contrast, lumbar spine BMD did not change in the intervention group, whereas it decreased in the control group.[103] The increase in bone turnover markers was also significant in both groups, but to a lesser extent in the intervention group, following the same pattern as changes in bone density.[103] This study is the only one that collected data on fracture and reported a traumatic rib fracture in the intervention group and 2 atraumatic fractures (radius, humerus) in the control group.[103]

These findings suggest a potential protective effect of a high vitamin D dose against bone loss following bariatric surgery. However, the optimal 25(OH)D level and/or vitamin D dose that result in improved skeletal outcomes could not be defined, and procedure-specific conclusions could not be drawn.

Effect of Vitamin D Supplementation on Weight and Cardiometabolic Parameters

None of the randomized trials showed any vitamin D dose–dependent weight loss following bariatric surgery. One study showed a significant improvement in lipid parameters over time, after 12 weeks, in subjects who received 200 IU/d and 3400 IU/d of D_3, but there were no significant differences between the 2 arms.[98] In contrast, the decrease in glycemic and inflammatory indices was only significant in the placebo arm.[98] Another study showed a higher hypertension resolution rate: 75% in the high-dose group versus 32% in the low-dose group (P = .029).[100]

Comparison of Vitamin D Replacement in Sleeve Gastrectomy Versus Roux-en-Y Gastric Bypass

Two small studies assessed the impact of the surgical procedure on bone and vitamin D metabolism, using the same vitamin D replacement dose in both study arms.[110,111] The first compared the effect of RYGB (n = 7) or SG (n = 8) on bone loss at 1 year after

surgery in participants who received cholecalciferol 600 IU/d.[111] Although participants had comparable BMIs at study entry (RYGB, 43.1 (3.9) kg/m^2; SG, 43.5 (3.2) kg/m^2), as expected, RYGB patients lost more weight compared with SG patients (follow-up BMI, 26.2 (2.7) kg/m^2, and 30.5 (2.6) kg/m^2, respectively).[111] Serum 25(OH)D level increased significantly in the SG group, whereas it remained unchanged in the RYGB group.[111] Another study compared the effect of monthly cholecalciferol 100,000 IU (daily equivalent dose of 3333 IU/d) in 45 subjects undergoing RYGB and 55 who had SG.[110] Vitamin D deficiency was similar in both groups at baseline, but there was a significant reduction in the prevalence of vitamin D deficiency (from 84% to 48%) in the SG group.[110]

Although limited by the small number of studies and the restricted sample size, these findings possibly suggest a better response to vitamin D supplementation in SG compared with RYGB. Assuming adherence in the reported RCTs, and a normal distribution for serum 25(OH)D levels, our findings confirm that, as anticipated, vitamin D requirements post–bariatric surgery are higher than those of the normal population, of 600 to 800 IU/d.[89] Considering studies that lasted at least 12 months (see **Fig. 2**), a dose of 800 IU/d would not enable > 97.5% of the patients who undergo RYGB to achieve a serum 25(OH)D level above 20 ng/mL. Based on the Goldner dose ranging study, it may be closer to 2000 IU/d, but the sample size consisted of only 41 subjects.[101] There is no clear evidence of a need for a loading dose. The limited evidence from RCTs for patients undergoing SG does not allow any solid conclusions regarding dosing in this population.

Ongoing Vitamin D Studies in Bariatric Surgery

The authors identified 5 observational studies, all with a sample size less than 50, being conducted in Europe and the United States (Appendix 1 provides details on outcomes of interest). The authors also identified 6 ongoing RCTs, mostly using cholecalciferol, at doses ranging between a daily equivalent of 3333 and 10,000 IU, most being of short duration (<12 weeks), and the longest follow-up of 12 months. Four studies are being conducted in Western countries and 2 in the Middle East (see Appendix 1). The sample size is less than 100 in 4 studies, and greater than 100 in 2 studies. The target population as specified is obese adults undergoing RYGB or SG (3 studies) or bariatric surgery in general (3 studies). The primary outcomes are serum 25(OH)D level (3 studies), PTH level (1 study), and BMD (1 study), and 25(OH)D level is a secondary outcome in 1 study (see Appendix 1).

