Impact of Roux-En-Y Gastric Bypass on Vitamin D and Iron Metabolism a Systematic Review Literature

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Abstract: There has been a steady rise in the number of individuals who are morbidly obese. The divided RYGB is the most commonly performed bariatric surgical procedure in the world and is considered the gold standard. Physicians need to be aware of the important peri-operative complications that can occur after gastric bypass. In addition, gastrointestinal physicians are seeing patients who seek advice and care for symptoms that develop or persist after RYGB. Physicians should be able to predict and manage most postoperative medical and nutritional disorders related to RYGB and should be prepared to assess patients for potential referral for surgical intervention or revision.

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Keywords: Roux-En-Y Gastric Bypass, Vitamin D and Iron Metabolism

1. Introduction

Obesity has become an important public health priority because it increases the risk of comorbid conditions, including diabetes, cardiovascular disease and several types of cancers. In addition, it affects life quality and expectancy (1). The impact of obesity on life expectancy has been well documented. Worldwide, over 2.5 million deaths annually can be attributed to obesity. Of particular concern is the growing economic burden that the care of obesity and its complications imposes on society and the health care system (2).

Over the past decades, Roux-en-Y gastric bypass (RYGB) has been a classical bariatric surgery with 85% of patients receiving this restrictive / malabsorptive procedure. (3-4)In this procedure, gastric capacity is reduced by 90–95%. However, adverse effects such as nutritional deficiencies and gastrointestinal symptoms have been observed following RYGB, including disturbances of anatomical and physiological functions. (5) A wide range of prevalence and severity of anaemia after RYGB surgery has been reported and the related causes are not yet fully understood. (6)

Vitamin D, the primary regulator of calcium metabolism in humans, maintains adequate calcium and phosphate levels required for bone formation—thereby enabling proper functioning of parathyroid hormone by promoting calcium absorption in the intestines. (7) Vitamin D deficiency has been described as a common cause of disorders of calcium metabolism and metabolic bone disease after weight loss surgery that can result in clinically significant long-term morbidity, leading to bone loss and possibly fractures.(8)

According to a recent report from the American Society of Hematology, people who have undergone bariatric procedures show the highest risk for anemia, with 33%-49% of operated patients presenting anemia within 2 years after surgery (9). As expected, the average prevalence of anemia is lower following LSG (17%) and reaches 45%-50% after RYGB and BPD. It should be noted that, as underlined for other nutrient deficiencies, up to 10%-12% of obese patients already have anemia before surgery (10); thus, baseline screening for anemia is recommended in all patients who are scheduled for bariatric procedures.

Aim of the Work

Systematic review on Impact of Roux-en-Y gastric bypass on vitamin D and Iron metabolism.

2. Materials and Methods

This systematic review is to evaluate the Impact of Roux-en-Y gastric bypass on vitamin D and Iron metabolism

- Pubmed, Medline, Googlescholar, Cochrane searches will be done on the following keywords:
  - Roux-en-Y Gastric bypass
  - Vitamin D deficiency
  - Iron deficiency anemia
  - Post Roux-en-Y mal-absorption syndrome
- Inclusion criteria for the search will include:

1. English literature only.
2. Human study only.
3. Randomized control trial & case series related to post-operative follow up of vitamin D and anemia post Roux-en-Y gastric bypass.

- The exclusion criteria for the search will include:

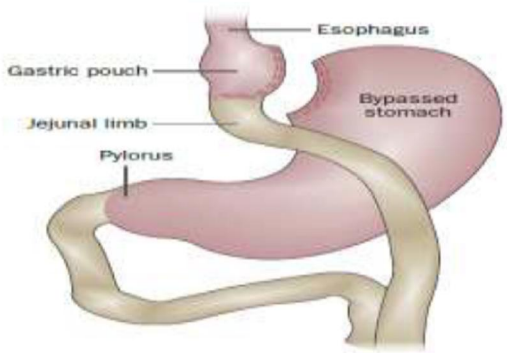
1. Duplicated articles by the same authors unless with longer follow-up studies.

2. Non English studies.

Articles in this study will include up to date the Impact of Roux-en-Y gastric bypass on vitamin D and Iron metabolism.

Roux-en-Y gastric bypass (RYGB)

Among the bariatric procedures, the RYGB (Figure 1) is currently the most commonly performed in the USA and Canada. With RYGB, the native stomach is divided completely using a surgical stapler—the resulting gastric pouch should provide a volume of less than 30 ml. The jejunum is then divided 30–70 cm distal to the native duodeno-jejunal junction. Use of an open versusa laparoscopic surgical technique can alter the site and orientation of the gastro-jejunal anastomosis. To facilitate the construction of the anastomosis and possibly decrease the risk of an anastomotic leak, anastomosis is now often constructed with the use of surgical staplers rather than being hand sewn. The location of the jejuno-jejunalanastomosis determines the length of the Rouxlimb, and, equally important, the length of the common channel that extends from this second anastomosis to the ileocecal valve. A short common channel (≤100 cm long) results in a more severe malabsorptive condition. The complexity of the RYGB surgical procedure means that there are serious and potentially preventable perioperative complications that physicians must be aware of. The increasing use of bariatric surgery means that, when consulted, gastrointestinal physicians should be able to assess and refer patients as appropriate. The worst-casescenario is the potential to overlook a life-threatening anastomotic leak or bowel strangulation secondary to aninternal hernia, so much so that some postoperative exploratory laparoscopy or laparotomy maybe justifiable, even if the findings are negative. Several complications are specific to bariatric surgery and to morbidly obese patients, who may respond or present differently symptomatically and systemically than non-obese individuals. When preoperative complications do occur, the best outcomes result from early diagnosis and aggressive treatment. When evaluating and managing the chronic complications and adverse effects of bariatric surgery, it is worth noting that RYGB alters both the anatomy and physiology of the stomach and small intestine. The approach to the recognition, expectation and/or prevention of chronic complications or adverse effects should, therefore, be based on a basic understanding of the effect of RYGB on gastric and intestinal function. This Review provides an overview of the complications and adverse effects of RYGB, discussing the spectrum of postoperative disorders for physicians who see patients postoperatively. As many of the sub-acute complications of RYGB are similar to the acute post-operative complications, it is important for gastrointestinal physicians to understand both the various presenting symptoms of these complications and the appropriate diagnostic approaches. The most serious symptoms including peritonitis, tachycardia, hypotension, vomiting, hemorrhage, fever, dyspnea, oliguria and diarrhea—are discussed individually below with their various presentations. With any of these post-operative disorders, the first priorityis to consider and exclude potentially life-threatening complications, including anastomotic leak, intestinal obstruction, wound problems, and postoperative emergencies, to avoid the serious morbidity of delayed diagnosis (and its potential medico-legal implications).



Picture 1 RYGB

Macronutrient and micronutrient disorders

Too rapid a weight loss induced by RYGB is not uncommon and occurs from inadequate calorie intake (owing to gastric restriction), possibly combined with a relative protein and fat malabsorption (dependent on the length of the common channel). The rapid phase of weight loss occurs within the first 6–12 months after RYGB in most individuals. Maintaining proper nutrition after RYGB is, therefore, a complex challenge currently facing physicians. The requirement for proper nutritional surveillance is especially important in those individuals who have undergone a malabsorptive bariatric procedure, such as a duodenal switch (a type of bilio-pancreatic diversion) or a distal gastric bypass. Despite the routine use of postoperative nutritional supplements, a substantial number of postoperative patients develop common macronutrient and micronutrient deficiencies that can lead to preventable morbidity. Routine postoperative laboratory testing and surveillance for the detection of nutrient deficiencies is, therefore, advised for all patients who have undergone bariatric surgery. As the extent of the malabsorptive surgical procedure often induces a variable deficiency of essential fatty acids and the fat-soluble vitamins (A,D, E and K), the frequency of laboratory testing must be determined on a case-by-case basis. In general,

laboratory testing is advised at the 3-month postoperative visit, every 6 months for the first 3 years, and then once yearly thereafter. Common short-term complications include protein malnutrition exacerbated by insufficient postoperative protein intake, the presence of preoperative deficiency of micronutrients (for example, vitamin D and thiamine [vitamin B1] and postoperative deficiency of micronutrients for which there are minimal body stores, such as thiamine. The more common, long-term complications involve deficiencies of micronutrients of which there are large body stores, including calcium, iron and vitamin B12.

