Minireview

Vitamin D alteration associated with obesity and bariatric surgery

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Impact statement

Obesity and severe obesity constitute growing serious health problems reaching epidemic proportion in most countries with a prevalence increasing from 6.4 in 1975 to 14.9% in 2014. This present review summarizes currently available data on vitamin D deficiencies in the obese population before and after bariatric surgery. The important evidence emerging from our evaluation confirms that obese patients are at risk of multiple nutritional deficiencies, especially vitamin D deficiency, before bariatric surgery. Our survey confirms that the precise role of the gut microbiome and its associated changes on the vitamin D metabolism after the different bariatric surgery procedures has not yet been studied. Furthermore, whether differences in the microbiota may alter the therapeutic responses to vitamin D is not known.

Abstract

Obesity and severe obesity constitute growing serious health problems reaching epidemic proportion in most countries. Interactions and relationships between obesity and bone tissue and its metabolism are complex but are more and more studied and recognized. Obesity is associated with an altered hormonal profile including particularly bone-regulating hormones like vitamin D. Bariatric surgery procedures, thanks to their effectiveness to achieve therapeutic endpoints for comorbidities associated with obesity, have had an increasing success. However, these surgeries by producing mechanical restriction and or malabsorption syndrome lead to nutritional deficiencies including vitamin D. In this review, we aim to (1) discuss the nutritional deficiency of vitamin D in the obese, (2) to summarize the different surgical options in bariatric surgery and to present the evidence concerning these procedures and their associated profile in vitamin D post-operative insufficiency, (3) to present the different recommendations in clinical practice to prevent or treat vitamin D deficiencies or insufficiencies in patients treated by bariatric surgery and finally to introduce emerging assumptions on the relationship between vitamin D, microbiota composition and circulating bile acids.

Keywords: Vitamin D, obesity, bone mineral density, bariatric surgery, bone health, endocrinology metabolism

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Introduction

The continuous increase in the prevalence of overweight and obesity is a global phenomenon.[1] Estimate trends in body mass index (BMI) in women have shown that age standardized prevalence of obesity increased from 6.4% in 1975 to 14.9% in 2014.[2] Obesity is considered a very serious public health issue because it is associated with multiple co-morbidities[3] including damage to organs as diverse as the heart, brain, liver, lungs, vessels, as well as to joints[4] and bone skeleton.[5]

Epidemiology and definition of obesity

Overweight and obesity are defined by the World Health Organization (WHO)[6] as abnormal or excessive fat accumulation that may affect health. The definition of overweight and obesity is based on the calculation of BMI, calculated by the weight in kilograms divided by height in m^2. It defines respectively the overweight and obese in grade I, grade II, and grade III by a BMI of 25 to 29.9; 30 to 34.9; 35–39.9 and over 40 kg/m^2. Obesity has become one of the most important health problems worldwide, according to WHO estimates, made in 2005, the projections anticipate that 2.3 billion adults will be overweight and more than 700 million clinically obese (http://www.who.int/mediacentre/factsheets/fs3a/eu/index.html, assessed June 2016).

The National Health and Nutrition Examination Survey of 2007–2008 placed the overall prevalence of adult obesity in the United States at 33.8%; with 32.2% for males and 35.5% in women.[7] The prevalence of obesity (BMI (30 kg/m^2) in Europe lies in the range of 10 to 20% of adult men and 15 to 25% among adult women; almost half of the European population is overweight or obese (BMI ($\geq$25 kg/m^2).[8] In this concert of global epidemic, France is no slouch. A national epidemiological survey carried out by Inserm on overweight and obesity (weight and height declarative), indicated that 32.3% of French adults over 18 years would be overweight with 15% clinically obese.[9] (http://www.roche.fr/content/dam/corporateroche_fr/doc/obepi-2012.pdf; carried out June 2016).