VITAMIN D REPLACEMENT GUIDELINES FOR PATIENTS UNDERGOING BARIATRIC SURGERY

Several guidelines on the postoperative care of obese patients undergoing bariatric surgery are summarized in **Table 2**.[112–117] The Endocrine Society (ES)[112] and the National Health Service (NHS) England Obesity Clinical Reference Group[116] used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to derive their recommendations, whereas the American Association of Clinical Endocrinologists (AACE), American Association of Metabolic and Bariatric Surgery (ASMBS), and The Obesity Society (TOS) guidelines used the AACE Protocol for Standardized Production of Clinical Practice Guidelines methodology.[113] The British Obesity and Metabolic Surgery Society (BOMSS) report was based on a review of the available guidelines (AACE/TOS/ASMBS, ES, Interdisciplinary European guidelines, ASMBS Position Statement, and the Canadian Agency for Drugs and

Table 2
Guidelines on vitamin D screening, monitoring, and replacement in bariatric surgery

Society	Screening and Monitoring	Replacement Dose	Case of Severe Malabsorption
Endocrine Society 2010[112]	Checking 25(OH)D level before, all types of bariatric surgery, and after RYGB, BPD, and BPD/DS, at 6, 12, 18, 24 mo and annually thereafter	First phase (weeks 1–2, liquids): oral vitamin D 50,000 IU daily. Second phase (weeks 3–6, soft food): calcitriol D 1000 IU daily. Vitamin D can be provided with ergocalciferol, 50,000 IU 1 to 3 times per week; no grading[a] Malabsorptive surgical procedures: *Vitamin D supplementation is recommended postoperatively for malabsorptive obesity surgical procedures and the doses be adjusted by a qualified medical professional based on serum markers and measures of bone density.* Strong recommendation with moderate quality of evidence	*50.000 IU vitamin D 1–3 times daily* - No grading
American Association of Clinical Endocrinologists, American Association of Metabolic and Bariatric Surgery and The Obesity Society[113]	Checking 25(OH)D level before any bariatric surgery, and after RYGB and BPDDS, at 1, 3 and 6–12 mo thereafter	RYGB and LSG: *Vitamin D at least 3000 IU daily, titrate to >30 ng/mL* grade A, BEL 1[b] LAGB: *At least 3000 IU of vitamin D daily (titrated to therapeutic 25-dihydroxyvitamin D levels)* RYGB, BPD, BPD/DS: *Treatment with oral calcium citrate and vitamin D2 or D3 is indicated to prevent or minimize secondary hyperparathyroidism without inducing frank hypercalciuria*: grade C, BEL 3	*Oral D2 or D3 may need to be as high as 50,000 units 1–3 times weekly to daily, more recalcitrant cases may require concurrent oral calcitriol (1,25(OH)$_2$ D)*: grade D
British Obesity and Metabolic Surgery Society 2014[114]	*Vitamin D level should be monitored following SG, gastric bypass and BPD/DS. If vitamin D supplementation is adjusted, the serum 25OHD levels should be rechecked after a minimum of three months*	Gastric bypass and SG: *Usual practice is in the region of a minimum of 800–1200 mg calcium and 20 mcg [μg] (800 IU) vitamin D per day. Additional vitamin D supplementation will also be needed following the BPD/DS* *Preparations may be given as:* • *50,000 IU capsules, one given weekly for 6 wk (300,000 IU)* • *20,000 IU capsules, two given weekly for 7 wk (280,000 IU)* • *800 IU capsules, five a day given for 10 wk (280,000 IU)* *This may then be followed by maintenance regimens 1 mo after loading with doses equivalent to 800 to 2000 IU daily*	NA

(*continued on next page*)