Protein deficiency

In standard protocols, patients are instructed to maintain a daily intake of 60–70 g of protein after RYGB. Achieving this goal is not easy for the patient and may require intensive counseling with a nutritionist. In patients who have a short common channel (malabsorptive procedure), protein intake is even more important, because the subsequent relative protein malabsorption may further increase the risk of protein malnutrition. A common, early manifestation of protein malnutrition after any type of bariatric surgery can be hair loss. Long-term manifestations of protein malnutritioncan include symptoms and signs of muscle-mass wasting. Severe protein deficiency similar to Kwashiorkor has been described after RYGB and especially after a distalgastric bypass. No specific parameters should necessarily be monitoredvia blood testing for protein malnutrition. The serum albumin concentration can be checked, but this may be of limited use in certain situations because it is an acute phase reactant.63 Regular follow-up of the overall health of patients, with emphasis on their protein intake and specific attention given to the condition of their skin and hair and also the presence of generalizededema (supporting the presence of hypoproteinemia) are the most important steps in preventing and recognizingprotein malnutrition. In patients with hypoalbuminemia, which is an acute inflammatory process, an underlying hepatic disorder (perhaps as the result of steatohepatitis) and SIBO should all be considerations.

vitamin B12 deficiency and folic acid

vitamin B12 deficiency after RYBG has been well described and is a potential cause of late-onset anemia (due to the large body stores of vitamin B12) in individuals. Folate deficiency is not reported after RYGB. Indeed, we have reported42 that elevation of folate levels after RYGB is related to SIBO. Another group has also reported elevated or normal folate levels following RYGB. However, there have been isolated case reports of neural tube defects attributed to folate deficiency following pregnancy in women who have undergone RYGB but not complied with their recommended daily multivitamin intake. This finding confirms how important it is that patients comply with daily supplementation and supports the idea that daily folic acid supplementation should be considered in women of child-bearing age. The mechanisms underlying vitamin B12 malabsorption include a lack of acid, R factor and intrinsic factor, which are secreted by parietal cells within the gastric remnant, and consumption of vitamin B12 related to SIBO. The vast majority of the parietal cell mass is the main site of both R factor and intrinsic factor production. When RYGB is performed appropriately, there should be minimal or no acid in the proximal gastric pouch; this lack of acid is relevant because vitamin B12 in the diet is ingested as cyanocobalamin conjugated to multiplepteryl groups and requires acid to break off the pteryl groups to allow absorption of the cyanocobalamin. In addition, RYGB leads to decreased intrinsic factor production from the proximal pouch, which is necessary for vitamin B12 absorption. Finally, SIBO may involve bacterial utilization of vitamin B12. Routine monitoring includes obtaining a serum vitamin B12 level every 6 months for the first 3 years, and yearly thereafter. Described treatments of vitamin B12deficiency include oral free vitamin B12 (cyanocobalamin)350–500 micg per day, intra muscular vitamin B12 1,000 micgevery month or 3,000 micg every 6 months, or a nasal orsublingual preparation that is absorbed locally and thus 'bypasses' the gut. Oral cobalamin is con sidered to be less effective than the intra muscular preparation and, therefore, must be taken daily.

Iron deficiency

Iron deficiency after RYGB can manifest as anemia. Iron malabsorption is related primarily to disruption of the normal absorption of iron from the duodenum and proximal jejunum, which are bypassed at the time of RYGB. It is not clear in these patients how important the absence of acid in the gastric pouch might be for oxidation of Fe2+ to the better-absorbed Fe3+ cation. Iron deficiency is probably the most easily recognized and treatable nutrient deficiency. Patients who have normal hemoglobin levels can have low ferritin levels after RYGB, supporting the addition of iron supplementation at that time. Iron deficiency anemia can be monitored by checking hemoglobin levels, hematocrit and mean corpuscular volume as part of a complete blood count. Routine treatment of iron deficiency includes treatment with an iron and vitamin C complex or with150–200 mg daily of oral elemental iron in a preparation that is best tolerated by the patient (for example, gluconate, sulfate, fumarate). Gastrointestinal specialists should be consulted when anemia does not correct with iron and vitamin B12 supplementation, to first exclude blood (iron) loss from a colon source, a stomal ulcer, a duodenal ulcer

or antritis within the excluded pancreatic obiliary limb. After excluding the much more serious complication of blood loss from the proximal gastric pouch and colon, blood loss from the small intestine can be studied by performance of small bowel capsule endoscopy. Blood loss from the gastric remnant can at times be identified by an extended upper endoscopy performed using a pediatric colonoscope or preferably with double balloon enteroscopy. The lengths of the Roux limb and the pancreatico biliary limbmay preclude direct endoscopic visualization of the duodenum and bypassed stomach. If the bypassed stomach and duodenum need to be visualized, this can be accomplished by intra operative endoscopy performed through alaparoscopically assisted gastrotomy, which allows insertion of an endoscope directly into the bypassed stomach. If these sources of potential blood loss are excluded, amalabsorptive etiology is probably the cause of the iron deficiency and it may require supplementation with parenteral iron (almost always in premenopausal women who experience heavy menses). Multiple bariatric programs have reported that anemiais a common, postoperative disorder after RYGB. If there have been incomplete responses to oral iron therapy and vitamin B12, and an evaluation by a gastrointestinal specialist has not provided a specific diagnosis, additional micronutrient deficiencies and other origins of the anemia must be considered. Other nutritional origins of anemia must be excluded by examining levels of folate, zinc, copper and vitamins A and E.

Vitamin D Deficiency And Calcium Malabsorption

Timing	Laboratory test
Routine	
3 months postoperatively	Complete blood count, glucose, glycosylated hemoglobin*, lipids
At 6-month intervals during the first 3 years, then once yearly	Chemistry group, complete blood count, lipids, ferritin, zinc, copper, magnesium, total 25-hydroxyvitamin D, folate, whole blood thiamine, vitamin B12, 24 h urinary calcium, serum alkaline phosphatase (with fractionation if levels are above normal)
As indicated	
Visual symptoms	Vitamin A, vitamin E, whole blood thiamine
Bleeding disorder	Complete blood count, prothrombin time and/or INR
Refractory vitamin D deficient	Parathyroid hormone
Neurologic symptoms	Vitamin B12, vitamin E, copper, whole blood thiamine, plasma niacin
Anemia	Ferritin, vitamin B12, folate, zinc, copper, vitamin A, vitamin E

Picture 2 routine and as indicated laboratory testing after RYGB

Metabolic bone disease as a result of vitamin D deficiency has been well described after RYGB.64 vitamin D deficiency is a key factor in activating a metabolic cascade that results in decreased calcium absorption and insufficient calcium availability, with subsequent hypocalcemia, secondary hyperparathyroidism and the development of osteoporosis and osteomalacia. It is, therefore, important to consider the potential for vitamin D deficiency and calcium malabsorption at the same time. Clinically, patients will present with a wide variety of complaints of bone pain, back pain or aching of their limbs. For monitoring purposes, it is common to consider taking a 24 h urinary calcium and serum alkaline phosphatase measurement at least every 6–12 months. If the urine calcium excretion is low and the serum alkaline phosphatase activity is increased, alkaline phosphatase should then be fractionated. If the alkaline phosphatase is of bone origin, then the serum parathyroid hormone level should be measured. If it is increased, this support aggressive supplementation with additional vitamin D and calcium and subsequent surveillance. Preliminary studies have demonstrated that patients who undergo RYGB maintain normal serum calcium concentrations by increasing the release of calcium from bone and decreasing urinary calcium secretion. Isolated measurements of serum calcium concentrations are not adequate markers of calcium metabolism after RYGB. Urine calcium secretion can also be altered by concomitant use of diuretics. It is important to obtain a total25-hydroxyvitamin D level every 12 months or sooner if a patient has a low 24 h urinary calcium excretion. Low vitamin D levels can have several explanations. vitamin Dmal absorption can be induced by bile salt deficiency, patients in the rapid weight loss phase require additional vitamin D, and preliminary studies have suggested that SIBO may further interfere with vitamin D absorption. To try to prevent the development of vitamin D deficiency and secondary metabolic bone disease, we recommend that postoperative RYGB patients take at least 1.2 g of elemental calcium daily and 800 international units (IU) of vitamin D daily. In those patients who have

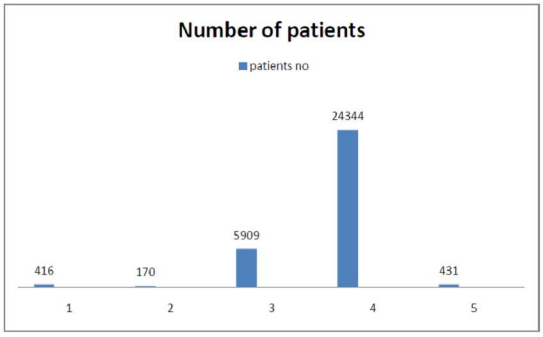
low serum levels of 25-hydroxyvitamin D, we suggest they take 50,000 IU of vitamin D (ergocalciferol) orally once per week for 6–8 weeks and that the 25-hydroxyvitamin D level is rechecked after 8 weeks to confirmrepletion.69 The reported dose for treatment of rickets is at least 600,000 IU of vitamin D, which has been given as rapidly as 150,000 IU taken four times during 1 day of treatment.

3. Result

A- Impact of RYGB on iron metabolism

Iron deficiency after RYGB is due to a combination of factors and is the main cause for developing anemia after an RYGB. Absorption is dependent on the pH of the stomach. Acid reduces iron from a ferric state (Fe3+) to a ferrous state (Fe2+), which is readily absorbed in the duodenum and proximal jejunum. Due to the RYGB configuration, iron passes through the small gastric pouch without being reduced to the ferrous state. This effect is further enhanced by the prescribed proton pump inhibitors and calcium. After ingestion, iron bypasses the absorptive surface of the duodenum and jejunum. Iron intake is further reduced by the frequently found intolerance for red meat. A normal individual requires 1-2mg of iron daily as a minimum. Especially premenopausal female are prone for developing iron deficiency. online search revealed 5 studies from 2011 to 2017 accounting for total of 31270 patients included in the final analysis as following *{ E. O. Aarts, et al at 2011} {total 416 patients},{ Carina Andriatta Blume, et al at 2012}{total 170 patients},{ Ting-Chia Weng, et al at 2014 }{total 5909 patients},{ Tyler Knight, et al at 2015}{total 24344 patients},{ Christos Karefylakis, et al at 2015}{total 431 patients}.*

Author		Year of publication	Number of patients	Total number of patients
1	E. O. Aarts, et al	2011	416	31270
2	Carina Andriatta, et al	2012	170	
3	Ting-Chia Weng, et al	2014	5909	
4	*Tyler Knight, et al*	2015	24344	
5	*Christos Karefylakis, et al*	2015	431	



E. O. Aarts, et al at 2011:

Before surgery, anemia was present in 27 (7%) patients. After twelve months, 66 (19%) patients had developed anemia denovo, of which 19 (29%) were microcytic. In these patients mean Hb levels dropped from 8.2 mmol/L to 7.1 mmol/L ($P < 0.001$). Total prevalence of anemia diagnosed in the first year, including preoperative anemic patients, was25%. Preoperative laboratory results are shown A total of 93 patients were diagnosed with or developed anemia during the first postoperative year. The percentage of deficiencies in patients with anemia are separately. The percentage of patients with iron, folic acid, and vitamin B12 deficiencies were 66%, 15%, and 50%, respectively. In 86% of patients, anemia was accompanied by one of these deficiencies.

