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Vitamin D and Intestinal Calcium Transport After Bariatric Surgery

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Abstract

Bariatric surgery is a highly effective treatment for obesity, but it may have detrimental effects on the skeleton. Skeletal effects are multifactorial but mediated in part by nutrient malabsorption. While there is increasing interest in non-nutritional mechanisms such as changes in fat-derived and gut-derived hormones, nutritional factors are modifiable and thus represent potential opportunities to prevent and treat skeletal complications. This review begins with a discussion of normal intestinal calcium transport, including recent advances in our understanding of its regulation by vitamin D, and areas of continued uncertainty. Human and animal studies of vitamin D and intestinal calcium transport after bariatric surgery are then summarized. In humans, even with optimized 25-hydroxyvitamin D levels and recommended calcium intake, fractional calcium absorption decreased dramatically after Roux-en-Y gastric bypass (RYGB). In rats, intestinal calcium absorption was lower after RYGB than after sham surgery, despite elevated 1,25-dihyroxyvitamin D levels and intestinal gene expression evidence of vitamin D responsiveness. Such studies have the potential to shed new light on the physiology of vitamin D and intestinal calcium transport. Moreover, understanding the effects of bariatric surgery on these processes may improve the clinical care of bariatric surgery patients.

Keywords

bariatric surgery; gastric bypass; sleeve gastrectomy; calcium; vitamin D; malabsorption

1. Introduction

As obesity has reached epidemic proportions, surgical weight loss (bariatric surgery) has become increasingly common. Bariatric surgery produces marked and durable weight loss, shown to persist through 15 years' follow-up [1,2]. Obesity comorbidities improve

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postoperatively, and mortality declines [1,3–5]. As these benefits became apparent, the estimated annual number of bariatric operations performed in the US rose almost 10-fold from 1998 to 2009 (from 25,000 to 220,000) [6], fueled by surgical advances and decreased complication rates, and surgery has maintained its popularity. The most commonly performed procedures at this time are the Roux-en-Y gastric bypass (RYGB) and the sleeve gastrectomy, followed at a distance by the adjustable gastric band and, still less frequently, the biliopancreatic diversion with or without duodenal switch [7,8].

Despite its metabolic benefits, bariatric surgery has negative skeletal effects [9,10]. This is most clearly documented for RYGB. RYGB results in impressive increases in bone turnover, with numerous studies documenting doubling and even tripling of biochemical markers of bone resorption; markers of bone formation increase but to a lesser extent, indicative of net bone loss [10]. Bone mineral density (BMD) decreases after RYGB, with one-year declines of 5% to 11% consistently reported at the proximal femur by dual-energy X-ray absorptiometry (DXA), and declines of 3% to 7% reported at the spine by DXA and quantitative computed tomography (QCT) in some—although not all—studies [11–15]. The extent to which BMD declines after sleeve gastrectomy is uncertain, due to a paucity of studies, and the skeletal effects of gastric banding appear to be attenuated compared to RYGB [9,10]. On a microstructural level, cortical thickness decreases and cortical porosity increases at the appendicular skeleton after RYGB, and estimated bone strength declines [16]. Concerns about bone fragility have been corroborated by recent reports that fracture risk is higher after bariatric surgery, with the increased risk driven predominantly by RYGB [17–19].

The negative skeletal effects of bariatric surgery are presumably multifactorial [20–23]. Candidate mechanisms include the mechanical unloading of the skeleton with weight loss, sensed and orchestrated by the osteocyte; changes in levels of fat-secreted hormones (adipokines) and sex steroids; loss of muscle mass, which is the primary source of anabolic mechanical stimuli for bone; changes in levels of gut-derived hormones; potential effects of bone marrow adipose tissue; and nutritional factors, including vitamin D deficiency, inadequate calcium intake, and calcium malabsorption.

This review summarizes and discusses vitamin D status and intestinal calcium absorption after bariatric surgery. It begins with a review of normal intestinal calcium transport, including recent advances in our understanding of its regulation by vitamin D. Human and animal studies of bariatric surgery have the potential to shed new light on these processes and, more broadly, on the control of calcium homeostasis. Moreover, understanding vitamin D and calcium absorption after bariatric surgery may lead to improved clinical care for bariatric surgery patients. While there is increasing interest in the non-nutritional mechanisms of negative skeletal effects of bariatric surgery [20–22], such as changes in levels of fat-derived and gut-derived hormones, nutritional factors are modifiable and thus represent potential opportunities for the prevention and treatment of skeletal complications.