Table 2 (*continued*)

Society	Screening and Monitoring	Replacement Dose	Case of Severe Malabsorption
		(occasionally up to 4000 IU daily), given either daily or intermittently at a higher equivalent dose: no grading	
Interdisciplinary European 2014[115]	*A metabolic and bone evaluation before surgery, and follow up after surgery was suggested* (details on type of surgery and timing not provided)	AGB and RYGB: *Vitamin and micronutrient supplements (oral) should routinely be prescribed to compensate for their possible reduced intake and absorption.* BPD: *Lifelong daily vitamin and micronutrient supplementation (vitamins should be administered in a water-soluble form): Vitamins A, D, E and K*: no grading	NA
National Health Service England Obesity Clinical Reference Group 2016[116]	*All patients should have their vitamin D status assessed and treated prior to surgery and should have replacement prescribed after surgery*: grade B[a]	NA	NA
Ontario Bariatric Network 2016[117]	25(OH)D level at baseline and at 3, 6, 12 mo and then annually thereafter	NA	NA

In the presence of several guidelines versions, the latest version is included in this table. Sentences in italic are taken verbatim from the original guidelines document.

Abbreviations: AGB, adjustable gastric banding; BEL, best evidence level; BPD, bilio-pancreatic diversion; BPD/DS, BPD and duodenal switch; LAGB, laparoscopic adjustable gastric banding; LSG, laparoscopic SG; NA, not available.

[a] GRADE approach was used for the rating of the quality of evidence and the strength of the recommendations.

[b] The American Association of Clinical Endocrinologists protocol for standardized production of clinical practice guidelines methodology was used for the rating of the quality of evidence and the strength of the recommendations.

Technologies in Health Technical Report [Ottawa, Canada]), in addition to recent publications on the topic.[114] The other guidelines did not provide details on the methodology used or any quality rating of their recommendations (see **Table 2**).[115,117]

A critical appraisal of the ES, AACE/ASBMS/TOS and Interdisciplinary European guidelines is available elsewhere.[49]

Screening and Monitoring for Hypovitaminosis D

Although screening for vitamin D deficiency is not recommended for the general healthy population, it is recommended for obese patients undergoing bariatric surgery.[118–120] In 2009, a review of European and US guidelines and expert recommendations available at that time suggested monitoring serum 25(OH)D level for gastric bypass every 3 months during the first year, twice yearly in the second year, and yearly thereafter, and for SG and adjustable gastric banding (AGB), once yearly after surgery.[121] The ES (2010) and the AACE/ASMBS/TOS guidelines (2013) both recommend screening with serum 25(OH)D level before all types of bariatric surgery and then periodically every 3 to 6 months for a duration of 1 to 2 years, in patients having RYGB, BPD, and BPD and duodenal switch (BPDDS).[112,113] The Interdisciplinary European Guidelines (2014) recommend a metabolic and bone evaluation before surgery and at follow-up, without specifying when and what tests should be performed. The BOMSS guidelines (2014) recommend monitoring serum 25(OH)D level in patients on supplementation after SG, GB, and BPDDS,[114] and to check serum 25(OH)D level and adjust the dose 3 months postprocedure.[114] The NHS England Obesity Clinical Reference Group recommends the evaluation of vitamin D status before bariatric surgery (SG, RYGB, and BPDDS) but is silent on monitoring postoperatively.[116] The Ontario Bariatric Network Task Force document provides a summary table on the laboratory investigations required following bariatric surgery and for monitoring of vitamin D status at baseline, 3 months, 6 months, 12 months, and then annually, without any specification of the type of bariatric surgery.[117]