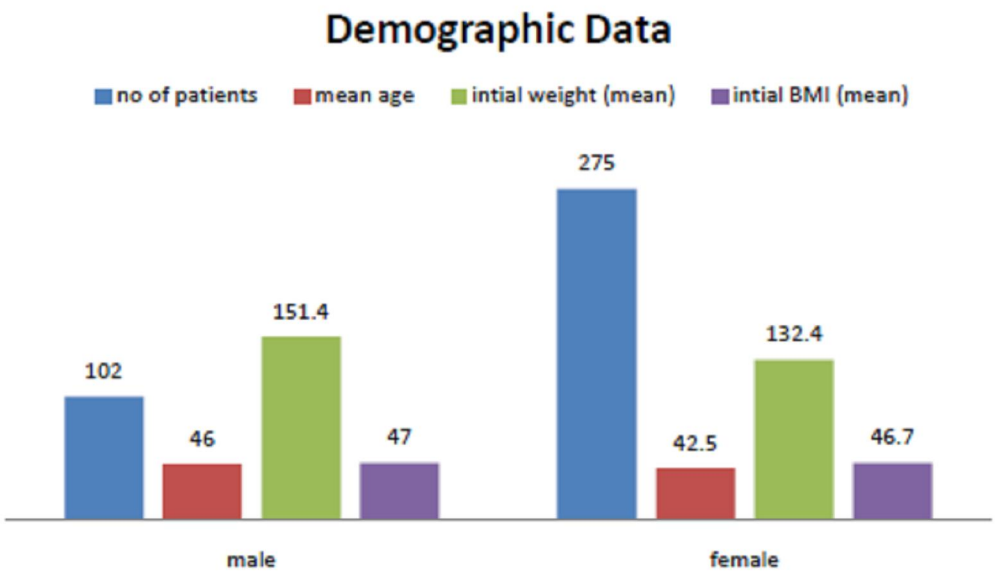
Table 1: Demographics.

Parameter	Values (standard deviation)
Number of patients	377
Male	102 (27.1%)
Female	275 (72.9%)
Age	43.4 (18–63)
Age male	46.0 (20–63)
Age female	42.5 (18–62)
Initial weight in kg	137.5 (±22.6)
Male	151.4 (±22.1)
Female	132.4 (±20.6)
Initial BMI in kg/m^2	46.8 (±6.3)
Male	47.0 (±6.4)
Female	46.7 (±6.2)

Table 3: 12 Month evaluation of anemic patients.

		Anemia preoperative (%)	Anemia de novo (%)	Anemia total (%)
N patients		27 (7.1%)	66 (18.8%)	93 (24.7%)
MCV	Micro	10 (37.0%)	19 (18.8%)	29 (31.2%)
	Macro	0 (0%)	1 (1.5%)	1 (1.0%)
High TIBC		4 (14.8%)	10 (15.2%)	14 (15.1%)
Iron deficiency		21 (77.8%)	40 (60.6%)	61 (65.6%)
Folic acid deficiency		4 (14.8%)	11 (16.7%)	15 (16.1%)
Vitamin B12 deficiency		14 (52%)	33 (50.0%)	47 (50.4%)
Total deficiency		23 (85.2%)	57 (86.4%)	80 (86.0%)

In the anemia preoperative column, laboratory results are shown of patients with anemia preoperative. In the anemia de novo column, patients with anemia preoperative were excluded. In the anemia total column, all patients are evaluated.



Variable	Preoperative		1 month		6 months		12 months		24 months		36 months		*p*
	%	SE	%	SE	%	SE	%	SE	%	SE	%	SE	
Low hematocrit (♂<40 %; ♀<38 %)	20.0	6.9	29.4	6.4	31.8	6.3	32.9	6.3	44.7	5.7	43.5	5.8	<0.001
Low hemoglobin (♂<13 g/dL; ♀<12 g/dL)	6.5	7.4	20.6	6.8	21.8	6.8	18.8	6.9	34.1	6.2	33.5	6.3	<0.001
Low iron (♂<49 µg/dL; ♀ <37 µg/dL)	5.9	7.5	17.1	7.0	5.9	7.5	1.2	7.7	8.8	7.3	8.2	7.3	<0.001
Low ferritin (♂<22 ng/mL; ♀<10 ng/mL)	5.3	7.5	2.4	7.7	4.1	7.5	4.1	7.5	15.9	7.0	23.5	6.7	<0.001
Low folic acid (<2.8 ng/mL)	6.5	7.4	2.9	7.5	4.7	7.5	1.2	7.7	1.8	7.7	0.6	7.7	0.009
Low vitamin B12 (<211 pg/mL)	2.9	7.5	1.2	7.7	3.5	7.5	3.5	7.5	5.3	7.5	7.1	7.4	0.036
Low albumin (<3.5 g/dL)	1.2	7.7	4.7	7.5	0.6	7.7	2.9	7.5	1.8	7.7	5.9	7.5	0.020
High glycemia (≥100, ≤125 mg/dL)	34.1	6.2	31.2	6.4	12.4	7.2	6.5	7.4	3.5	7.5	3.5	7.5	<0.001
High glycemia (≥126 mg/dL)	14.7	7.1	6.5	7.4	1.8	7.7	–	–	1.8	7.7	–	–	<0.001
High cholesterol (>200 mg/dL)	54.7	5.2	26.5	6.6	18.2	6.9	17.6	7.0	19.4	6.9	19.4	6.9	<0.001
High triglycerides (>150 mg/dL)	38.2	6.0	39.4	6.0	10.6	7.3	11.2	7.2	10.0	7.3	6.5	7.4	<0.001
High LDL-c (>100 mg/dL)	80.6	3.4	60.0	4.9	55.3	5.1	45.3	5.7	39.4	6.0	41.2	5.9	<0.001
Low HDL-c (♂<35 mg/dL; ♀<45 mg/dL)	31.8	6.3	64.1	4.6	32.9	6.3	17.6	7.0	12.9	7.1	8.2	7.3	<0.001

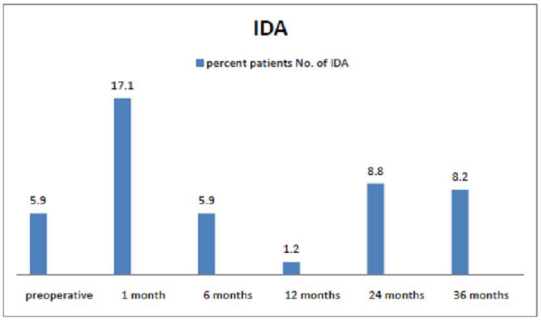
Results are expressed in percentage of patients and standard error of proportion. Reference values according to the laboratory of Hospital São Lucas PUCRS

LDL-c low-density lipoprotein, *HDL-c* high-density lipoprotein, *SE* standard error of proportion

Carina Andriatta, et al at 2012:

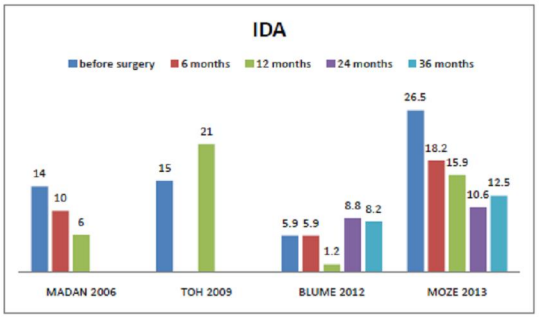
In the biochemical analysis, hematocrit levels displayed a significant reduction 1 year following surgery, while hemoglobin and iron were reduced at 1 month postoperatively.

However, ferritin concentration increased significantly1 month following surgery when compared to other postoperative evaluations and decreased at 24 months following surgery when compared to the preoperative period. Women with regular menstruation represented 66.2 % of the sample, and their hematocrit, hemoglobin, and ferritin levels were significantly lower ($p<0.05$) than the postmenopausal women in the sample in a majority of the assessment periods. In addition, women in the study had lower levels ($p<0.05$) in all hematologic parameters mentioned above, including iron, compared to men in the study. Vitamin B12 and folic acid showed the lowest mean values before RYGB, with significant increases at 1 and 12 months, respectively. Albumin levels did not show a statistically different change at any assessment time after surgery.