2. Intestinal calcium transport: Normal physiology

Calcium plays a crucial role in numerous biological processes, ranging from muscle contraction and protein secretion to neuronal excitability and blood clotting [24]. These processes require that the serum ionized calcium concentration be maintained within a narrow range, and contributions from the intestine, kidney, and skeleton make this possible. Adequate intestinal absorption is essential for calcium acquisition. Adaptations in renal reabsorption assist to maintain calcium balance, with the kidneys typically reabsorbing most of the filtered calcium. The skeleton is the body's major calcium reservoir, and while normal calcium balance involves equivalent amounts of calcium released by bone resorption as deposited by bone formation, bone resorption may increase if needed to maintain the serum calcium concentration. However, when excess resorption occurs, it occurs at the expense of bone mass and quality. Calcium homeostasis is regulated primarily by parathyroid hormone (PTH) and 1,25-dihyroxyvitamin D [1,25$(OH)_2$D] [25]. A reduction in serum calcium concentration stimulates release of PTH from the parathyroid glands, which enhances calcium reabsorption in the kidney and bone resorption. PTH also stimulates the conversion of 25-hydroxyvitamin D [25(OH)D] to 1,25$(OH)_2$D, which in turn enhances intestinal calcium absorption. 1,25$(OH)_2$D may have direct effects on bone as well, increasing resorption and inhibiting bone matrix mineralization [26]. Together, these measures return the serum calcium concentration to normal.

Intestinal calcium transport occurs through an active, energy-dependent, saturable (presumably transcellular) pathway as well as through a passive, diffusional, nonsaturable (presumably paracellular) pathway [27]. The active, transcellular pathway predominates in the setting of low calcium intake, while passive, paracellular transport increases in importance in the setting of high calcium intake. Active, transcellular transport involves three steps [28], for which the molecular mechanisms have become better elucidated in recent years [29]: 1) entry of luminal calcium into the intestinal cell through the apical calcium channel transient receptor potential vanilloid type 6 (TRPV6); 2) binding to the calcium binding protein calbindin-D_{9k} and diffusion across the cytosol; and 3) extrusion of calcium across the basolateral membrane and into the blood by the intestinal plasma membrane calcium ATPase (PMCA1b).

Active, transcellular calcium transport is primarily regulated by 1,25$(OH)_2$D, which induces TRPV6, calbindin-D_{9k}, and PMCA1b. Intestinal calcium absorption is decreased in Vitamin D receptor *(Vdr)*-null mice, fueling the development of rickets [30–32]; these mice display reduced intestinal TRPV6 and Calbindin-D9k mRNA [32]. However, these specific targets of 1,25$(OH)_2$D do not seem to be absolutely necessary for active, transcellular calcium transport [33–35], indicating that the molecular actions of 1,25$(OH)_2$D on the intestine are complex and include redundancy. Indeed, recent genome-wide analyses revealed a whole network of intestinal genes and their regulatory components involved in 1,25$(OH)_2$D-mediated calcium absorption in mice [36], and a recent study of growing mice reported additional genes modulating calcium absorption in the setting of low calcium intake [37]. In animal models and in humans, transcellular absorption capacity is increased in the setting of habitually low calcium intake, due to increased PTH secretion and activation of 1,25$(OH)_2$D, provided that there is sufficient substrate 25(OH)D [38]. Early human studies

noted, however, that the ability to adapt to low calcium intake decreases with age [39–42]. Other hormonal regulators of transcellular calcium transport include estrogen [43], growth hormone [44], and glucocorticoids [45].

Dietary factors influencing calcium absorption besides calcium intake include intakes of fat and fiber [46–48]. In addition, in the setting of achlorhydria (reduced gastric acidification), fasting absorption of certain forms of calcium is diminished. In 11 fasting subjects with achlorhydria, using a modified dual isotope method, Recker demonstrated mean fractional calcium absorption of 45% ±13% with calcium citrate vs. 4% ±2% with calcium carbonate [49]. In contrast, in 9 fasting normal subjects, mean absorption was not different for calcium citrate vs. carbonate (24% ±5% vs. 23%±11%). When the subjects with achlorhydria consumed the calcium carbonate with a meal, calcium absorption was 21% ±6%, within normal range. However, studies of gastric acid-reducing medications have not shown a clear effect on calcium absorption [50,51], and so the clinical significance of achlorhydria is uncertain.

In passive, paracellular calcium transport, calcium diffuses across tight junctions and intercellular spaces [52]. This process is non-saturable and directly related to the concentration of calcium in the intestinal lumen, thus it increases and achieves particular importance when calcium intake is high. Paracellular diffusion is also influenced by sojourn time through the intestinal tract. Therefore, the ileum's contribution in the setting of high calcium intake is impactful given that the time ingested calcium spends in the ileum is longer than for other intestinal segments [27]. While paracellular transport has traditionally been thought to be independent of vitamin D, recent research has revealed regulation by $1,25(OH)_2D$ [27,29]. For example, $1,25(OH)_2D$ appears to induce specific intestinal claudins, which are major components of tight junctions [36,53]. The vitamin D dependence of paracellular transport is much less defined than that of transcellular transport, and additional research in this area is needed.

Overall, on average, approximately one-third of a typical dietary calcium load is absorbed by the human gut [27], but the actual fraction of calcium absorbed depends on the amount of that "typical" load and on factors discussed above including vitamin D status, age, and calcium solubility (*e.g.,* pH of the intestinal lumen). Because passive, paracellular transport is non-saturable, its relative contribution to the total absorbed calcium increases with increasing calcium intake. In contrast, with low calcium intake, less diffusional transport occurs, but the efficiency of the active, transcellular process is augmented by increased secretion of PTH and production of $1,25(OH)_2D$.