Recommended Replacement Doses

The ES guidelines recommend vitamin D supplementation for malabsorptive procedures, adjusting the dose based on serum and bone parameters (strong recommendation with moderate quality of evidence). They suggest a vitamin D dose of 50,000 IU 1 to 3 times per week, increasing to 50,000 IU 1 to 3 times per day in cases of severe malabsorption (no grading).[112] The AACE/TOS/ASMBS guidelines recommend 3000 IU of vitamin D daily for RYGB, laparoscopic SG, and laparoscopic AGB to reach a 25(OH)D level of greater than or equal to 30 ng/mL (grade A; best level of evidence, 1).[113] Similar to ES guidelines, a vitamin D dose of 50,000 IU 1 to 3 times weekly, with increments to daily doses is recommended in cases of severe malabsorption (grade D).[113] Both guidelines suggested that active vitamin D can be used in refractory cases.[112,113] The BOMSS guidelines suggest a minimum of 800 IU/d, and additional doses for BPD procedures, such as a loading dose of 50,000 IU weekly for 6 weeks, or 40,000 IU weekly for 7 weeks, or 4000 IU daily for 10 weeks, followed by 800 to 2000 IU/d vitamin D (no grading).[114] The other guidelines do not provide any recommendations/suggestions regarding the doses needed (see **Table 2**).

In summary, the guidelines available to date differed between societies in terms of dosing, had comparable monitoring intervals when specified, and only AACE/TOS/ASMBS specified a desirable 25(OH)D level of 30 ng/mL, based on their recommended desirable levels in the general population.[113] The guidelines do not fulfill

optimal guidance development criteria, in part because of limited resources, and are mostly based on expert opinion because of the scarcity of high-quality evidence available.

SUMMARY, KNOWLEDGE GAPS, AND FUTURE CONSIDERATIONS

Hypovitaminosis D [mean serum 25(OH)D level $\leq$20 ng/mL] before and after bariatric surgery is common, with the exception of a few observational studies using a loading dose followed by a maintenance dose of vitamin D postoperatively. The data are most abundant post-RYGB. Results of randomized trials of similar nature were not always consistent, possibly because of small sample size, confounding by various predictors, type and vitamin D regimen used, cointervention with calcium and other supplements, variability in follow-up, and patient adherence.

Low 25(OH)D levels are often accompanied by secondary hyperparathyroidism postoperatively, and this may be more severe after RYGB. High remodeling and bone loss has been observed, but it is not clear that vitamin D and PTH levels are the main regulators of these changes in bone metabolism postoperatively. Data on fractures are scarce and conflicting and there is no clear evidence for a role of a low vitamin D level in causing these fractures.

Several replacement regimens are available to date, and some are recommended in guidelines issued from relevant scientific societies. However, the quality of the evidence for the dosing and regimens recommended is limited, and the efficacy and effectiveness of recommended doses in increasing 25(OH)D level and improving major outcomes have not been shown.

A desirable serum 25(OH)D level is one that prevents secondary hyperparathyroidism and osteomalacia, improves calcium balance and BMD, and decreases fracture risk. Such data in patients undergoing bariatric surgery are for the most part lacking, and the desirable vitamin D level in this population remains unknown. It is likely that regimens differ by type of surgery because of the additional decreased absorption of vitamin D in RYGB procedures. Vitamin D dose-ranging trials will help define the optimal regimen (dose, frequency, and vehicle [liquid, sublingual tablet, capsule, or injection]) by type of surgery, to reach a 25(OH)D level greater than 20 ng/mL (a putative desirable level extrapolating from the general population). Assessment of surrogate markers of calcium balance and mineral metabolism will help define the desirable level in this population. This assessment is best complemented by systematic reviews of high-quality randomized trials that investigate the effect of bariatric surgery on bone density, bone quality in the various skeletal compartments, muscle mass, falls, and fractures as end points. Adequate reporting on adherence and adverse events is also essential.

The number of vitamin D randomized trials, identified from 2 major trial registries, currently being conducted in bariatric surgery patients, and their duration, are suboptimal to investigate the changes in vitamin D levels that occur within the first year postsurgery. It is hoped that several more are in progress. Although some data are gathered from Western countries, data from non-Western countries, where obesity is fastest growing, is almost inexistent. The obesity epidemic and its implications for health in general and skeletal health in particular in the pediatric population are also of great concern, in view of the potential deleterious impact of hypovitaminosis D, and other nutritional deficiencies, on the growing skeleton at a critical time for bone mass accretion.