This latest study Ob-Epi-Roche conducted in 2012 estimated that approximately 6,922,000 people in France were obese, or 15.7%of women and 14.3% of men.[9]

In a national study carried out in 2006 and conducted in a population aged 18 to 74 years, the prevalence of obesity and overweight (weight and height measured) was, respectively, 16.9% and 32.4%.[10]

This present review summarizes currently available data on vitamin D deficiencies in the obese population before and after bariatric surgery. Data from the adult population are reviewed. Potential mechanisms explaining vitamin D deficiencies in obese patients and management of vitamin D deficiencies are discussed in the light of the most recent international recommendations. For this review, Pubmed articles were reviewed through 1 August 2014 by both authors using the search terms ''obesity,'' ''vitamin D,'' ''bariatric surgery,'' ''vertical sleeve gastrectomy (VSG),'' ''vertical banded gastroplasty,'' ''Roux-en-Y gastric bypass (RYGB),'' ''laparoscopic adjustable gastric band (AGB),'' ''biliopancreatic diversion (BPD) with duodenal switch'' and ''bone''. References from the retrieved articles and publications in both authors library were also used.

Owing to the heterogeneity of existing evidence in this field, the results of this review have been structured as a narrative covering the following domains:

- Nutritional deficiency of vitamin D in the obese.
- Bariatric surgery.
- Nutritional deficiency in vitamin D after bariatric surgery.
- How to treat vitamin D deficiency?

We accordingly provided a data synthesis in each section.

Nutritional deficiency of vitamin D in the obese

An excess of calorific intake in connection with insufficient energy expenditure is at the origin of an imbalance of the energy balance and contributes to the occurrence of a state of positive energy balance and obesity. Despite a high calorific consumption, the associated nutritional quality is often poor, with low protein, vitamin, and mineral intake. Thus, the term malnutrition or state of ''malnutrition, high calorie'' has been proposed.[11,12] It was established that obesity altered food absorption, metabolism, distribution and excretion; moreover, obesity affects the storage and availability of metabolic substrates.[12,13]

Many studies have been interested in the micronutritional status and vitamin intake of obese patients.[11–17] The largest study took into consideration the case of 232 patients with morbid obesity status (BMI $\geq$40 kg/m^2) evaluated for bariatric surgery.[15] In this population, 48.7% of patients had a deficiency of vitamin D, vitamin B12, and zinc.[15] Phosphate deficiency was highlighted in 5 to 10% of the patients; however, less than 5% of patients were deficient in magnesium.[15] Prevalence figures as high as 80 to 90% of vitamin deficiency could be reported, the extent of the deficiency ranging from discreet to severe.[18] Vitamin D deficiency is one of the most commonly occurring micronutrients in the obese population.[11,13–16,19,20] The causes of vitamin D deficiency are multifactorial. Among the selected causes are (insufficient) low exposure to solar radiation,[21] a reduction in the bioavailability of vitamin D in relation to sequestration (storage) of this fat-soluble vitamin in adipose tissue present in excess in case of obesity.[22] This vitamin D deficiency could be linked to inadequate vitamin D intake by food and supplements despite overall high calorific intake.[23] In addition, a decrease in hepatic production of 25-hydroxy vitamin D due to hepatic steatosis and a decrease in synthesis of vitamin D through the skin may also intervene.[19,24] A US study showed that individuals with the most severe obesity were those whose ethnicity was African-American and those with low sun exposure appeared to be most at risk of deficiency in vitamin D.[19] In this latest study, it was highlighted that for each increase of one kg/m^2 of BMI, there was a decrease of 1.3 nanomole/l of serum 25 – OHD.[19]

Hyperparathyroidism is also common in obese subjects, and although this anomaly may be secondary to vitamin D deficiency, an independent association of vitamin D between parathyroid hormone and obesity has been reported.[25,26] A mechanism of impaired calcium homeostasis in obesity has been raised to explain the high levels of PTH.[27] These authors have highlighted a shift to the left of the calcium PTH curve in patients with morbid obesity resulting in a lowered threshold of the ''set point'' calcium for PTH response given.[27]

Potential role of vitamin D in obesity

Several studies reported an association between obesity and vitamin D deficiency.[28,29] Recently, meta-analyses based on cross-sectional and observational studies strongly suggested that the prevalence of vitamin D deficiency was significantly different between control and obese group.[29,30]