Considerable discussion and debate has focused on the locations in the intestine at which active, transcellular calcium transport vs. passive, paracellular calcium transport occur, and on the relative importance of the two processes [54–56]. Uncertainty has stemmed in part from the evolution of evidence about $1,25(OH)_2D$ influence on paracellular transport (described above), and also from the extent to which $1,25(OH)_2D$-mediated transcellular transport happens in the distal small intestine and colon. Active, transcellular transport is prevalent in the duodenum and jejunum (proximal small intestine), has been thought by some not to occur in the ileum, and occurs to a small extent in the colon, while paracellular

transport occurs throughout the gut [27]. However, some have challenged the notion that active, transcellular transport is absent in the ileum and of limited importance in the colon [56–58], and new experiments provide additional evidence in this regard. It was known that transgenic expression of *Vdr* in the intestine of otherwise *Vdr*-null mice prevents the abnormal calcium homeostasis and bone defects of the *Vdr*-null state [59]. Recently, transgenic mice were generated with *Vdr* expression exclusively in the ileum, cecum, and colon (and otherwise *Vdr*-knockouts). Even just this distal intestine *Vdr* expression prevented the disrupted calcium metabolism and skeletal phenotype of the *Vdr*-null mouse [60]. This either suggests that meaningful active, transcellular transport occurs in the ileum, cecum, and colon, or it reflects $1,25(OH)_2D$ involvement in paracellular transport. In another recent study, transgenic mice with *Vdr* deletion from the large intestine and kidneys had reduced TRPV6 and Calbindin-D9k mRNA expression in the colon, four- and threefold greater expression in the duodenum, and modestly lower femoral bone density [61]. This suggests that colonic *Vdr* impacts whole-body calcium metabolism, although the duodenum may be able to compensate in part for colonic and kidney *Vdr* deletion. Additional studies are needed to better understand the mechanisms of calcium absorption in different segments of the intestine.

3. Bariatric surgical procedures

Operations for weight loss may restrict food intake, cause the malabsorption of nutrients, and induce neurohormonal effects that change energy balance. A number of bariatric surgical procedures have been developed, and each produces weight loss through one or more of these basic mechanisms [62]. The most commonly performed operations at this time are the RYGB and the sleeve gastrectomy [7,8], and this review will focus on those procedures, with most emphasis on the RYGB.

The RYGB procedure involves first the creation of a small gastric pouch (less than 30 mL), which restricts caloric intake. The small intestine is divided at the midjejunum, and the distal portion is anastomosed to the gastric pouch to create the Roux limb, also called the alimentary limb. Food thus travels from the gastric pouch directly into the midjejunum and does not come in contact with the duodenum or proximal jejunum. The proximal small intestine (the bypassed portion, which carries secretions from the pancreas, liver, and gastric remnant) is connected 75 to 150 cm distally from the gastrojejunostomy, creating a biliopancreatic limb. Postoperatively, digestion and absorption of nutrients largely occur in the resulting common channel, where ingested food mixes with bile and pancreatic enzymes [63].

Sleeve gastrectomy involves the resection of about 80% of the body of the stomach, leaving a narrow gastric tube to serve as an alimentary conduit [62]. The intestine is not altered surgically.

4. Vitamin D and bariatric surgery

Vitamin D is produced by the skin upon exposure to sunlight, and it is acquired from the diet and from dietary supplements [64]. The intestinal absorption of fat-soluble micronutrients,

including vitamin D, depends on processes responsible for fat absorption and metabolism. After RYGB, because ingested food and supplements do not mix with bile and pancreatic enzymes until the Roux limb and biliopancreatic limbs of the intestine join to form the common channel (see Section 3), malabsorption of vitamin D may occur. In addition, overall dietary intake is severely restricted after RYGB, so consumption of vitamin D-containing foods may decrease [65].

RYGB-induced problems with vitamin D intake and absorption may be compounded by the high prevalence of vitamin D insufficiency or deficiency in morbid obesity. An inverse relationship between body mass index (BMI) and 25(OH)D level is very well documented [66–68] and largely attributed to volumetric dilution of the fat-soluble vitamins in adipose tissue [69,70]. Lifestyle factors such as sun exposure may play a role. Further, it has been shown that obese women have decreased expression of enzymes involved in 25-hydroxylation and 1α-hydroxylation in adipose tissue compared to lean women [71], suggesting that vitamin D metabolism may be impaired in obesity. Regardless of the mechanism, many undergoing RYGB may have suboptimal vitamin D status even preoperatively.

Indeed, in studies of obese individuals preparing for bariatric surgery, mean preoperative 25(OH)D levels are consistently below 30 ng/mL and often below 20 ng/mL [72]. After RYGB, prevalence of vitamin D insufficiency or deficiency remains high [65,72], although reported prevalence varies substantially due to heterogeneity in approach to postoperative supplementation. Even at a given supplement dose, response to supplementation is highly variable after RYGB [65,72], with some individuals achieving 25(OH)D levels above 30 ng/mL on just 400 IU daily while others require 50,000 IU daily or more. As a result, professional organizations recommend repletion of low 25(OH)D levels preoperatively and routine vitamin D supplementation postoperatively, then surveillance of 25(OH)D levels with adjustment of supplement dose as needed [73–75].

