1 **A place for vitamin supplementation and functional food in bariatric surgery ?**

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Abstract:

- **Purpose of review:** This article summarizes the recent literature concerning vitamin deficiency and required supplementation post bariatric surgery (BS), with a focus on vitamin (and associated clinical adverse effect on bone loss) and on the potential implication of the gut microbiota.
- **Recent findings:** BS improves health outcomes in terms of weight loss and metabolic alterations yet with major inter-individual variability. Indeed, although BS is efficient in most patients, some display poor response (i.e. patients with the lowest weight loss at one year or weight regain afterwards, or patients who do not undergo metabolic disease remission). Furthermore, despite systematic vitamin supplementation post-BS, some patients develop vitamin deficiencies leading to poor clinical outcomes. Specifically, a major recently described adverse outcome is vitamin D deficiency associated in part with observed bone mass loss and fractures. Recent mechanistic studies have been performed to better understand the involved physiopathology. Furthermore, different intervention studies tested on top of BS (using vitamin supplementation, diet or nutrients acting as functional food) have evaluated whether they could improve these nutritional adverse outcomes and are summarized herein. Importantly, gut microbiota involved in food digestion and metabolization as well as vitamin synthesis, is largely perturbed during severe obesity and is partially restored post-BS, yet again with large inter-individual variability. Whether differential modification of the gut microbiota could be associated with those vitamin deficiencies is an open question.
- **Summary:** Future clinical research studies will need to evaluate whether add-on intervention to BS using vitamin, diet or specific food items could help prevent nutritional deficiencies and improve clinical response observed post-BS. More importantly, personalizing the add-on intervention after BS upon gut microbiota composition should be tested in predicted poor

responders to BS as already performed during diet intervention to further improve metabolic health.

- **Keywords:** bariatric surgery, vitamins, functional food, microbiota

Introduction

Obesity progresses worldwide. Thus the number of bariatric surgeries (BS) reserved for the most severe cases (i.e. body mass index (BMI) $\geq 40 \text{ kg/m}^2$ or $\geq 35 \text{ kg/m}^2$ associated with specific comorbidities [1]) increases in parallel [2]. Several BS procedures exist among which vertical sleeve gastrectomy (VSG) and Roux-en-Y gastric bypass (RYGB), the two most commonly performed [3], followed by adjustable gastric banding (AGB) and biliopancreatic diversion (BPD), respectively. However, if BS decreases weight and improves metabolic diseases and global health [4], it also leads to secondary effects among which frequent vitamin deficiencies [1]. As reviewed in length in [5], the mechanisms involved in vitamin and mineral malabsorption include reduced gastric pouch and caloric intake and rearrangement of the digestive tract inducing pH modification (both in VSG and RYGB) and decreased nutrient absorption in RYGB. Modification of the gut microbiota could also be involved as discussed later in more details.

The American Society for Metabolic and Bariatric Surgery (ASMBS) has reviewed the current literature for vitamin deficiencies. They observed large interindividual variability among studies and patients [6]. Monitoring vitamin deficiencies before and mostly post-BS as well as prescribing systematic vitamin and mineral supplementation is largely recommended post-BS.

The gut microbiota represents a recently described organ involved amongst others in digestion, intestine homeostasis, vitamin biosynthesis and metabolite production all of which playing important roles for the host health [7,8]. Murine studies exploring gut microbiota composition as well as experiments using transfer of microbiota from mice or humans into germ-free mice have demonstrated

that the gut microbiota is a novel factor involved in obesity pathophysiology as reviewed in details in [9–11]. Human studies have reported that obesity is characterized by a major gut microbiota dysbiosis (i.e. large perturbation of the gut microbiota composition and functionality). In particular, obesity is characterized by decreased microbial gene richness and modified composition when compared to lean individuals [12,13]. This dysbiosis is exacerbated during severe obesity [14]. Interestingly, BS has been shown to dramatically modify gut microbiota composition [5,15,16] in general post-RYGB [14,17] but also in some cases post-VSG [18]. However, after RYGB the rescue of gut microbiota is incomplete [14,19]. Importantly, some changes in gut microbiota composition are associated with improvement in clinical outcomes (such as improved corpulence and reduced inflammation). Yet, half of these associations are dependent on calorie and nutrient consumption [20,21] suggesting the important role of food items in both the shaping of gut microbiota and also on the host's metabolic health.

In this context, the field of functional food has emerged over the past ten years; functional foods are defined as biologically active ingredients considered functional since they are associated with physiological health benefits related to the maintenance or improvement of health (such as for example fibers, flavonoids or polyphenols). Amongst them, some specific food or ingredients can even be related to prevention or even treatment of several chronic diseases [22]. Importantly, the digestion of some food items requires the gut microbiota to be metabolized into metabolites with beneficial effects for health. A most commonly cited example lays with fibers transformed into short chain fatty acids (SCFA)[8] [23]. Thus, functional food seems partly related to the gut microbiota activity as discussed in [24].