Although the cross-sectional studies supported an increase in insulin sensitivity following vitamin D supplementation,[31] the meta-analyses[29,30] did not show any weight reduction in obese patients. Yet, intermediate biomarker of obesity demonstrated an inverse relationship between adiposity and low vitamin D levels.[32] However, as highlighted by Ibero-Baraibar *et al.*,[33] no causal relationship has been proved. Note also that, this relationship could be also altered by the volumetric dilution and sequestration of vitamin D in adipose tissue.[34]

A low-grade chronic inflammation through the activation of several signalling pathways could lead to the promotion of pro inflammatory cytokines as a consequence of obesity.[35] Conversely, vitamin D has been recognized for its anti-inflammatory benefit on various immune cells type although not confirmed in randomized controlled trials.[36]

More debates are currently progressing on the relationship between cancer, obesity, and vitamin D.[37] Yet, two studies including large sample of patients showed no significant relationship.[38,39] However, more recently, Swami *et al*. explored that the breast cancer-ovariectomized mice model revealed that vitamin D played a role in decreasing the delay in tumor appearance and the progression of the mammary tumors through several signaling pathways.[37]

Bariatric surgery

Obesity and overweight lead to a decrease in life expectancy and reduced quality of life. European data indicate that 7.7% of all deaths are attributable to excess weight, which would lead to the figures of one death out of 13 each year which may be related with overweight.[40] The risk of death at the age of 50 years, in men and women non-smokers whose BMI is greater than 40 kg/m^2, is increased by 3.82 and 3.79, respectively.[41] The rate of mortality among severely obese males is more than 12 times higher than that of young men of normal weight.[42]

Bariatric surgery has shown a tremendous growth in recent years because of the development of laparoscopic surgery on the one hand and on the other hand, the effectiveness of bariatric surgery in terms of sustained weight loss in time,[12,43] regression of complications of obesity[44,45] and a decrease in mortality.[46,47]

The regression of the co-morbidities associated with obesity and weight loss is a function of the type of procedure used for bariatric surgery.[48] Surgical techniques are restrictive or malabsorptive by nature or even combine dietary restriction with malabsorption (Figure 1).

Based solely on the gastric restriction techniques, reduced food intake is achieved by reducing the stomach volume and/or delaying the emptying of the stomach. The banded adjustable gastric laparoscopy or AGB is with the vertical banded gastroplasty and the so-called longitudinal gastrectomy in sleeve or ''VSG'' major surgical procedures to restriction. In the event of AGB, the proximal part of the stomach is reduced (a small pocket is created) (Figure 1) which can only contain small amounts of food. In the VSG, more than 80% of the stomach is reduced (Figure 1). Nutrients quickly pass the residual stomach, leading to an alteration in intestinal hormones.

Mixed techniques associated with a gastric restriction contribute to the creation of intestinal malabsorption by creating a short circuit gastric (''gastric by-pass'') or a BPD. The ''RYGB'' technique, the name of the Swiss surgeon who originally performs this technique, combines restrictive and malabsorptive procedures. The restriction is associated with the creation of a small stomach pouch from the proximal part of the stomach. This pocket is anastomosed to the proximal jejunum to create a digestive tract. In this situation, the food bowl blends with the bile and secretions pancreatic in distal jejunum (Figure 1).