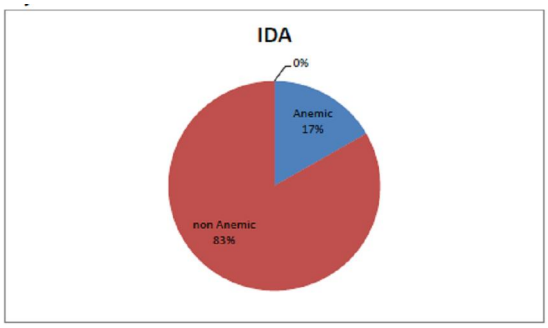
Ting-Chia Weng, et al at 2014:

The proportion of patients with anaemia increased significantly by 8.4% (95% CI 2.8% to 14.0%) 1 year after the surgery (included nine studies, 3932 patients), from baseline 12.2% (95% CI 8.8% to15.6%) to 20.9% (95% CI 14.7% to 27.1%). Prevalence of anaemia at 24 and 36 months of follow-up elevated to25.9% (95% CI 17.9% to 33.8%) and 23.1% (95% CI,13.6% to 32.7%), respectively. In parallel, a continuous decline in haemoglobin (11 studies, 4548 patients) and haematocrit (three studies, 620 patients) levels after surgery was also observed. To elucidate the cause of anaemia after RYGB, iron deficiency was first investigated, with ferritin and iron levels. The proportion of study participants with low ferritin levels rose by 4.1% (95% CI −2.2% to 10.4%) at12 months after surgery, from 7.9% (95% CI 0.95% to14.8%) at baseline to 13.4% (95% CI 3.5% to 23.4%) (included four studies, 685patients). The proportion of patients with low ferritin levels rose to 23.0% (95% CI 9.1% to 36.9%) and 26.5%(95% CI 20.6% to 32.4%) at 24 and 36 months, respectively. Pooled estimates for mean serum ferritin levels (four studies, 1512patients) had the baseline at 87.6 ng/mL (95% CI 75.4to 99.9), which declined to 55.5 ng/mL (95% CI 43.0 to68.0) at 24 months follow-up. In contrast, the proportion of study participants with low levels of serum iron (four studies, 685 patients) and mean serum iron concentration (six studies, 2072 patients) did not change significantly.



Tyler Knight, et al at 2015:

Of the gastric bypass surgery patients, there were16.7% with anemia (n = 2,035) and 83.3% without anemia (n = 10,153) The mean age of the overall patient population of 24,344 was approximately 46 years and was consistent across the groups with and without anemia. Both patient groups had a higher distribution of females over males. In the anemia group, 83.9% were female, while 78.7% were female in the group without anemia. A significant difference ($P < 0.001$) was noted in the proportions of patients with anemia with laparoscopic banding surgery compared with gastric bypass surgery. Conditions with the highest prevalence within the overall study population included obesity (n = 1,512), hypertension (n = 1,316), diabetes (n = 1,151), and sleep apnea (n = 802). Clinical characteristics observed with P values < 0.05 included heart disease ($P = 0.005$) and gallbladder disease ($P = 0.037$). The average time (days) observed until anemia diagnosis was 279 days (9 to 10 months) in the anemia patient population. Most (78.5%) anemia patients received a test for iron in the post-index period, and 9.1% of all anemia patients received IV iron treatment; iron dextran (3.8%) and iron sucrose (3.4%) were the most common treatments (average days until IV iron treatment = 406 days). Prescription oral iron was used in 4.9% of all anemia patients (average days to oral iron treatment = 476.7 days). Approximately 9% of all anemia patients received a blood transfusion, and the average time (days) until blood transfusion was approximately 304.8 days.



Christos Karefylakis, et al at 2015:

Follow-up was completed in 431 patients (58 %), mean age51.3±10 years, and 85 % female. Of those, 297 have been operated with primary RYGB whereas 134 underwent gastricbypass as a revisional procedure. Preoperative BMI was42.4±6.8 kg/m2, and it was reduced to 32.0±5.8 kg/m2 at11.6±2.7 years. At follow-up, %EBMIL was 58.9 and62.2 % of the patients who reached 50 % EBMIL or more Preoperatively, 35 patients had anemia, and 12 of those (34 %) had anemia postoperatively as well. Of all patients, 27 % had anemia postoperatively and related deficiencies; iron, folic acid, and vitamin B12 was seen in 20,12, and 2 %, respectively. Prevalence of anemia and related deficiencies were not found to differ significantly between those operated with primary RYGB and those who underwent a revisional operation. At follow-up, 29.9 % of patients reported using iron supplementation, 73.7 % vitamin B12, 19.5 % folate, and 23.9 % multivitamins. Of the patients that had iron deficiency at follow-up, 75.3 % reported that they did not use iron supplementation, 92 % of those with folic acid insufficiency reported that they did not use folate supplementation, and none of those with vitamin B12 insufficiency reported using vitamin B12 supplementation. A total of 45.5 % of patients reported that they had yearly or in the last year medical checkups concerning their gastric bypass surgery.

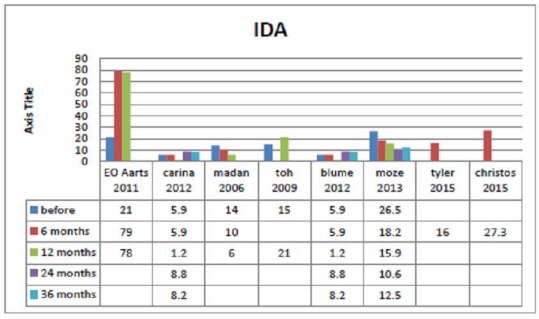
Table 1 Baseline data for the whole group and then divided into two subgroups dependently on the presence of anemia

	N=431	Anemia		
		Yes *N*=118	No *N*=313	*p* Value
Age	51.3±10.1	49.5±10.5	51.9±9.8	0.02
Sex	Male 67 (15.5 %) Female 364 (84.5 %)	Male 21 (17.8 %) Female 97 (82.2 %)	Male 46 (14.7 %) Female 267 (85.3 %)	0.43
Follow-up (years)	11.6±2.7	11.8±2.8	11.6±2.7	0.39
Preoperative BMI (kg/m^2)	42.4±6.8	42.7±6.8	42.3±6.8	0.55
Postoperative BMI (kg/m^2)	32.0±5.8	31.7±5.9	32.2±5.8	0.45
EBMIL%	58.9±35.2	63.5±32.2	57.1±36.2	0.10

Student's *t* test was used for comparison between the groups except for the variable "sex" where Pearson's Chi squared test was used

BMI body mass index, *EBMIL%* percent excess BMI loss

The summation of studies' results is shown in the following chart.

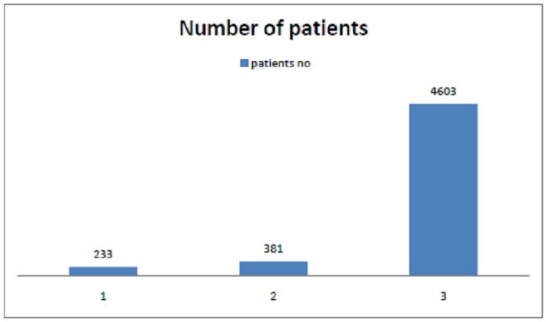


B- **Impact of RYGB on vitamin D**

Preliminary studies have demonstrated that patients who undergo RYGB maintain normal serum calcium concentrations by increasing the release of calcium from bone and decreasing urinary calcium secretion. Isolated measurements of serum calcium concentrations are not adequate markers of calcium metabolism after RYGB. Urine calcium secretion can also be altered by concomitant use of diuretics. It is important to obtain a total25-hydroxyvitamin D level every 12 months or sooner if a patient has a low 24 h urinary calcium excretion. Low vitamin D levels can have several explanations. vitamin Dmal absorption can be induced by bile salt deficiency patients in the rapid weight loss phase require additional vitamin D, and preliminary studies have suggested that SIBO may further interfere with vitamin D absorption. To try to prevent the development of vitamin D deficiency and secondary metabolic bone disease, we recommend that postoperative RYGB patients take at least 1.2 g of elemental calcium daily and 800 international units

(IU) of vitamin D daily. In those patients who have low serum levels of 25-hydroxyvitamin D, we suggest they take 50,000 IU of vitamin D (ergocalciferol) orally once per week for 6–8 weeks and that the 25-hydroxyvitamin D level is rechecked after 8 weeks to confirmrepletion.69 The reported dose for treatment of rickets is at least 600,000 IU of vitamin D, which has been given as rapidly as 150,000 IU taken four times during 1 day of treatment. online search revealed 3 studies from 2011 to 2017 accounting for total of 31270 patients included in the final analysis as following *{ Jason M. Johnson, et al at 2011} {total 233 patients},{ Kerstyn C Zalesin, et al at 2012}{total 381 patients},{ M Chakhtoura, et al at 2016 }{total 4603 patients}*.