One might assume that vitamin D insufficiency or deficiency would not be a postoperative complication of sleeve gastrectomy, as the intestinal, biliary, and pancreatic anatomy remains intact after that operation. However, deficiencies do occur postoperatively [72,76,77], likely because those undergoing sleeve gastrectomy may have suboptimal vitamin D status preoperatively and then are subject to restricted dietary intake postoperatively. Because of this uncertainty, clinical guidelines about vitamin D supplementation and monitoring after sleeve gastrectomy are extremely limited at this time [73–75,78].

5. Intestinal calcium transport after bariatric surgery

5.1 Roux-en-Y gastric bypass

Based on the altered anatomy and physiology after RYGB (Sections 3 and 4) and on what is understood about normal intestinal calcium transport (Section 2), one might hypothesize that intestinal calcium absorption capacity would be substantially impaired after RYGB. First of all, vitamin D insufficiency or deficiency may limit $1,25(OH)_2D$-mediated calcium transport. In addition, the bypassed duodenum and proximal jejunum, which are usually the

predominant sites of active, transcellular calcium transport, no longer come into contact with food or supplements after RYGB. Thus, direct malabsorption of calcium may result, independent of vitamin D status. Further, calcium absorption could be impaired due to achlorhydria from the operation itself and from the common use of proton pump inhibitors for the prevention of marginal ulcers [79,80]. Alternatively, one might hypothesize that sufficient calcium absorption capacity could be maintained after RYGB, if vitamin D status and calcium intake are robust. As detailed in Section 2, there may be meaningful active, transcellular, $1,25(OH)_2D$-mediated calcium transport in the distal intestine [56,60], and moreover, non-saturable diffusion of calcium by paracellular transport occurs throughout the length of the gut [27].

5.1.1 Human studies—Riedt and colleagues used dual stable isotope methodology to assess intestinal fractional calcium absorption before and 6 months after RYGB in 21 obese women [81]. Mean weight loss was 39 kg over the 6 months, and mean ± standard deviation (SD) fractional calcium absorption declined from 36% ±8% to 24% ±9%. This study was important for documenting a postoperative decrease in intestinal calcium absorption capacity and also for examining potential causes for the decrease. However, post-operative calcium intake was highly variable, with mean less than 1000 mg. In addition, over half of the women had 25(OH)D levels less than 25 ng/mL, and while it is uncertain below which 25(OH)D level calcium absorption is affected, it is possible that vitamin D deficiency might have influenced calcium absorption for some women. Thus, it remained unclear to what extent the portion of the intestinal tract still in contact with food and supplements can participate in active and passive calcium transport.

To address that gap in knowledge, we determined the effects of RYGB on fractional calcium absorption before and 6 months after RYGB in 33 obese women and men, in the setting of a goal 25(OH)D level of at least 30 ng/mL and calcium intake of 1200 mg daily [15]. We expected that by maintaining the robust vitamin D status and controlled calcium intake, we would mitigate postoperative declines in calcium transport.

As reported previously [15], women and men 25–70 years old were enrolled as they were scheduled for RYGB procedures. Upon enrollment, low 25(OH)D levels were repleted to a target level ≥30 ng/mL, and based on dietary intake, total daily calcium intake was brought to 1200 mg through personalized dosing of a calcium citrate supplement. Postoperatively, 25(OH)D levels and dietary calcium intake were monitored, and each participant's supplement doses were adjusted to maintain the study goals. Fractional calcium absorption was measured preoperatively and 6 months post-operatively with a dual stable isotope technique [82], with one stable calcium isotope administered orally to label dietary calcium (a 10 mg dose of oral calcium-44 administered in the middle of a standardized test breakfast) and another stable calcium isotope (a 3 mg dose of calcium-43) administered intravenously to measure calcium removal from the blood. Blood was drawn 24 hours later, and isotope enrichment was determined by mass spectrometry. Fractional calcium absorption was determined as the ratio of oral to IV isotope in the blood sample, adjusted for the dose of each isotope.

Mean weight loss over 6 months was 33 kg, which was a mean 26% of preoperative weight. Median 25(OH)D levels, following individualized vitamin D repletion and supplementation, were 41 ng/mL preoperatively and 37 ng/mL postoperatively (Table). Preoperatively, mean fractional calcium absorption was 33% ±14%, within the range expected for a group of mostly middle-aged women [46,83]. Postoperatively, fractional calcium absorption decreased precipitously to a mean of 7% ±4% (Figure 1). Given that total daily calcium intake (from diet plus supplements) was 1200 mg at both time points, mean total daily absorbed calcium decreased from 392 ±168 mg to 82 ±45 mg [15].

Consistent with the intestinal calcium absorption decline, calciotropic hormone levels and urinary calcium excretion changed (Table). Median (interquartile range) PTH increased from 41 (32–53) pg/mL preoperatively to 48 (39–59) pg/mL postoperatively ($p=0.02$), and $1,25(OH)_2D$ increased from 37 (34–46) pg/mL to 51 (41–63) pg/mL ($p<0.001$). Median 24-hour urinary calcium decreased from 191 mg to 109 mg ($p<0.001$) [15].