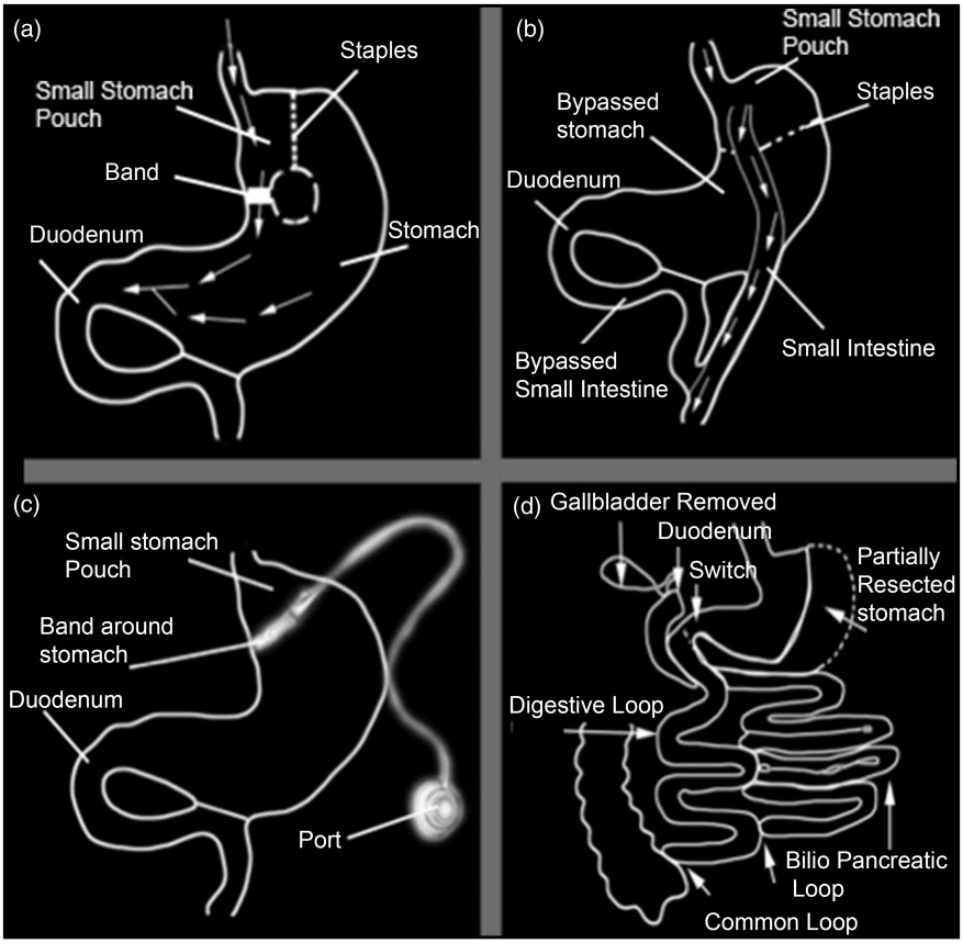

Figure 1 The different types of weight loss surgery. (a) Vertical banded Gastroplasty, (b) Roux-en-Y Gastric Bypass, (c) Gastric Lap Band Surgery and (d) biliopancreatic diversion surgery

In the derivation BPD combined with duodenal switch, the food bowl is subject to a short circuit of most of the small intestine; the longitudinal gastrectomy is associated with an anatomose distal ileum where the food bolus mixes with digestive enzymes. In these last two procedures, the intestinal surface area available for the absorption of the food bowl and the calories is reduced, leading to malabsorption of mineral and fat-soluble vitamins including vitamin D.

Nutritional deficiency in vitamin D after bariatric surgery

Although consecutive to bariatric surgery nutritional deficiencies are well-documented,[49–52] the literature emphasizes methodological weaknesses in studies addressing the phosphocalcic metabolism and bone sounding in patients who have had bariatric surgery.[50,51] The limitations of the studies in terms of interpretation of data are linked most often to the weakness of samples of patients, the lack of consistency of the measurements made, out of study patients substantial rates, especially as soon as the track exceeds one year. The heterogeneity of patients studied in terms of age, gender, ethnic group, and surgical techniques is also a source of limits. Finally, in many studies, calcium and vitamin D supplementation is part of the routine clinical care and is often subject to ancillary study to the main study protocol, thus persistence and adherence to treatment with vitamin D are not evaluated.[51]

The type of bariatric surgery will influence the degree of weight loss, calorific deficit, and malabsorption. Thus, in the procedure known as RYGB, the longer the intestinal loop, known as the Roux loop, the shorter the common circuit, (i.e. the rest of the distal jejunum, ileum and colon), the higher the degree of malabsorption.[53–55] The type and degree of vitamin deficiency and minerals are also bound to possible post-operative complications such as problems of bacterial overgrowth, food intolerance, or vomiting.