Author		Year of publication	Number of patients	Total number of patients
1	Jason M. Johnson, et al	2011	233	5217
2	Kerstyn C Zalesin, et al	2012	381	
3	M Chakhtoura, et al	2016	4603	



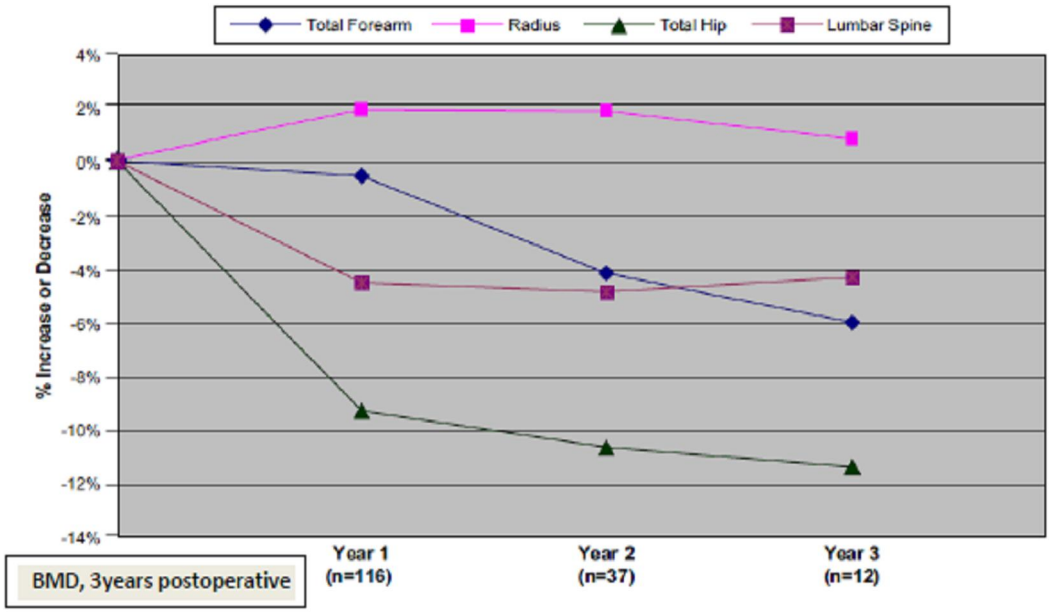
Jason M. Johnson, et al at 2011:

During the study period seven biliopancreatic diversions and 226 gastric bypasses were performed. Of the gastric bypasses performed, 82% (n 5 192) were performed laparoscopically. The conversionrate for the laparoscopic cases was 8.1%. The average preoperative body mass index was 50.5 kg/m2for the group as a whole (49.6 kg/m2 for women [n 5 187] and 54.4 kg/m2 for men [n 5 46]). The average age was 38.6 years for women and 43.4 years for men. At the beginning of the gastric by pass experience all patients were administered 500 mg of oral calcium (Tums) and a multivitamin three times per day. BMD scans of the total forearm (TF), radius bone (RB), total hip (TH), and/or lumbar spine (LS) were performed preoperatively on 230 patients. Most of the patients who underwent preoperative BMD scans had TF or RB measured because of the weight limitations in obtaining LS and hip BMD measurements. Fifteen patients had osteopenia preoperatively, and three patients subsequently developed osteopenia within the first year postoperatively as determined by their BMD scans. No patients had or developed osteoporosis during follow-up, as demonstrated by their BMD scans. At 1 year, BMD values for TF decreased by 0.55% (n591; P5.03) and RB increased by 1.85% (n523; P5.008). TH and LS bone density decreased by 9.27% (n522; P!.001) and 4.53% (n 521; P.001), respectively, during the first postoperative year.

During the second postoperative year, TF bone density continued to decrease an additional 3.62% (n 514; P!.001), whereas RB, TH, and LS bone density stabilized. The number of patients eligible for 3-yearfollow-up is small (n 5 23). After the initial decrease in BMD the first 1 to 2 years after surgery, bone density seemed to stabilize with no further decreases, but it did not start to increase to the preoperative levels. Each patient was used as his or her own control, and the results were compared with the previous BMD scans. Mean serum calcium decreased from 9.8 mg/dL (nl 8.4–10.2 mg/dL) to 9.2 mg/dL (not significant [NS]) during the first postoperative year and then to 8.8 mg/dL by year 2 (NS). Conversely, PTH levels increased from a preoperative level of 59.7 pg/mL (nl 10–65 pg/mL) to 63.1 pg/mL at year 1 (NS) and then up to 64.7 pg/mL by year 2 (NS). No difference was noted between 25-hydroxy vitamin D levels preoperatively (25.3 ng/mL [quoted laboratory normal:10–65 ng/mL]), at 1 year (34.4 ng/mL), and at 2years (35.4 ng/mL). Fifty patients demonstrated preoperative evidence of elevated PTH values (65 pg/mL). Of the patients with a preoperative elevated PTH level, all had normal calcium levels, and only one had a low25-hydroxy vitamin D level. Although the mean PTH level at 1 and 2 years was within normal levels, 37 patients at year 1 and 18 patients at year 2 had elevated PTH levels, of which only one individual had a low 25-hydroxy vitamin D level. Preoperative vitamin D levels were between 20 and 30 ng/mL in 17patients, 10 and 20 ng/mL in 20 patients, and less than 10 ng/mL in four patients. Despite elevations in PTH levels, serum calcium remained consistent with only one person exhibiting hypocalcaemia (8.2 mg/dL). Hypocalcaemia did not develop in any patients throughout the study period.

Table 1. Bone mineral density values from different areas to 3 years postoperatively

	Year 1			Year 2			Year 3		
	% Decrease	n	*P*	% Decrease	n	*P*	% Decrease	n	*P*
Total forearm (TF)	−0.55% ± 2.43%	91	.03	−3.62% ± 3.56%	31	<.001	−1.83% ± 2.42%	9	NS
Radius bone (RB)	1.85% ± 4.06%	23	.008	0.06% ± 3.06%	14	NS	−1.03% ± 2.23%	8	NS
Total hip (TH)	−9.27% ± 3.42%	22	<.001	−1.35% ± 3.24%	6	NS	−0.73% ± 3.76%	3	NS
Lumbar spine	−4.53% ± 3.83%	14	<.001	−0.32% ± 2.42%	6	NS	0.53% ± 2.15%	3	NS



Kerstyn C Zalesin, et al at 2012:

Coates and colleagues evaluated 25 postoperative RYGB patients and compared bone turnover markers with 30 obese controls. Patients in the control group had a greater BMI than those in the postoperative group measured at 48 ± 7 and 32 ± 5 kg/m2, respectively. A significant increase of u-NTX measured at 93 ± 38 versus 24 ± 11 nM/mmol Cr, ($p < 0.001$), as well as a higher osteocalcin, measured at 11.6 ± 3.4 versus 7.6 ± 3.6 ng/ml ($p < 0.001$), among surgery compared with control cases. A subgroup analysis evaluated 15 patients (12 women and three men) prospectively for 9 months from surgery and likewise noted an increase in u-NTX scores with time, 174 ± 168% at 3 months ($p < 0.01$) and 319 ± 187% at 9 months ($p < 0.01$). All postoperative patients were instructed to take a vitamin supplement with calcium (1200 mg daily) and vitamin D 400–800 IU daily. The subgroup lost 37 ± 9 kg and had a 29 ± 8% decrease in BMI ($p < 0.001$). Bone mineral density (BMD) scores among this group were significantly decreased at the hip (7.8 ± 4.8%; $p < 0.001$), trocanter (9.3 ± 5.7%; $p < 0.001$) and total body (1.6 ± 2.0%; $p < 0.05$) after surgery. Other markers of bone metabolism, such as PTH serum calcium and 24-h urinary calcium, were unchanged between control and postoperative groups. 25-hydroxyvitamin D levels were low in both groups, yet unchanged with surgery. These results indicate that bone turnover may be noted as early as 3 months after RYGB surgery, with the hip being the most affected site, and suggests that vitamin D is not the only mediator of increase bone turnover after bariatric surgery. The authors recommend supplementation of calcium and vitamin D as well as screening for MBD in this population. Youssef *et al.* recently published the effects of RYGB on calcium, alkaline phosphatase, PTH, and 25-hydroxyvitamin D. The study enrolled 193 female patients and prospectively followed them for 2 years. Daily calcium citrate 1200 mg with vitamin D 400 IU were recommended daily for all subjects. They noted 53.3%of patients had an elevated PTH level with mean time to development after surgery at 9.1 months. There was a 2.5-fold elevated risk in the African–American population compared with the Caucasian population ($p < 0.05$), and a 1.8-times higher risk in subjects aged over 45 years

compared with younger counterparts ($p < 0.05$), to develop secondary hyperparathyroidism. Vitamin D deficiency, which was defined as less than 20 ng/ml, was described in 18.2% of the patients, while 30% of patients with secondary hyperparathyroidism had concomitant vitamin D deficiency. This study likewise identified factors other than vitamin D deficiency as predictive of MBD, namely age and race. The authors cautioned that aggressive supplementation with calcium and vitamin D is necessary due to cumulative effects of malabsorption with hypovitaminosis D magnifying risks of MBD. Johnson *et al.* prospectively monitored BMD, calcium, PTH and vitamin D and compared baseline results to annual postoperative findings for 2 years subsequently. Calcium intake recommendations were 600–1000 mg with 400–800 IU of vitamin D per day. A total of 226 patients, who had undergone RYGB, and seven who underwent biliopancreatic diversion (BPD), were included in a combined analysis, with each patient serving as their own control. They found that 15 patients were osteopenic preoperatively, and three subjects developed osteopenia within the first year. None of the study patients had or developed osteoporosis. At the 1 year evaluation ($n = 116$), total forearm BMD had decreased $0.55 \pm 2.43\%$ ($p = 0.03$), radius BMD increased $1.85 \pm 4.06\%$ ($p = 0.008$), while total hip and lumbar spine BMD decreased by $9.27 \pm 3.42\%$ ($p < 0.001$), and $4.53 \pm 3.83\%$ ($p < 0.001$), respectively. At the second year ($n = 37$), BMD at the total forearm decreased an additional $3.62 \pm 3.56\%$ ($p < 0.001$), while no significant further losses at the total hip or lumbar spine were appreciated. At the third year follow- up ($n = 12$), there were no statistically significant losses noted at total forearm, radius bone, total hip or lumbar spine. In fact, BMDs at the spine and hip areas were not significantly different from baseline after the first year, indicating that there may be regain in BMD in some patients over time at the hip, spine and total forearm locations among the remaining small sample. Calcium trended in a declining pattern, while PTH and 25-hydroxyvitamin D levels both increased after surgery; however, none of these parameters were significantly changed. This study demonstrates that the rate of bone loss is greatest after the first year, and plateaus or even slightly improves in subsequent years. This bone loss appeared partially independent from a vitamin D mechanism, as there was no association between vitamin D or PTH levels to BMD results in this study. The authors indicate that bone loss is not an ongoing process after the first year; however, they do advocate annual screening to detect MBD and BMD changes in individuals at increased risk.