It is unclear why we observed a more dramatic decline in fractional calcium absorption than Riedt and colleagues, and potential explanations include differences in isotope methodology or surgical approach [15,81]. We used higher stable isotope doses than Riedt and colleagues, and we used the same isotope doses preoperatively and postoperatively, whereas they used variable, weight-based doses. Surgical Roux limb length (*i.e.,* distance from gastric pouch to the junction with biliopancreatic secretions) was roughly similar between studies, but we cannot rule out differences in biliopancreatic limb length (*i.e.,* the length of proximal jejunum bypassed), as that length is not as precisely measured and documented during the operation. If biliopancreatic limb length is longer at our institution, and if the most proximal portion of the jejunum is crucial for calcium absorption, that might help explain the lower postoperative calcium absorption in our study. The dramatic decline we documented is reminiscent of the results of early studies of calcium absorption after jejunoileal bypass, an older bariatric operation [84,85]. It is clear, though, that maintaining robust vitamin D status and calcium intake after RYGB does not mitigate the fractional calcium absorption decline.

Both RYGB studies utilized a rigorous dual stable isotope technique that assessed calcium absorption capacity over 24 hours, a time period ample for the complete absorption of calcium in the normal gastrointestinal tract (small intestine and colon) [86]. RYGB patients have been shown to have orocecal transit times similar to obese controls, with a median 3 hours for ingested material to reach the beginning of the colon [87]. Calcium thus spends the majority of a 24-hour post-ingestion period in the colon and should have ample time for passive absorption. While some human calcium absorption studies in the past used test meals with small calcium loads in order to look specifically at active, transcellular absorption [39,41], both RYGB studies used robust test meal calcium loads (≥200 mg) in order to examine passive absorption as well.

Given the profound physiologic changes induced by RYGB, both RYGB studies sought to identify potential determinants of the calcium absorption impairment. We found that participants with greater percentage weight loss had greater declines in calcium absorption [15]. This association might be confounded by surgical approach, if those with more intestine bypassed experienced more weight loss and also a greater impact on calcium

absorption. Alternatively, this finding may be consistent with studies demonstrating that nonsurgical weight loss results in a decline in fractional calcium absorption compared to weight maintenance [88,89]. For example, in one study, 82 overweight or obese postmenopausal women were recruited for diet protocols designed for weight maintenance or weight loss (with a mean achieved weight loss of 3.8% over 6 months) [89]. Women were randomly assigned to vitamin D supplement vs. placebo administration (2500 IU vs. 400 IU daily) during the 6-month dietary intervention period. Fractional calcium absorption assessed by dual stable isotopic tracers decreased modestly during weight loss compared to weight maintenance, and increased modestly with vitamin D compared to placebo, with absolute fractional calcium absorption changes from baseline −2.6% ±3.7% (weight loss/placebo), −0.3% ±3.0% (weight maintenance/placebo), −0.6% ±3.7% (weight loss/vitamin D), and +3.7% ±4.9% (weight maintenance/vitamin D) [89].

After RYGB, Riedt and colleagues observed that postoperative estradiol and $1,25(OH)_2D$ levels correlated with fractional calcium absorption [81]. In our RYGB study, we observed correlations with other parameters that reflect weight loss, but otherwise we did not find evidence that the extent of changes in particular hormone levels (*e.g.* estradiol and IGF-1) or nutrient intakes was important. We suspect that the dramatic surgical alteration to the intestinal tract might have eclipsed subtle contributions from other factors.

Biochemical markers of bone turnover increased dramatically after RYGB, with a near tripling of the bone resorption marker serum C-telopeptide (CTx) over the 6 postoperative months (Table) [15]. Areal BMD decreased at the proximal femur, with a mean decrease of 4.6% at the femoral neck, and spinal volumetric BMD by QCT declined by 6.5%. Participants with greater percentage declines in fractional calcium absorption or lower post-op fractional calcium absorption had greater increases in CTx (Figure 2). We did not find a statistically significant correlation between the extent of the declines in calcium absorption and BMD, likely because other factors were also affecting BMD, and potentially because a period longer than 6 months is required for the full manifestation of calcium absorption effects. Participants with greater increases in PTH did have greater declines in femoral neck BMD.

The key aspects of calcium homeostasis (Section 2) thus appear to be reflected in the observations from our RYGB study (Figure 3): Impaired intestinal calcium absorption after RYGB threatened serum calcium concentration, which increased PTH secretion. PTH enhanced renal calcium reabsorption (decreasing urinary calcium excretion), and it stimulated conversion of 25(OH)D to $1,25(OH)_2D$, but even with sufficient 25(OH)D, the $1,25(OH)_2D$ was unable to bring intestinal calcium absorption capacity back to a normal level. PTH also increased bone resorption as another measure to maintain serum calcium concentration, perhaps in conjunction with direct skeletal effects of $1,25(OH)_2D$, likely contributing to the observed decline in bone mass.