The duodenum and proximal jejunum are the main sites of absorption of calcium by passive diffusion, and on the other hand by the effects of vitamin D. Calcium deficiencies are most often the result of intolerance of patients to products containing calcium, like milk and milk products, but is also a result of the short circuit of the duodenum in the RYGB procedure.

The main causes determining vitamin D deficiency in patients after bariatric surgery are:

- The initial vitamin D deficiency, prior to any surgical procedure of obese patients, already described above.
- Inadequate vitamin D supplementation during rapid weight loss induced by bariatric surgery.
- Bile salt deficiency associated with bariatric surgery procedures (the absorption of vitamin D requires the presence of bile salts).
- Malabsorption of vitamin D sometimes due to intestinal bacterial overgrowth problems.[56]
- The absorption of vitamin D which basically occurs next to the jejunum and ileum can be affected by the delayed blend of nutrients ingested with bile acids and pancreatic enzymes.[57,58]

Below, we describe the effects of the main procedures of bariatric surgery on the metabolic impact of vitamin D.

Most commonly used procedures are currently number 4: gastric ring (or AGB), the longitudinal gastrectomy or sleeve gastrectomy so-called ''vertical sleeve gastrectomy (VSG), the procedure of the RYGB, the BPD with duodenal switch (Figure 1).

In the case of an AGB, it is usual to observe a weight loss in the order of 20 to 30% of the initial weight of patients[59] and a loss in the range of 41 to 54% of excess weight as defined by a BMI greater than ideal, i.e. more than 25 kg/m^2 weight.[60] It seems that despite well-documented pre-operative vitamin D deficiency, this type of surgery does not disrupt the serum vitamin D levels that remain stable or increase, as well as the rate of PTH, which remains stable.[61,62]

The VSG procedure can show a weight loss in the order of 20 to 30% after two years, which equates to a loss of excess weight in the range of 45 to 64%.[59,63–65] In one of the first studies that focused on the phosphocalcic metabolism in this type of procedure, it was shown that if 95% of the patients were vitamin D-deficient and had high levels of PTH in the study prior to surgery, in post-operative, 25-hydroxy vitamin D levels increased and those of PTH decreased.[63] However, it should be noted that no information was available in this work concerning the use of supplementation and therapeutic adherence. A prospective study published in Spanish in patients with higher initial vitamin D found that the PTH levels did not vary and that vitamin D had increased.[66]

More data are available on the metabolism of vitamin D after the RYGB procedure. Typically, after this type of surgery, patients can lose up to 35% of their initial weight, which equals a loss of 62 to 75% of their excess weight.[60,67–69] As early as the third month after this surgery, calcium malabsorption was observed[70,71] with a reduction in the fraction of absorbed calcium.[57]The first studies on the effect of the RYGB on vitamin D highlighted the high rates of vitamin D deficiency.[72,73] This data has led us to adopt an aggressive therapeutic attitude of vitamin D repletion. However, the observed improvements were not proportional to the proposed supplementations. For example, in a study where an increase of 200% of vitamin D intake was given (corresponding to average intakes of 658 IU per day at the beginning of study and 1698 IU per day at 12 months), vitamin concentrations remained stable.[70] No increase in serum 25-hydroxy vitamin D levels was noted in a study where the daily intakes of supplementation were in the region of 5000 IU per day.[74] If, respectively, lower vitamin D and higher PTH levels were observed in a study comparing the effects of the RYGB 3 aged over one year post-operative, no information on adherence to the supplementation was specified.[75]

The procedure for BPD associated with duodenal switch is responsible for the most weight loss and is usually reserved for patients with very severe morbid obesity (BMI $\geq$ 50 kg/m^2). With this type of surgery, loss of excess weight can go up to 70–80%.[76–78] Despite supplementation to a very good dose after this surgery, more than 50% of patients have a deficiency in vitamin D.[77,79–81] Comparison

of the values of 25-hydroxy vitamin D in post-operative rates in a clinical trial with the surgical procedure (RYGB versus BPD) randomization has shown deficits more pronounced in the BPD group compared to the RYGB group. In addition, the use of vitamin supplementation D was higher in the BPD versus RYGP Group.[82]

It has been recently reported that despite the severe vitamin D deficiency following bariatric surgery, the vitamin D supplementation proposed by guidelines[83] permitted to reach wear optional levels of serum 25 (OH) D.[84]

How to treat vitamin D deficiency?