Goode *et al.* assessed 44 females (23 were premenopausal and 21 postmenopausal), 3 or more years following RYGB. There was an average weight loss of 31% and a current BMI average of 34 kg/m2. A comparison of bone mineral content (BMC), bone turnover markers, PTH levels and 25-hydroxyvitamin D levels with an age- and weight-matched historical control group who had previously been assessed for bone mass ($n = 65$). This study achieved a 72% follow up rate and found no difference in BMC in premenopausal groups (42 ± 5 years); however, in postmenopausal women (55 ± 7 years), BMC was higher in the lumbar spine ($p < 0.05$) and lower in the femoral hip ($p < 0.001$). A subgroup of 13 postoperative RYGB patients with a mean BMI of 34 kg/m2, seven premenopausal and six postmenopausal, with low BMCs, were provided supplements of 1200 mg of calcium and 8 µg of vitamin D per day for 6 months, while BMC and serum bone markers were monitored. This group was compared with a 13-member weight matched control group, seven premenopausal and six postmenopausal, who had previously completed a 6-month unsupplemented weight maintenance study. No difference in BMC was noted in the subgroup analysis (100% follow-up rate) with supplementation. PTH and serum markers of bone turnover were higher in the RYGB group ($p < 0.001$), yet were not significantly altered with supplementation. While there was a significant increase in 25-hydroxyvitamin D in RYGB patients with supplementation ($p < 0.0001$), no differences in 25-hydroxyvitamin D or osteocalcin were demonstrated between control and postoperative groups. This study found MBD risks to be more prominent with postmenopausal status at cortical bone sites, namely the femoral neck and radius, and raised the concern that standard vitamin D and calcium supplementation may be insufficient to suppress PTH and prevent bone loss after bariatric surgery. Direct correlation of vitamin D levels and markers of MBD after surgery have been noted. In another 243-subject study led by the Johnson group, a prospective evaluation of the effects of RYGB, both long limb ($n = 41$) (LL-GBP), defined as a Roux limb greater than 100cm, and short limb, defined as 100cm or more ($n = 202$) (SL-GBP), on calcium, vitamin D and PTH was compiled. BMI levels were greater in the LLGBP measuring 60.6 ± 8.3 kg/m2, as opposed to the SL-GBP group, which was 49.1 ± 8.8 kg/m2. All study subjects were supplemented with 1200 mg of calcium and 800 IU of vitamin D. Patients in the SL-GBP were followed for a mean of 3.1 ± 3.6 years, while the LLGBP group was followed for 5.7 ± 2.5 years ($p < 0.0001$). They found that the average 25-hydroxyvitamin D level was lower in the LLGBP group, 16.8 ± 10.8 ng/ml, while the SLGBP group

levels were 22.7 ± 11.1 ng/ml (p =0.0022). The average PTH levels were higher in the LL-GBP group 113.5 ± 88.0 compared with SL-GBP 74.5 ± 52.7 pg/ml (p = 0.0002). Study patients had normal calcium levels without differences between SL and LL-GBP groups. Inpatients with low vitamin D levels, (defined as<8.9 ng/ml), 89% had an elevated PTH, (defined as >65 pg/ml). In patients with a vitamin D level up to 8.9 ng/ml, 58% had an elevated PTH. When evaluating 25-hydroxyvitamin D at less than 30 ng/ml, 55.1% had secondary hyperparathyroidism while those with vitamin D level up to 30 ng/ml, 28.5% had secondary hyperparathyroidism (p = 0.0007).

Study	Design	Duration	n	Supplement use	Outcomes: 25(OH)D/bone markers	Outcomes: BMD
Goode *et al.*	Retrospective observational, controlled	3 years	44 RYGB 65 CNT	Not defined	N/A	Similar BMD in premenopausal, Postmenopausal ↓ FN, ↑ LS*
	Prospective	6 months	13 RYGB with ↓ BMD 13 CNT	1200 mg Ca^{2+} 8 µg vitamin D	↑ PTH, uNTX 6 months* ↑ 25(OH) D* Similar OC	Similar LS BMD and BMC
Youssef *et al.*	Prospective observational	2 years	193 female RYGB	1200 mg Ca^{2+} 400 IU vitamin D	↑ PTH *	N/A
Sánchez-Hernández *et al.*	Prospective observational	3 years	64 RYGB	No routine supplements	↑ 25(OH)D ↓ Alk phos, PTH after RYGB*	N/A
Ybarra *et al.*	Prospective control	3 years	64 RYGB, 80 obese CNT	No routine supplements	Similar Ca^{2+}, alk phos, PTH, 25(OH)D	N/A
de Prisco *et al.*	Case series, retrospective observational	10–12 years	3 RYGB 1BPD	Varied	↑ PTH, 1,25 vitamin D, alk phos ↓ Ca^{2+}, 25 vitamin D	N/A

M Chakhtoura, et al at 2016:

1- **25(OH)D status before bariatric surgery**

Thirty six studies assessed 25(OH)D status before bariatric surgery (Appendix). Figure 2 represents studies that have a number of participants of at least 50 per study group or subgroup, based on bariatric surgery type. It shows that mean 25(OH)D levels were ≤ 20 ng/ml in fifteen studies, and between 20 and 30 ng/ml in the others. The weighted mean 25(OH)D levels (ng/ml) did not differ between studies, classified according to the baseline participants' mean BMI (mean BMI ≥ 50 kg/m2, mean BMI between 45 and 50 kg/m2 and mean BMI ≤ 45 kg/m2) (Figure 2). Similarly, the weighted mean 25(OH)D levels of studies divided into 2 categories (mean BMI ≥ 50 kg/m2 versus mean BMI <50 kg/m2) also did not differ significantly (data not shown). Two other studies, in addition to the restrictive procedure arm of a third one were not represented on Figure 2, as the number of participants per surgical procedure group was < 50. These studies also showed a mean 25(OH)D level of less than 20 ng/ml before bariatric surgery (Appendix). Mean 25(OH)D level was surprisingly high, reaching 39.4 ng/ml, in a group of obese individuals undergoing Roux-en-Y Gastric Bypass (RYGB); However, this study did not provide the mean BMI of participants, and therefore. Finally, four studies did not report 25(OH)D levels, but they provided the pre-operative proportion of individuals with 25(OH)D level < 20 ng/ml, of 66% [81], or < 30–32 ng/ml, varying from 23 to 98 %.

2- **Vitamin D levels following bariatric surgery with and without vitamin D supplementation**

Forty six studies assessed 25(OH)D status within 1 to 11 years following bariatric surgery (Appendix). These were divided into categories according to the type of the surgical procedure and the dose range of vitamin D supplementation. Only eight studies showed a mean 25(OH)D level > 30 ng/ml at 6 to 24 months post operatively. Thirteen studies showed a mean 25(OH)D level < 20 ng/ml at 6 months to 11 years post operatively. The remaining studies, almost half, reported a 25(OH)D level between 20 and 30 ng/ml.

3- **Vitamin D supplementation dose and response in bariatric surgery**

There was a high variability in vitamin D supplementation regimens administered post operatively, including enteral and parenteral preparations, daily and intermittent schedules (i.e. weekly, biweekly, monthly or every 3 months) and a wide range of equivalent daily doses, from 200 IU

[57] to 28,500 IU. Several studies used additional supplemental regimens in subjects who were deficient, as shown in Figure 3 and detailed in the Appendix. The timing of 25(OH)D status assessment also varied, from as early as 3 months, to as late as 11 years post operatively.

4- Dose response between the administered vitamin D dose and the increments in serum 25(OH)D levels

Thirty studies evaluated 25(OH)D level before and after bariatric surgery, at 3 months to 10 years postoperatively. Figure 3 represents mean 25(OH)D level in studies that included at least 50 participants in each surgical procedure group, and that assessed 25(OH)D status pre and 1 year post operatively. There was a trend for larger increments in mean 25(OH)D levels with higher doses. However, these increments were not consistently in concordance with the dose administered, and the statistical significance of the change in 25(OH)D level was not assessed in all the studies Starting at a mean baseline 25(OH)D level of 13–25 ng/ml, the change in 25(OH)D level did not exceed 8 ng/ml at 6 to 12 months post operatively, even with daily dosing up to 2,000 IU daily], with only one exception. Furthermore, 25(OH)D level did not change or even decreased in several studies at one year follow up, despite supplementation (equivalent daily dose range 200–800 IU). Avgerinos et al. showed an initial increase followed by a drastic decrease in 25(OH)D level at 1 year following RYGB, despite sustained vitamin D supplementation of 800 IU daily; findings that remain unexplained. De Luis et al. showed an increase in mean 25(OH)D level of 15 ng/ml at 2 years after BPD, with administration of a small dose of vitamin D of 200 IU daily, followed by a decline and return to baseline level at 3 years. Hamoui et al. assessed the effect of limb length in duodenal switch (DS) on 25(OH)D status, and demonstrated that a long common channel of 100 cm allowed a better improvement in 25(OH)D level at 18 months, compared to a short common channel of 75 cm (a difference in 25(OH)D level of 14.7 ng/ml between the 2 sub-groups at 18 months).Conversely, studies administering a maintenance vitamin D supplementation of 400–2,000 IU daily, and additional doses to deficient and/or insufficient individuals (additional equivalent dose range 1,100 IU–7,100 IU, total daily dose received 1,500–9,100 IU), with the exception of Fish et al., consistently demonstrated an increase in mean 25(OH)D level of 9–13 ng/ml at six months, and at one year post operatively. The mean baseline 25(OH)D level in this group of studies was 13–25 ng/ml.