This review will address the current knowledge on vitamin deficiencies and supplementation required post-BS and its most recent raised adverse outcomes in particular impacting the bone. We will discuss how and which diet items (if any) considered as functional food could help prevent or improve BS-induced nutritional complications or even further enhance beneficial clinical outcomes observed post-

BS. A pending question is whether the modified gut microbiota composition could be involved in vitamin deficiencies observed post-BS. [25].

Vitamin deficiency and need for supplementation following bariatric surgery:

Recent guidelines recommend [6] systematic vitamin supplementation following BS in order to reach an adequate nutritional intake and to limit vitamin deficiencies [26–28] on top of the usual diet. In principle, such vitamin supplementation should prevent vitamin-deficiency associated complications which may impair overall health. Nevertheless, despite good compliance, some vitamin deficiencies and protein malnutrition can still be observed [26–28]. Recently, the ASMBS has reviewed the current knowledge concerning BS vitamin follow-up and supplementation after BS and proposed an updated version of these recommendations including 79 new proposals [25]. However, the level of evidence upon which these recommendations have been proposed is in general intermediate or weak due to the lack of sufficiently powered studies or randomized control studies (RCT). Overall, ASMBS experts propose to systematically supplement patients with folate, iron, calcium, B vitamin (B1 Vitamin/thiamin and cobalamin/vitamin B12), lipid soluble vitamin (A, D, E, K), zinc and copper, whatever the surgery type. Noteworthy for most malabsorptive surgery models (most particularly BPD and to a lesser extend RYGB), an increase in the dosage of the systemic vitamin and mineral supplementation is recommended for calcium, vitamin A, K, iron, copper and zinc [25], in order to meet the official daily requirement intakes thus taking into account BS induced malabsorption. New forms of multivitamins actually contain the adequate proportion of these micronutrients and vitamins needed post-BS and seem to be associated with less occurrence of vitamin deficiencies during follow-up [29]. New means of delivery are also being tested (i.e. transdermal vitamin patch) but only one small powered study has evaluated its

efficacy to prevent vitamin deficiencies [30]. These new forms of multivitamins will need evaluation on larger sample size to examine both reduced vitamin deficiencies and reduction of related clinical events.

Importantly, recent retrospective studies have evaluated the prevalence of nutritional deficiencies despite the use of oral systematic supplementation. Vitamin deficiencies are found after both RYGB and VSG [31] independently of the amount of weight-loss. Importantly, studies reveal that vitamin D deficiency is the most common one during the first year post-BS and increases thereafter in both VSG and RYGB, despite systematic supplementation [32]. As a consequence, increased parathormone levels were observed post-RYGB [31], in line with previous data [1]. Noteworthy, transdermal vitamin patch delivery performs even worse than oral pills to prevent vitamin D deficiency [30]. In studies with longer follow-up (i.e. 5 [33] to 10 years [34]), the prevalence of vitamin D insufficiency or deficiency reaches up to 60% of patients [33,34]. More worryingly, this is present in a large proportion of patients having a bone mineral density (BMD) below the normal range, or even osteopenia and osteoporosis, thus increasing the risk of low-energy bone fractures [34]. This adverse effect represents one of the recent concerns arising in the mid and long term post-BS.

If these clinical observations are frequently observed at mid-term post-RYGB [35,36], the precise mechanisms underlying this BMD loss and deleterious changes in bone microarchitecture [37] are not yet completely understood and probably go beyond vitamin deficiency. A recent mouse study demonstrated that VSG per se may induce both loss of trabecular and cortical bone mass and bone weakness, independently of weight-loss, diet, sex or gut hormones [38]. Furthermore, VSG may induce a reduction of bone formation and mineralization as well as a myeloid cell expansion and an increase of circulating G-CSF both in mice and humans post-VSG. The increase of G-CSF per se recapitulated at least partially the BMD decrease in mice. Indeed, other mechanisms independent of G-CSF are also involved in BMD loss post-VSG since G-CSF KO mice undergoing VSG were not completely protected against bone loss [38]. Importantly, the effect of vitamin D deficiency on top of these myeloid modifications were not

evaluated in this study and further explorations are needed. A number of other factors are involved in this BMD loss as discussed in detail in [39]. Among them, the gut microbiota might also be involved since germ-free mice models display increased bone mass due to reduction in bone resorption [40]. Another indirect proof of the link between gut microbiota and PTH-vitamin D status lays in a recent retrospective study which reports a positive correlation between increased PTH levels (secondary to decreased calcium absorption) and loose stools post-BS [41]. Loose stools have been associated with a specific dysbiotic microbiota composition and reduced microbial gene richness with contribution of a proinflammatory context [42]. One could thus hypothesize that gut microbiota changes might be involved in increased bone resorption function in some individuals post-BS.