Serum 25-hydroxy vitamin D seems to be routinely checked before surgery.[51] However, although 25-hydroxy vitamin D concentrations are lowest in obese or overweight patients or overweight than in subjects of normal or low BMI otherwise comparable, current clinical recommendations are based on the same threshold to define deficiency in vitamin D in patients of normal weight and obese subjects.[84–86] The National Union of Sickness Assurance decided in January 2014 to not to authorize payment for 25-hydroxy vitamin D dosing in limited indications selected by the high authority of health (HAS). The surgical treatment of obesity in adults is one of the indications listed by the HAS.[87] The proposed extension of the indications of the determination of 25-hydroxy vitamin D before and after bariatric surgery to other clinico-biological situations of mal absorption is discussed.[88]

Obesity defined as the presence of adult BMI 30 kg/m2 is also indicated at a dosage of 25-hydroxy vitamin D by several learned societies.[89–91] In the HAS document, the quality criteria for the evaluation and improvement of practices in the case of Bariatric Surgery and support pre and post-operative patient care[48] stated that the result of the determination of vitamin D should be included in the patient record. Also, stated in the same document,[48] it was recommended that after malabsorptive surgery, systematic supplementation with vitamin D would be made and that supplementation should be discussed in ''the clinical and biological balance'' function after restrictive surgery.[48]

European recommendations advise biological monitoring in the case of restrictive surgery to monitor the nutritional and metabolic state on the one hand and on the other hand to prevent vitamin deficiencies and enable appropriate supplementation as necessary on a regular basis without specifying the precise rhythm.[92] On the other hand, the rhythm of blood tests for determination of the 25 OHD is specified in case of gastric short circuit and BPD, respectively, on an annual basis and in 1 month, 4 months, 12 months, and then annually.[92]

In the past, because of the technical surgery involved, very specific bone consequences associated with deficits in vitamin D and calcium could be observed, as for example the creation of a brown tumor,[93] case of osteomalacia, secondary hyperparathyroidism, but also confirmed histologically osteoporosis.[94–96] The recommendations of supplementation with calcium and vitamin D in patients who are going to have bariatric surgery as well as the most recent surgical procedures now allow us to expect a better prevention of bone loss and possible fractures. The risk of fracture after bariatric surgery remains a matter of controversy; a study showed twice the risk in patients who have had bariatric surgery compared to the rates of incidence based on the general population,[97] the other study showing no increase of the risk of fracture in the first two years after surgery compared to a non-operated obese population.[98]

There are very many recent recommendations in clinical practice focusing on patients treated with bariatric surgery[84,99,100] (Table 1). While these recommendations are the subject of extreme care by their authors using all of the relevant and available data literature, certain recommended measures are not always based on medical data

Table 1 Pre and post-operative bone health recommendations of the post-bariatric surgery patient

	Apovian et al.[86]	Endocrine society[87]	AACE/TOS/ASMBS[36]
Pre-operative	Monitor for deficiencies in vitamin D and calcium If deficiencies in vitamin D: repletive doses	Monitoring and screening of vitamin D, calcium, intact PTH. Assessment of bone mineral density and composition.	No preoperative assessment of BMD by DXA outside formal clinical practice guideline by the National Osteoporosis Foundation in patients with LAGB. Appropriate nutritional evaluation including micronutrient measurements.
Post-operative		Monitor vitamin D, calcium, phosphorus, alkaline phosphatase levels every 6 months. DXA for bone density performed yearly until stable.	In patients with RYGB, BPD or BPD/DS, bone density measurements with use of axial (hip and spine) DXA may be indicated to monitor for osteoporosis at baseline and at about two years.
		Suppletive doses of vitamin D and calcium post-operatively for malabsorptive obesity surgical procedures. Doses to be adjusted by a qualified medical professional based on serum markers and measures of bone density.	Appropriate therapy for calcium and vitamin D insufficiency. Evaluation should include PTH, total calcium, phosphorus, 25-hydroxyvitamin D and 24-h urine calcium levels.