One might find it curious that while there was a statistically significant rise in PTH level following RYGB in our study, PTH did not rise more dramatically in light of the dramatic decline in intestinal calcium absorption. Nordin and colleagues have argued that calcium deficiency (whether due to low intake or low absorption) does not cause secondary

hyperparathyroidism *per se* based on fasting PTH levels; rather, it prevents the fall in PTH that normally occurs during the day in response to eating [90]. Studies of RYGB reporting counts of individuals with PTH levels above vs. within the normal range may thus miss an important physiological nuance. Moreover, PTH levels must rise only to the extent necessary to maintain normocalcemia. As discussed in Section 1, it is thought that a number of nutritional, mechanical, and hormonal changes increase bone resorption after RYGB [20–23], and the huge increases in biochemical markers of bone resorption noted consistently across studies make a multifactorial process likely. If non-PTH-mediated stimulation of bone resorption occurs due to mechanical unloading or changes in adipokine, sex steroid, or gut-secreted hormone levels, then enhanced mobilization of calcium from the skeleton will dampen the impetus for higher levels of PTH (Figure 3).

5.1.2 Animal studies—Several groups have evaluated the skeletal effects of RYGB using rodent surgical models and sham-operated controls [91–94]. All have used adult animals. Among these, Abegg and colleagues included assessment of net calcium absorption, determined as 24-hour [intake (mg) – fecal loss (mg)]/intake (mg)], as well as intestinal and renal gene expression studies [91]. The group's experiments were also unique in the inclusion of a sham-operated control group with food restriction to match the postoperative body weight of RYGB rats, in addition to a sham-operated ad lib diet control group. All rats were fed standard laboratory chow without calcium or vitamin D supplementation. RYGB rats had lower BMD by quantitative microCT than both sham-operated control groups, as well as impaired bone mass and structure by histomorphometry. Compared to the sham controls, RYGB rats had lower serum 25(OH)D levels. Two weeks after surgery, intestinal calcium absorption was lower in RYGB rats than sham controls. PTH levels were not significantly higher in RYGB rats than in sham controls, but there was increased renal expression of the vitamin D-activating enzyme 1-α-hydroxylase (CYP27B1) mRNA at the time of sacrifice, and serum $1,25(OH)_2D$ levels were more than twofold higher. In the intestine, TRPV6 mRNA expression was upregulated in the duodenum (in the biliopancreatic limb, excluded from nutrient flow) and, at far lower levels, in the jejunum (in the Roux limb, in contact with food but not bile or pancreatic enzymes). The investigators also detected TRPV6 mRNA expression in the ileum, albeit at low levels similar to those in the jejunum, and observed a trend towards increased ileal expression (in the common channel) [91].

If Abegg and colleagues had documented simply the low 25(OH)D levels and low net calcium absorption in RYGB rats compared to sham-operated controls, it would not have been possible to discern whether the impaired calcium absorption was due to vitamin D malabsorption or to a direct calcium malabsorption independent of vitamin D. However, by also demonstrating high $1,25(OH)_2D$ levels and high intestinal expression of TRPV6 mRNA (indicating intestinal responsiveness to $1,25(OH)_2D$), it seems that vitamin D deficiency is not the cause of the calcium malabsorption. Instead, it seems more likely that the proximal intestine's appropriate responsiveness to $1,25(OH)_2D$ was futile, since the proximal intestine was not in normal contact with food, and that active transport in other intestinal segments and passive, paracellular calcium transport were inadequate for compensation. (Standard chow without calcium supplementation might not have produced a sufficiently high luminal

calcium concentration.) The investigators speculate that with time, RYGB rats might have experienced an increase in passive absorption as the gut adapted to the altered surgical anatomy, which could explain why calcium absorption seemed to increase partially between 2 and 7 weeks postoperatively [91]. The investigators' conceptual model also includes a role for systemic chronic metabolic acidosis, which they observed in RYGB rats and hypothesize could have contributed to the high $1,25(OH)_2D$ levels; metabolic acidosis might also explain the unexpected finding of increased urinary calcium excretion in RYGB rats, and it might have contributed to the increased bone resorption and decreased bone mass observed. Metabolic acidosis after RYGB was also noted by one of the other groups to have studied skeletal outcomes in a rodent RYGB model [92].

Of note, Abegg and colleagues' finding of upregulated TRPV6 mRNA expression in RYGB rats is at odds with the one published human study to examine calcium transport proteins after RYGB. Elias and colleagues determined jejunal protein expression in 7 adults who underwent biopsy at the time of RYGB and then 6–8 months postoperatively by endoscopy (with biopsy of the Roux limb, in contact with food but not bile or pancreatic enzymes) [95]. VDR protein expression levels increased, but TRPV6 levels decreased; the authors attribute this to reduced levels of heat-shock protein 90β, a mediator of VDR signaling. Additional animal and human studies are required before conclusions can be drawn about effects of RYGB on calcium transport proteins.

5.2 Sleeve gastrectomy

The recent increase in popularity of sleeve gastrectomy is largely due to evidence that the procedure's lower invasiveness results in fewer complications than RYGB, including fewer nutritional deficiencies [96–98]. However, the specific effects of sleeve gastrectomy on calcium metabolism and skeletal health have not been defined.