Awaiting high-quality evidence studies, the authors suggest starting with regimens of 2000 to 4000 IU of vitamin D_3 per day, selecting the higher end of this range for

patients undergoing RYGB. Loading does not seem necessary unless patients have severe vitamin D deficiency preoperatively. The sublingual and injectable forms, which bypass the gastrointestinal tract, may be particularly attractive. Recommendations regarding adequate hydration are important to minimize the risk of stone precipitation. In consideration of the large variations in serum 25(OH)D levels achieved, and the number of confounders, periodic monitoring of such levels at 1, 3, 6, and 12 months postoperatively, and annually thereafter, allows therapy to be tailored to individual patients' risk profiles.

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APPENDIX 1: SUMMARY OF ONGOING/COMPLETED OBSERVATIONAL STUDIES AND RANDOMIZED TRIALS ON VITAMIN D IN BARIATRIC SURGERY

Trial Identifier	Principal Investigator Center Country	Study Design/Surgery Type Intervention/Duration	Sample Size (N) Eligibility Criteria	Outcomes (Primary and Secondary)	Start and Completion Dates
Observational Studies					
NCT00627315 First received: February 28, 2008 Last updated: July 28, 2016 Last verified: July 2016	Judith Korner, MD, Associate Professor of Medicine Columbia University United States	Study design: Observational, prospective cohort Intervention: Gastric bypass or GB Duration: 5 y	N: 240 Inclusion criteria: • >18 y of age • Scheduled for bariatric surgery Exclusion criteria: • Vitamin D deficiency • Primary hyperparathyroidism, osteomalacia • Lithium or thiazide diuretics • Untreated hyperthyroidism, liver disease, renal disease, Cushing syndrome, rheumatoid arthritis, myeloma or Paget disease • Antiobesity medications for >2 wk 90 d before study • Any research study 90 d before study • Malabsorption syndromes such as celiac sprue • Previous bariatric surgery	Primary: Change in bone density Secondary: Change in serum calcium and vitamin D and PTH levels	Start date: March 2015 Study completion date: January 2017 Primary completion date: January 2017

NCT01385098 First received: June 28, 2011 Last updated: Sep. 24, 2015 Last verified: August 2013	Vadim Sherman, MD The Methodist Hospital Research Institute Houston, Texas, United States	Study design: Single arm Surgery type: RYGB SG Intervention: Vitamin D_3 supplementation 2000 IU and calcium 1500 mg Duration: 12 wk	N: 23 Inclusion criteria: • Adult women obese patients undergoing either RYGB or SG • BMI >40 kg/m^2 or BMI >35 kg/m^2 with a comorbidity Exclusion criteria: • Vitamin D deficiency (<20 ng/mL) • Hypercalcemia or hypocalcemia • Renal disease • History of primary hyperparathyroidism • Medications that interfere with vitamin D metabolism • Significant sun exposure or travel to sunny climates during the study	Primary: Serum 25(OH)D level Secondary: The percentage response above baseline comparing RYGB and SG patients	Start date: July 2011 Completion date: September 2015 Primary completion date: May 2013

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(*continued*)