AACE: American Association of Clinical Endocrinologists; ASMBS: American Association of Metabolic and Bariatric Surgery; BMD: bone mineral density; BPD: biliopancreatic diversion; BPD/DS: biliopancreatic diversion with duodenal switch; DXA: Dual energy X-ray absorptiometry; LAGB: laparoscopic adjustable gastric band; PTH: parathyroid hormone; RYGB: Roux-en-Y gastric bypass; TOS: The Obesity Society

or evidence. This is especially true for vitamin D supplementation.

The randomized trials evaluating the best diet of vitamin D in terms of effectiveness and tolerance have been worthwhile. They established that daily doses up to 800 IU are inadequate to restore good levels of vitamin D in cases of deficiency in patients who have had a procedure type RYGB.[101–103] A randomized study showed that taking 50,000 IU ergocalciferol weekly gave at one year higher values of 25-hydroxy vitamin D than in the daily intake of 800 IU. Daily doses of 800, 2000, 5000 IU were given randomly to patients having also an RYGB procedure.[104] In this last work, 25-hydroxy vitamin D rates increased in all patients, supplementations to 2000 and 5000 IU were associated with a greater increase of serum 25-hydroxy vitamin D. However, this work included serious limitations: small sample ($n = 47$), variable adherence of a group to another, many dropout of study and differences at the beginning of study for the rate of PTH and vitamin D.[104] In addition, it should be noted that the variability of the required contributions from one individual to another, argues for the importance of regular monitoring of the rate of PTH, calcium and vitamin D in patients after bariatric surgery.[105,106]

Vitamin D deficiency on one hand and overweight or obesity on the other hand which are two possible causes of low back pain[107,108] might be prevented to limit the global burden of low back pain which is associated with high disability.[109] In addition, a non-linear association between vitamin D levels and obesity with mortality has been discussed highlighting the need to manage this situation.

Conclusions and perspective

Obese patients are at risk of multiple nutritional deficiencies, especially vitamin D deficiency, before bariatric surgery.

The vitamin D insufficiency is very prevalent in obese subjects. Many causes have been suggested to explain this fact, but the most important mechanism appears to be the sequestration of vitamin D in adipose tissue. The availability of vitamin D stored in the fatty tissues and the mechanisms that govern its mobilisation to the serum are still poorly elucidated.

Bariatric surgery and substantial weight losses associated with it expose even more obese patients to multiple nutritional deficiencies including vitamin D. Malabsorptive surgical procedures are associated with a higher risk of deficiency in vitamin D than those of restrictive surgery.

Revise and update recommendations from the 2008 interdisciplinary European guidelines on metabolic and bariatric surgery include 25OH Vit D3 among the laboratory tests that should be evaluated annually both after food limitations operations and after operations limiting absorption of nutriments.[110]

The latest recommendations of the learned companies of American Endocrinology, Obesity, and Bariatric Surgery focus on the interest of the measurement of the rate of vitamin D blood before and after bariatric surgery procedure and offer patients should be treated with 3000 IU of vitamin D daily substitution, in order to obtain 25-hydroxy vitamin D levels greater than 30 ng/ml.[83]

Recently, a putative role for circulating bile acids and farnesoïd-X receptor signaling (FXR) to the metabolic improvements seen after bariatric operations has been evidenced.[111]

In turn, both FXR signaling and modified bile acid homeostasis might be implicated in the drastic change in microbiota composition after bariatric surgery.[112] The precise role of the gut microbiome and its associated changes on the vitamin D metabolism after the different bariatric surgery procedures has not yet been studied. In addition, whether differences in the microbiota may alter the therapeutic responses to vitamin D is not known.

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