Direct assessment of calcium absorption capacity (*i.e.,* determination of fractional calcium absorption using a dual stable isotope technique) has never been undertaken in sleeve gastrectomy patients. On the one hand, the intact intestine after sleeve gastrectomy would suggest unimpeded calcium absorption. On the other hand, vitamin D insufficiency or deficiency due to obesity or restricted dietary intake may limit $1,25(OH)_2D$-mediated calcium transport. Even if vitamin D status is optimized, sleeve gastrectomy diminishes gastric acidity, which may be compounded by postoperative proton pump inhibitor use. Further, sleeve gastrectomy produces marked weight loss, and as stated in Section 5.1.1, it has been shown that nonsurgical weight loss results in a decline in fractional calcium absorption compared to weight maintenance [88,89]. Hormonal determinants of calcium absorption capacity (*e.g.,* estrogen levels) may change with weight loss, and dietary determinants (*e.g.,* intakes of fat and fiber) change. All together, these phenomena might be sufficient to impair postoperative calcium absorption, but this hypothesis has not yet been tested.

6. Summary and future directions

Human and animal studies of bariatric surgery are opportunities to apply and test our understanding of intestinal calcium transport and its regulation by vitamin D. After RYGB,

the altered anatomy prevents the duodenum and proximal jejunum from participating in active, transcellular, $1,25(OH)_2D$-mediated calcium transport, resembling to some extent a proximal intestine-specific *Vdr* knockout animal model. In our human study, even with optimized 25(OH)D levels and recommended calcium intake, fractional calcium absorption decreased dramatically after RYGB [15]. In one study in rats, intestinal calcium absorption was lower after RYGB than after sham surgery, despite elevated $1,25(OH)_2D$ levels and increased expression of TRPV6 mRNA in the duodenum and jejunum, indicating intestinal vitamin D responsiveness [91].

These findings raise a number of questions and highlight directions for future research. Why are the distal small intestine and colon, which are still in contact with nutrient flow, unable to compensate adequately with active transport or passive diffusion? Additional studies should examine expression of calcium transport-related proteins including TRPV6 and also calbindin-D_{9k} and PMCA1b in various segments of the intestine. Does concurrent stimulation of bone resorption due to non-PTH- and non-$1,25(OH)_2D$-mediated factors, such as mechanical unloading or changes in adipokine, sex steroid, or gut-secreted hormones, enhance mobilization of calcium from the skeleton (Figure 3) and dampen the impetus for the even higher levels of PTH and $1,25(OH)_2D$ the intestine might need to overcome its altered anatomy? Do changes in colonic physiology after bariatric surgery—perhaps changes in colonic microbiota—mediate some of the decline in calcium absorption capacity?

Understanding vitamin D and intestinal calcium transport after bariatric surgery may result in improved clinical care for bariatric surgery patients. While there is increasing interest in the non-nutritional mechanisms of the negative skeletal effects of bariatric surgery [20–22], such as changes in levels of fat-derived and gut-derived hormones, nutritional factors are modifiable and thus may represent potential opportunities for the prevention and treatment of skeletal complications. The evidence to date suggests that even with optimized vitamin D status, RYGB patients may need high calcium intakes—higher than the 1200 mg daily our participants were given [15]—to prevent perturbations in calcium homeostasis. Reduced intestinal calcium absorption capacity may contribute to the well-documented decline in BMD after RYGB, and as sleeve gastrectomy becomes increasingly common, its effects on calcium absorption and skeletal health should be determined. Future research should establish the best approach to calcium and vitamin D supplementation after bariatric surgery and test interventions that might improve calcium bioavailability.

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Highlights

- Human and animal studies of bariatric surgery may shed new light on the physiology of vitamin D and intestinal calcium transport.
- Even with optimized vitamin D status and recommended calcium intake, fractional calcium absorption decreases after Roux-en-Y gastric bypass.
- Attention to calcium and vitamin D homeostasis after bariatric surgery may help prevent and treat potential skeletal complications of the procedures.

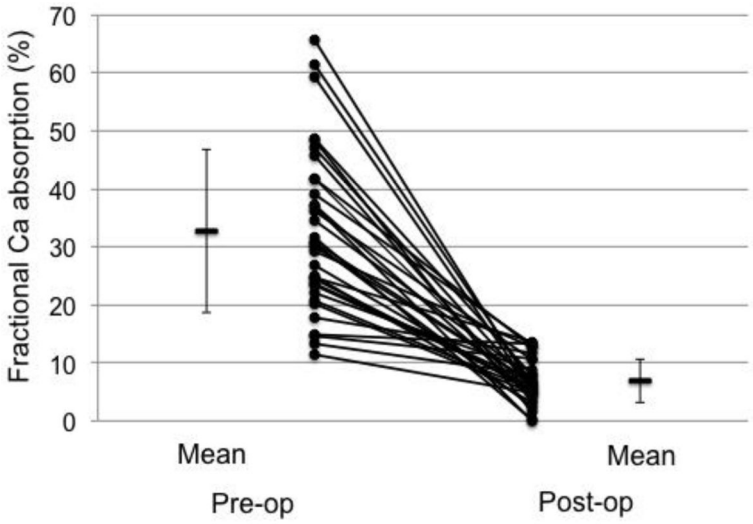

Fig. 1.