Trial Identifier	Principal Investigator Center Country	Study Design/Surgery Type Intervention/Duration	Sample Size (N) Eligibility Criteria	Outcomes (Primary and Secondary)	Start and Completion Dates
NCT01637155 First received: July 10, 2012 Last updated: NA Last verified: July 2012	Violeta Moize, MD Hospital Clinic Provincial de Barcelona Spain	Study design: Single group intervention Surgery type: Gastric bypass SG Intervention: Oral cholecalciferol dose of 50,000 IU to determine pharmacokinetics. After 28 d, patients take a period of 90 d of standardization of cholecalciferol based on baseline levels After this period, patients receive a second oral dose of 50,000 IU Duration: 4 mo	N: 44 Inclusion criteria: • ≥18 y old • Gastric bypass in the last 18 mo (±6 mo) • BMI 25–33 kg/m^2 • 25(OH)D level <20 ng/mL • Clinically stable Exclusion criteria: • Pregnancy, lactation • Menopause • High liver function test • Renal disease or previous renal lithiasis • Digestive disease to suggest malabsorption, granulomatous diseases, diabetic gastroenteropathy • Medication likely to interfere with the absorption of vitamin D, calcium, and bone metabolism, such as corticosteroids and anticonvulsants • Cholecalciferol hypersensitivity	Primary: Comparison of the pharmacokinetic parameters of vitamin D Secondary: • Secondary hyperparathyroidism • Urinary calcium and creatinine • Changes in total protein, albumin, phosphorus, magnesium and calcium, alkaline phosphatase levels • Change in body fat • Change in adherence in both surgeries • Adverse events	NA

NCT01871389 First received: June 4, 2013 Last updated: May 7, 2014 Last verified: May 2014	Lee Mallory Boylan, MD Professor Texas Tech University United States	Study design: Observational Surgery type: Gastric bypass Intervention: Monthly high-dose cholecalciferol (dose NA) Duration: 6 mo	N: 31 Inclusion criteria: • Morbidly obese meeting criteria for gastric bypass • Age >18 y Exclusion criteria: • Medications that affect vitamin D status, increased 25(OH)D or calcium level	Primary: Serum $25(OH)D_3$	Start date: February 2012 Completion date: August 2013 Primary completion date: August 2013
NCT01910792 First received: June 25, 2012 Last updated: January 11, 2016 Last verified: January 2016	Michael F Holick, PhD, MD Boston University Medical Center United States	Study design: Nonrandomized, open label, parallel assignment Surgery type: Gastric bypass Intervention: Group 1: patients with fat malabsorption syndromes use a UV lamp at home 3 times per week Group 2: patients with gastric bypass use a UV lamp at home 3 times per week Duration: 12 wk	N: 60 Inclusion criteria: • Men and women, age 18 y or older with skin types 2–5 • Fat malabsorption Exclusion criteria: • Treatment with vitamin D • Pregnancy and lactation • History of underlying photosensitivity, or skin type I (develop skin burns after UVB exposure) • History of chronic disease • Medications that cause photosensitivity or influence vitamin D metabolism • History of skin cancer • History of hypocalcemia, hypercalcemia • History of renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, or cerebral disease within 3 mo • Travel to sunny climate without sunscreen during 1 mo of the study start	Primary: Vitamin D status Secondary: Erythema	Start date: March 2011 Completion date: February 2014 Primary completion date: February 2014

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Trial Identifier	Principal Investigator Center Country	Study Design/Surgery Type Intervention/Duration	Sample Size (N) Eligibility Criteria	Outcomes (Primary and Secondary)	Start and Completion Dates
Randomized Studies					
NCT01138475 First received: June 4, 2010 Last updated: August 11, 2016 Last verified: August 2016	Kerstyn Zalesin, MD William Beaumont Hospitals Royal Oak, Michigan, United States	Study design: Randomized, double-blind parallel assignment Surgery type: RYGB Intervention: Group 1: paricalcitol 1 μg by mouth daily Group 2: cholecalciferol 5000 IU by mouth daily Group 3: placebo inactive substance, 1 capsule daily Duration: 6 wk	N: 55 Inclusion criteria: • After RYGB (>6 wk and ≤5 y) • >18 y • Negative pregnancy test for women • Normal serum levels of calcium, phosphorous, albumin, iPTH Exclusion criteria: • Vitamin D treatment or allergy to vitamin D • Pregnancy or lactating women • Renal disease or stones • History of hypercalcemia, hyperphosphatemia, or primary hyperparathyroidism • Malignancy within less than 1 year (except nonmelanoma skin cancer) or any history of bone metastasis • Comorbid conditions (malignancy, liver disease) with a life expectancy <1 y • Use of another investigational drug • Poorly controlled hypertension • Drugs affecting the bone or immunosuppressant therapy, steroids, inhibitors or inducers of cytochrome • HIV positive	Primary: Change from baseline in iPTH over 6 wk Secondary: Vitamin and mineral levels and laboratory surveillance	Start date: July 2010 Completion date: August 2015 Primary completion date: August 2015