5- Relationship of vitamin D dose, type of bariatric surgery, and achievement of a desirable 25(OH)D level

In studies where no vitamin D supplement was administered, mostly following RYGB procedures, the mean 25(OH)D level achieved post-operatively was in low to mid-teens, in ng/ml, across the board. Three studies conducted on patients undergoing laparoscopic sleeve gastrectomy (LSG) surgery suggest that a vitamin D dose less than 1,000 IU/d may not be sufficient to raise mean levels to above the desirable value of 20 ng/ml, even in restrictive procedures. Studies of malabsorptive or combination procedures, with supplementation up to 2,000 IU of vitamin D daily, achieved mean 25(OH)D levels at or above 20 ng/ml, provided mean levels did not start below such cutoff pre-operatively, When baseline 25(OH)D level was < 20 ng/ml, three studies showed an increase in mean 25(OH)D level to above the target [57,58,63], while three others did not Conversely, two studies that involved biliopancreatic diversion (BPD) and that administered very high doses of vitamin D (6,472 IU/d in one and the equivalent of 28,571 IU/d in another) showed mean 25(OH)D to remain in the low to mid-teens 5 years post-operatively. Finally, studies that administered vitamin D, as a maintenance dose to all participants (≤2,000 IU daily), and additional doses (range of equivalent daily doses: 1,100–7,100 IU, total daily dose received 1,500–9,100 IU) to vitamin D deficient/insufficient individuals, following malabsorptive and combination procedures, achieved a mean 25(OH)D level above 20 ng/ml in five studies, with mean baseline 25(OH)D level 13–21 ng/ml, and above 30 ng/ml in six studies, with mean baseline 25(OH)D level 15–25 ng/ml Assuming normality of the distribution of 25(OH)D levels, and considering studies of malabsorptive and combination procedures, we estimate that the proportion of participants achieving the target 25(OH)D level of 20 ng/ml, increased from 14–67% to 63–76%, on vitamin D doses of up to 2,000 IU daily. Considering studies of vitamin D deficient individuals, these proportions increased from 25–55% at baseline, to 70–93% of at study completion, on replacement doses and add-on to the vitamin D maintenance regimen.

6- Comparative effect of restrictive versus malabsorptive and combination procedures on 25(OH)D status in individuals undergoing bariatric surgery

We identified only five studies comparing 25(OH)D status before and after vitamin D supplementation, in restrictive versus malabsorptive or combination procedures, within the same study, and we could not identify the emergence of a consistent trend in results. DiGiorgi et al compared 25(OH)D levels following RYGB versus Laparoscopic Adjustable Gastric Banding (LAGB) in subjects who received vitamin D 800 – 1,200 IU daily and found no significant difference in mean levels both at 1 and 2

years post operatively, between the two groups. Similarly, Lanzarini et al. compared prospectively LSG versus Laparoscopic Roux-en-Y gastric bypass (LRYGB) patients, when all participants received the same dose of vitamin D supplementation for a 6-month duration. A significantly higher 25(OH)D level in LSG compared to LRYGB was reported only at 2 years follow up. A retrospective study showed lower 25(OH)D levels in RYGB compared to LAGB, when all participants received the same dose of vitamin D supplementation [69]. Coupaye et al. compared Adjustable Gastric Banding (AGB) to Gastric Bypass (GBP) procedures, and showed higher 25(OH)D levels in GBP patients [19.9(9.9) ng/ml], compared to AGB patients [11.9(4.2) ng/ml]; the GBP subgroup only received 500 IU of vitamin D3 daily. Vilarrasa et al. showed no significant difference in 25(OH)D level between RYGB and Sleeve Gastrectomy (SG) groups when vitamin D supplementation doses were 800 – 1,200 IU daily in the former group and 400 IU in the latter group. Three other studies were not included in our discussion; the first one did not provide 25(OH)D levels, the second did not report the standard deviation of 25(OH)D level following intervention and the third one did not administer vitamin D supplementation.

Author Year	Study design N° Surgery type	Vitamin D assay	Vitamin D Dose	25(OH)D at baseline (ng/ml)		25(OH)D following bariatric surgery ng/ml)		Author conclusion
				Mean (SD) or median (range)	Below cutoff %	Mean(SD) or median (range)	Below cutoff %	
DeGroy 2008 [58]	Prospective 40 GBP 11 LAGB	NA	All D800 – 1200 UI/d [68]	GBP : (?38) LAGB: 19(9) [b]	< 20 GBP: 67% LAGB: 58%	At 12 mo: GBP: 25(12); LAGB: 23(9) At 24 mo: GBP: 24(12); LAGB: 25(10) ? No difference between group [c].	< 20 At 12 mo: GBP: 17%; LAGB: 37% At 24 mo: GBP: 10%; LAGB: 33%	Same vitamin D requirements may be needed in both groups.
Coupaye 2009 [78]	Prospective 21 AGB 49 GBP	RIA	D 500 IU/d in GBP only.	AGB: 13 &3.6) GBP: 12.3 D.8) [c]	-	At 12 mo AGB: 11.9(4.2); GBP: 19.9(9.9) ? Significantly higher mean 25(OH)D level in GBP compared to AGB [c].	-	Results inconclusive
Fish 2013 [69]	Retrospective 79 RYGB 46 LAGB	NA	All: Pre op: D 10,000 IU 1 times/ week for 1 month for deficient. Post op: D 1,200 UI/d [68,69]	LAGB: 23(7-112) RYGB: 21(6-47) [b]	< 30 LAGB: 75% RYGB: 88%	At 12 mo LAGB: 22(12-51); RYGB: 28(5-49) ? Significantly lower mean 25(OH)D level in RYGB compared to LAGB [b].	< 30 At 12 mo: LAGB: 41%; RYGB: 63%	RYGB may require higher vitamin D supplementation dose.
Vilarrasa 2013 [79]	Prospective 31 RYGB 31 SG	Electro-Chemiluminescence based Immuno analysis	D 400 IU/d in SG and 400-800 IU/d in RYGB	RYGB: 23.1 8) SG: 17.6(8) [b]	-	At 12 mo RYGB 21.6(8.4); SG 20.1(7.2) ? No significant difference between the 2 groups [b]	-	RYGB may require higher vitamin D supplementation dose.
Lanzarini 2015 [60]	Prospective 96 LSG 66 LRYGB	ECLIA	D 400 IU/d Intervention group If 25(OH)D < 30 ng/ml at 3 or 6 mo follow up: D2 50,000 IU every 2 weeks for a maximum of 6 mo	LSG: 15.2 (7.0) LRYGB: 14.8 (2.1) [c] Intervention group LSG: 15.8(7.0) LRYGB: 12.8(6.3) [c] Non intervention group:	-	At 12 mo LSG : 27.6 (16.6 LRYGB: 21.0 (14.2) Intervention group LSG : 28.0 (11.8 LRYGB: 21.8 (15.8) Non-intervention LSG : 26.8 (13.4) LRYGB: 26.3 (10.6)	< 30 ng/ml At 12 mo Intervention group LSG: 67 LRYGB: 66 Non-intervention group LSG: 61 LRYGB: 62	RYGB may require vitamin D supplements for a longer duration.

4. Discussion

E. O. Aarts, et al at 2011:

Bypassing the duodenum and proximal jejunum leads to a decrease in absorption surface for specific nutrients and causes a reduction in the absorptive capacity. After an LRYGB the most common reported are iron and vitamin B12 deficiencies. Deficiencies in these micronutrients are well known causes for anemia. Published reports on metabolic deficiencies after RYGB with different follow-up periods found anemia varying from 18 to 35%. Iron deficiency was reported in 20–49% in these studies. Folate deficiency was found in 0–18% of the cases. Vitamin B12 deficiency varied from 26 to 70%. Although a relative short follow-up only one year, we found high percentages in folic acid and vitamin B12 deficiencies, of 19 and 36%, respectively. Iron deficiency after RYGB is due to a combination of factors and is the main cause for developing anemia after an RYGB. Absorption is dependent on the pH of the stomach. Acid reduces iron from a ferric state (Fe3+) to a ferrous state (Fe2+), which is readily absorbed in the

duodenum and proximal jejunum. Due to the RYGB configuration, iron passes through the small gastric pouch without being reduced to the ferrous state. This effect is further enhanced by the prescribed proton pump inhibitors and calcium. After ingestion, iron bypasses the absorptive surface of the duodenum and jejunum. Iron intake is further reduced by the frequently found intolerance for red meat. A normal individual requires 1-2mg of iron daily as a minimum. Especially premenopausal female are prone for developing iron deficiency. (11-12-13)

Carina Andriatta, et al at 2012:

A successful bariatric surgery can be determined by weight loss of over 50 % of excess weight following surgery. The results of excess weight loss were satisfactory and agreed with information provided in the literature, which reports maximum loss at 24 months after surgery. In our sample, at 24 months postoperatively, 96.4 % of the patients had lost more than 50 % of their initial excess weight, falling to 92.8 % at the end of the follow-up. By the 36th month, there was a reduction in excess weight loss, with significant regain of 3 % of initial weight, when compared to 24 months postoperatively. O'Brien et al., in a systematic review that analyzed medium-term and long term weight loss after bariatric surgery, also found reduced excess weight loss starting at 36 months postoperatively (mean062.5 versus 67.5 % at 24 months postoperatively), occurring gradually and progressively for up to 10 years (52.5 %) following surgery. However, Magro et al. reported regain starting in the 48th month postoperatively, with a 4 % increase in initial BMI in this period. In another study, also conducted at our center, Barhouch et al. reported that in the 60th postoperative month, there was an 8.7 % regain of initial weight, demonstrating a greater tendency for weight regain 5 years following surgery. Christou et al. demonstrated that, despite the weight regain following surgery, the long-term mortality rate of 3.1 % remained low. Some factors described in the literature seem to be predictors of weight regain after bariatric surgery, such as dilation of the gastric reservoir and gastrojejunostomy, increased calorie intake of high glycemic index carbohydrates and fats, intolerance to red meat, hormonal alterations resulting from the adaptive process, binge eating, alcohol and drug consumption, and absence of postoperative multidisciplinary follow-up. (14-15-16)

Ting-Chia Weng, et al at 2014:

Several studies reported that a substantial proportion of patients already had anaemia prior to RYBG surgery, as well as having deficiencies in iron, folate and vitamin B12. This can probably be explained by the fact that obesity is a known risk factor for nutrient deficiencies despite an excessive calorie reserve. Ourmeta-analysis observed a nearly twofold increase in anaemia occurrence at 12 months after RYGB surgery, with an exacerbating declining of haemoglobin/haematocritover time. However, the iron level may not decrease after RYGB and folate deficiency is correctable with oral multivitamin supplementation. It is important to intervene early on in cases of iron deficiency anaemia with ferritin profiling, and augmented supplementation is important for vitamin B12, the deficiency of which may occur later, from 12 months postoperation on. In our current meta-analyses, frequency of ferritin deficiency increased by twofold in patients at 6 months after surgery, and this trend became substantially aggravated at 24 and 36 months. However, no significant change in serum iron concentration after RYGB surgery was found. Since serum ferritin is a more specific and early indicator for iron deficiency anemia, the low ferritin levels with stable serum iron concentrations suggest reduced body iron capacity. Although ferritin is also an acute-phase protein, and elevation of ferritin has been reported as early as the first month after surgery. the decreasing trend in ferritin level is observed at 6 months or longer after surgery, when no active inflammation is expected. (17-18)

Tyler Knight, et al at 2015:

There has been a consistent, widespread increase in the prevalence and incidence of obesity in the U.S. population. Because of this trend, bariatric surgery has emerged as a safe, effective alternative for weight control, particularly in cases where diet, exercise, and behavior modifications have not been successful. Patients who undergo bariatric surgery are susceptible to IDA. As with any health condition, once a patient develops IDA, the resulting requirements for care and treatment lead to increased MRU and associated costs. Multiple studies have reported the correlation between IDA and increased direct and indirect cost burden. For example, in the study by Nissenson

et al. (2005), the investigators concluded that medical costs for anemic patients were twice as much as those for nonanemic patients with the same comorbid condition. These findings are similar to those in this study that focuses on postbariatric surgery patients. Based on observations of the study population, it was noted that most patients had some type of iron test results, and it appeared that gastric bypass patients were being monitored for IDA. However, 11.7% of the study sample received a diagnosis of IDA that is significantly lower than the 33% to 49% of patients who undergo gastric bypass surgery and then experience IDA that has been reported in the literature.18 This could infer that IDA was under diagnosed in this sample; IDA may be reported under an unspecified anemia ICD-9-CM

diagnosis code such as 285.9; or that the incidence was simply low in this study. (18-19)

Christos Karefylakis, et al at 2015:

Bariatric surgery is gaining popularity as an effective treatment for obesity; however, adverse events both in the short term and long term are a clinical reality. Anemia is one such complication and is in general secondary to iron, folic acid, and vitamin B12 deficiencies. The present study is to our knowledge the first study of anemia and related nutritional deficiencies after RYGB with a mean follow-up time of more than 10 years. We found that 27 % of patients had anemia postoperatively, 20 % iron deficiency, 12 % folate deficiency, and 2 % vitamin B12 deficiency, which is a concern, considering the rapidly growing numbers of bariatric operations worldwide. Anemia was correlated with iron deficiency and folate deficiency but not with vitamin B12 deficiency. The latter is possibly due to the low prevalence of vitamin B12 deficiency in the sample. The reported prevalence of anemia after RYGB has varied a lot due to small sample sizes and poor follow-up. In a large prospective study, Amaral et al. estimated the number to be 37 %, and two other studies found an anemia prevalence of 36 and 25 %, respectively. Iron, folic acid, and vitamin B12 deficiencies were diagnosed in 66, 15, and 50 % of patients, respectively, in the first year following RYGB. Näslund followed 57 morbidly obese patients who were randomized and operated upon with gastric bypass or gastroplasty, and with no postoperative iron or B12 supplementation. Prevalence of anemia was 0, 8, and 34 % for 1, 2, and 3 years postoperatively, respectively, in the gastric bypass group. (20-21)

Jason M. Johnson, et al at 2011:

As obesity continues to increase in the United States, the demand for obesity surgery will increase. The endocrine side effects of gastric bypass procedures are poorly studied. As the age of patients seeking morbid obesity surgery continues to decrease, the long-term clinical significance of endocrine derangements, especially bone turnover, becomes of utmost importance. Metabolic bone disease, hypocalcemia, hyperparathyroidism, and osteoporosis have been well described after gastric surgery, but the effects of Roux-en-Y gastric bypass (RYGB) for obesity on these same parameters are not as defined. Recently, more research has been performed to understand the effects of gastric bypass operations on bone turnover and density. Several authors have shown that both serum osteocalcin and urinary n-telopeptide, markers of bone turnover, are elevated in the first year after surgery in patients who undergo RYGB when compared with control groups.8,9 In addition, several small studies with short follow-ups have suggested that BMD decreases after gastric bypass procedures. (21-22)

Kerstyn C Zalesin, et al at 2012:

Much of the research indicates there is an accelerated rate of bone loss after bariatric surgery; however, this process may not be based exclusively on a vitamin D mechanism. Speculations of other proposed mechanisms include: thyroid, PTH-related peptide or even direct cytokine interactions between adipocytes and osteoclastic bone cells capable of directly stimulating resorption facilitated through IL-1, IL-6, TNFα, IL-11and prostaglandin E2 Alternatively, adiponectin, an adipose regulatory protein that increases after bariatric surgery, has been suspectedin playing a role in stimulating boneresoption with weight loss. Body weight, a major determinant of bone mass, amplifies bone density in the obese particularly at weight bearing locations. Traditionally, obesity has been regarded as protective against osteoporosis. Perhaps, with surgically induced weight-loss, an accelerated loss in bonemass is the direct result of the loss of the protective effect that obesity once provided bone density. Supporting this, researchers have identified accelerated bone losses coinciding with the period of most rapid weight-loss, which plateau with weigh stabilization. This concept has been echoed in the medical weight-loss literatureas well. Weight loss produced by a very low-calorie diet in a morbidly obese population resulted in an initial (2 months) rapid 22.4 kg loss. There was a coinciding 3.3% decline in BMC as well a san increase in MBD markers such as: serum osteocalcin and hydroxyproline: creatinine ratio within this time frame. However, when reassessed at 8 months, after an additional modest weight loss of 7.3 kg, no further changes in BMC were appreciated. This study demonstrates that the rapidity of weight loss coincides with the greatest losses of BMC. This may indicate that bone loss after weight loss is a natural process, owing to the minimized mechanical forces that the skeleton is required to support. The processes that govern bone metabolism with weight loss may, in fact, be heterogeneous. How these influences stimulate osteoblastic and osteoclastic cellular shifts remains unclear. The result promotes bone remodeling and exerts an evolutionary change on the skeleton, often promoting bone losses. (23-24)

M Chakhtoura, et al at 2016:

Our findings show that there is a high variability in the response to vitamin D supplementation in individuals undergoing bariatric surgery. In fact, in addition to the known predictors affecting the 25(OH)D level achieved in the general population, including baseline 25(OH)D levels and vitamin D dose, the effect of other predictors, specific to the bariatric surgery population, remain unknown. These predictors include: the amount of body fat in each

patient, the type of surgery and the degree of malabsorption following surgery. Therefore, it may be difficult to recommend one vitamin D dose that would be optimal to all, and an individualized approach seem reasonable. Indeed, following malabsorptive and combination procedures, monitoring of 25(OH)D level to assess the response to therapy has been recommended by the Endocrine Society and the American Association of Clinical Endocrinologists (AACE)/The Obesity Society (TOS)/American Society for Metabolic and Bariatric Surgery (ASBMS) guidelines on the perioperative care of patients undergoing bariatric surgery. While bi-annual monitoring was recommended by the ES guidelines, monitoring at 1, 3, 6 and 12 months was recommended by the AACE/TOS/ASBMS guidelines. Noteworthy, vitamin D doses as high as 9,000 IU daily have been used following bariatric surgery, and similar to doses up to 10,000 IU daily used in the general population, such doses have been shown to be safe. Indeed, vitamin D toxicity did not occur until 25(OH)D level exceeded 100 ng/ml. Active vitamin D supplementation is not recommended to patients undergoing bariatric surgery, but it has been suggested, exceptionally, in refractory cases with symptomatic hypocalcemia. (25-26)

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