Intestinal fractional calcium absorption before and 6 months after Roux-en-Y gastric bypass surgery. Values are mean ± SD. Reproduced from Schafer et al. [15], by permission of John Wiley & Sons.

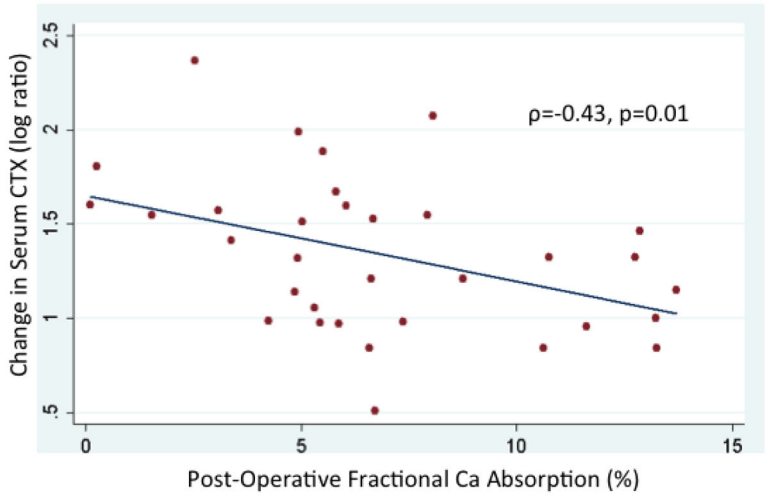

Fig. 2.

Correlation between fractional calcium absorption 6 months after Roux-en-Y gastric bypass surgery and change in serum CTx level. Reproduced from Schafer et al. [15], by permission of John Wiley & Sons.

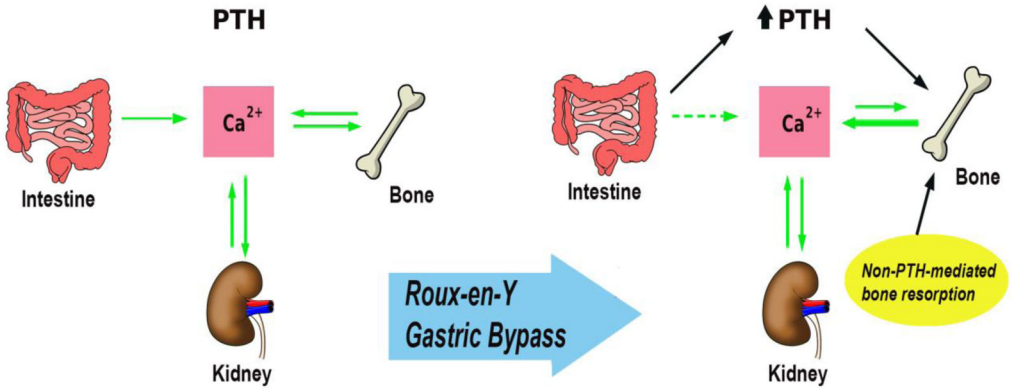

Fig. 3.

Effects of Roux-en-Y gastric bypass surgery on calcium homeostasis. After RYGB, impaired intestinal calcium absorption threatens serum calcium concentration, and PTH secretion increases. PTH enhances renal calcium reabsorption, stimulates conversion of 25(OH)D to $1,25(OH)_2D$, and increases bone resorption in order to maintain serum calcium concentration. There may be direct skeletal effects of $1,25(OH)_2D$ as well. Concurrent non-PTH-mediated stimulation of bone resorption likely occurs as well, due to factors such as mechanical unloading and changes in adipokine, sex steroid, and gut-secreted hormone levels, and the enhanced mobilization of calcium from the skeleton may dampen the impetus for greater PTH secretion.

Table

Intestinal calcium absorption and anthropometric, calcium homeostasis, and skeletal parameters, before and 6 months after Roux-en-Y gastric bypass surgery.

	Preoperative	Postoperative	p-value
Weight (kg)	125 ± 18	93 ± 14	<0.001
BMI (kg/m^2)	45 ± 7	33 ± 6	<0.001
Fractional Ca absorption (%)	33 ± 14	7 ± 4	<0.001
Total daily absorbed Ca (mg)	392 ± 168	82 ± 45	<0.001
25(OH)D (ng/mL)	41 (33–49)	37 (29–40)	<0.01
PTH (pg/mL)	41 (32–53)	48 (39–59)	0.02
1,25(OH)$_2$D (pg/mL)	37 (34–46)	51 (41–63)	<0.001
24-hour urinary calcium (mg)	191 (93–247)	109 (60–159)	<0.001
CTX (ng/mL)	0.293 (0.167–0.347)	0.975 (0.802–1.278)	<0.001
P1NP (ng/mL)	30.8 (25.1–42.7)	75.4 (55.5–91.7)	<0.001
Femoral neck areal BMD (g/cm^2)	0.973 ± 0.132	0.925 ± 0.110	<0.001
Spinal volumetric BMD (g/cm^3)	0.162 ± 0.040	0.152 ± 0.039	<0.001

Values are means ± SDs or medians (IQR). Adapted from Schafer et al. [15].