			• History of drug or alcohol abuse, liver or kidney transplant • History of CVA within the last 3 mo		
NCT02212652 First received: August 6, 2014 Last updated: August 29, 2016 Last verified: August 2016	Kimberley E Steele, MD, PhD Johns Hopkins University United States	Study design: Randomized, double-blind parallel assignment Surgery type: RYGB Vertical SG Intervention: Group 1: vitamin D_3 chewable gels 10,000 IU daily Group 2: placebo, gummy button Duration: Intervention duration: 30 d Study duration: 1 y	N: 70 Inclusion criteria: • RYGBP or vertical SG • 18–64 y of age • BMI of 35–49.9 kg/m^2 • Serum 25(OH)D concentration <30 ng/mL preoperatively Exclusion criteria: • Dietary restriction for beef gelatin • Expected poor compliance with the medical regimen • Medical conditions that could jeopardize the safety of the subject or the integrity of the study • Pregnancy	Primary: Improved postoperative serum 25(OH)D concentration Secondary: • Adverse surgical outcomes[a] • Clinical outcomes[b]	Start date: January 2017 Estimated primary completion date: April 2020
NCT02477956 First received: May 12, 2014 Last updated: June 22, 2015 Last verified: June 2015	David Syn, MD Texas Tech University Health Sciences Center United States	Study design: Randomized, single-blind (investigator), parallel assignment Surgery type: Bariatric surgery (type not specified) Intervention: Dietary supplement: vitamin D_3 (Replesta) 2 tablets (100,000 IU/mo) Active comparator: control, standard vitamin D Duration: 6 mo	N: 31 Inclusion criteria: • Morbidly obese and eligible for bariatric surgery Exclusion criteria: • <18 and >60 y of age • Increased serum vitamin D and calcium levels • Pregnant and lactating women	Primary: Difference in mean serum 25(OH)D level between groups	Start date: November 2012 Completion date: December 2013 Primary completion date: November 2013

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Trial Identifier	Principal Investigator Center Country	Study Design/Surgery Type Intervention/Duration	Sample Size (N) Eligibility Criteria	Outcomes (Primary and Secondary)	Start and Completion Dates
NCT02483026 First received: April 18, 2015 Last updated: March 6, 2017 Last verified: March 2017	Ram Elazary, MD Head bariatric surgeon Hadassah Ein Cerem Medical Center Israel	Study design: Randomized, double-blind parallel assignment Surgery type: SG Intervention: Supplements care 6 wk presurgery Group 1: multivitamin and vitamin D Group 2: placebo and vitamin D (dose NA) Duration: 1 y	N: 250 Inclusion criteria: • SG • BMI >35 kg/m^2 with comorbidity or >40 kg/m^2 • Vitamin D deficiency before surgery Exclusion criteria: • Previous bariatric surgery • Psychiatric illness • Endocrine problem that affects the weight that is unbalanced • Chronic kidney disease, nephrolithiasis • Metabolic bone disease before surgery, calcium disorders • Pregnancy, breastfeeding • Medications or disease affecting calcium or bone metabolism • Nutritional supplements 2 wk before the study	Primary: Bone density by DXA 1 y after surgery Secondary: • Weight (kg), % excess weight loss • 25(OH)D level (ng/mL) • Vitamin B_{12} level (pg/dL) • Iron level (μg/dL) • PTH level (pg/mL) • Folate level (ng/mL)	Anticipated start date: May 2017 Estimated completion date: October 2019 Estimated primary completion date: October 2018

NCT02817256 First received: June 19, 2016 Last updated: June 26, 2016 Last verified: June 2016	Juma Alkaabi, MD College of Medicine and Health Sciences, United Arab Emirates University United Arab Emirates	Study design: Randomized, double-blind parallel assignment Surgery type: SG Intervention: Group 1: ergocalciferol 300,000 IM every 3 mo; oral, vitamin B_{12} tablets daily (500 μg) calcium/D tables 600–200 mg, iron preparation (47 mg) daily Group 2: ergocalciferol 50,000 IU once every 2 wk, vitamin B_{12} 1000 μg IM every 3 mo, calcium/D tablets 600–200 mg, iron preparation (47 mg) daily Duration: 1 y	N: 105 Inclusion criteria: • 18–60 y • No medical or psychiatric contraindications • BMI>35 kg/m^2 with comorbidities or BMI >40 kg/m^2 before the bariatric surgery Exclusion criteria: • Micronutrient deficiency that requires treatment • Documented poor compliance • Inflammatory bowel disease, malignant or debilitating medical conditions • Hemoglobinopathies or pernicious anemia • Renal stones or history of hypercalcemia • Significant long-standing medical complications that affect micronutrient status • Severe psychiatric illness • Women who are lactating, pregnant, or planning pregnancy	Primary: Change in iron level Secondary: Complications resulting from IM injections Change in level of uric acid, calcium, vitamin A, vitamin D, serum folate, vitamin B_{12}, serum methyl malonate	Start date: October 2016 Estimated completion date: November 2018 Estimated primary completion date: November 2017

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Trial Identifier	Principal Investigator Center Country	Study Design/Surgery Type Intervention/Duration	Sample Size (N) Eligibility Criteria	Outcomes (Primary and Secondary)	Start and Completion Dates
NCT02686905 First received: February 4, 2016 Last updated: September 29, 2016 Last verified: September 2016	Rebecca McDorman, graduate student California State Polytechnic University, Pomona United States	Study design: Randomized, double-blind parallel assignment Surgery type: RYGB Vertical SG Intervention: Group 1: • PatchMD Vitamin D_3/Calcium Patch • PatchMD Multivitamin Patch • PatchMD B12 Energy Plus Patch Group 2: • Chewable Multivitamin with Iron • Chewable calcium • Quick Dissolve B_{12} (dose NA) Duration: 3 mo	N: 30 Inclusion criteria: • Vertical SG or gastric bypass • Nonpregnant women Exclusion criteria: • Metal objects in the body • Weight >270 kg (600 lb) • Revision surgery	Primary: Glucose (mg/dL) Calcium (mg/dL) Ferritin (ng/mL) B_{12} (pg/mL) Vitamin D (ng/mL) Hemoglobin A1c (%) Fat mass (kg) Weight (kg); Waist circumference (cm) Hip circumference (cm) Stadiometer measurement (cm) Total body water (kg)	Study date: January 2016 Estimated completion date: June 2017 Estimated primary completion date: June 2017

Abbreviations: CVA, cerebrovascular accident; HIV, human immunodeficiency virus; iPTH, intact PTH; UV, ultraviolet.
A search was conducted on August 11 for all trials completed before 2017, and no results were published.

[a] Surgical site infection, wound separation and dehiscence, anastomotic leak, prolonged length of hospital stay (>3 days), and readmittance to the hospital within 30 days postoperatively.

[b] Wound healing, weight loss, nutritional status, resolution of comorbidities, and other key markers of health, such as vital signs (eg, fever, blood pressure, heart rate, pain) and return of a regular menstrual cycle.

Data from ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) (March 2017); search strategy: vitamin D AND (bariatric surgery gastric bypass OR sleeve gastrectomy OR gastric banding OR weight loss surgery.)