Another concern following BS is the deficiency in vitamin B1 thus leading to Gayet-Wernicke encephalopathy, which can occur specifically in patients vomiting due to surgical complications post-BS [43]. Interestingly, if Gayet-Wernicke encephalopathy was initially described post-RYGB, a number of cases were also more recently reported post-VSG [43–45] which is the major BS worldwide [3]. Importantly, it was recently demonstrated that some gut bacteria were able to produce and to provide some vitamins (in particular thiamin) to the host [46]. One could thus hypothesize that some individuals are more prone to thiamin deficiency according to their gut microbiota profile and to differential post-BS changes across individuals. This research area has not yet been properly evaluated. Other deficiencies from the B vitamin group may also occur in particular for B12 after the first year [31] which may also involve the gut microbiota [47].

Functional changes in gut microbiota after bariatric surgery: links with vitamins and nutrients.

Literature has now repeatedly reported that gut microbiota composition is modified post-BS, whatever the surgery type, as reviewed in [5,15,16]. More importantly than microbial composition per

se, metagenomic studies post-SG have also observed switches in functional capacities of gut microbiota as compared to the ones present in the severely obese state. More importantly, the observed functional capacities of the gut microbiota 3 months post-SG were similar to those characterizing lean individuals [18] suggesting that BS could at least partially restore gut microbiota dysbiosis. As such, 3 months post-VSG, a number of enzymatic functions are modified upon BS-induced weight loss, including vitamin pathways (i.e. a decrease in thiamin metabolism and folate biosynthesis and an increase in riboflavin (B2) metabolism) but also impaired nutrient fermentation (decrease in carbohydrate metabolism) and amino acids biosynthesis and degradation [18]. Longer-term studies have observed a shift of intestinal fermentation towards reduced production of SCFAs and increased amino acid fermentation post-BS due to reduced carbohydrates intake and increased protein fermentation [17]. These changes seem to occur independently of diet modifications. These switches in functional gut microbiota capacities could in part be secondary to the universally demonstrated decrease in calorie intake post-BS especially with a massive reduction in fiber intake [27,28]. Nonetheless, the microbiota may adapt to compensate for these nutritional changes. For example, the phosphotransferase system increases post-BS and represents a transport system for sugars and their derivatives, uniquely present on bacteria, that enable the microbes to assimilate sugars despite the reduced calorie intake observed post-BS [17,48]. Likewise, bacteria display increased transport system for different vitamin and minerals including (vitamin B1, vitamin B12, manganese, iron, and zinc) probably to increase their availability post-BS since they are also essential for microbes functioning [48]. Overall, on top of digestive tract modifications, BS induces modification of the gut microbiota functional capacities which per se could play a role in the modifications of nutrient intake and vitamin status observed post-BS.

Since the gut microbiota capacity to metabolize and ferment food is modified post-BS, preferring food items capable of being utilized by the post-BS microbiota might enhance clinical benefits on top of those observed post-BS. Although appealing, the field of precision nutrition in the bariatric

surgery context remains scarce and still hypothetical [49]. Noteworthy, tools have been developed in clinical research during fiber-enriched diet intervention programs to help prescribe the adequate diet regimen for a specific individual, based on its metagenomic profile. For example, the casino tool box is a computational platform able to model the metabolomic effect of a diet regimen in a specific gut microbiota composition context (i.e. it predicts the level and type of circulating metabolites obtained after the ingestion of a known diet based upon the known composition of the gut microbiota). More importantly, its use could, in principle, help prescribe a personalized diet regimen to an individual in order to reach a healthier metabolic state and healthier gut microbiota based upon his specific baseline microbiota composition [50]. More recently, Korem et al observed large inter-individual variability in glycemic response upon bread consumption. Specifically, they showed that baseline metagenomic profile (i.e. microbiome based classifiers) enables to predict the glycemic response of an individual after the ingestion of a specific bread type [51,52]. These tools should be tested in the BS field to evaluate whether prescribing functional foods may improve clinical outcomes and possibly reduce secondary effects such as vitamin deficiencies. Research in this field is urgently needed.

Effects of supplementation on vitamin status and clinical outcomes

Different types of interventions have been tested to evaluate their efficacy in reducing adverse bone effects post-BS. Increasing the supplementation of vitamin D by adding 50,000 IU cholecalciferol monthly, enabled a decrease in the prevalence of patients presenting vitamin D deficiency, yet some were still observed [53]. However, this study did not assess whether this increased supplementation had any effect on BMD or the number of fractures. Another 12 weeks duration RCT comparing increased dosage of calcium supplementation (i.e. 1600mg daily) composed of citrate or carbonate forms, did not show any significant difference in PTH and vitamin D levels. Noteworthy, the citrate form was associated

with reduced bone turnover markers suggesting less bone resorption [54], yet BMD was not assessed. Interestingly, more complex interventions seem to prevent BMD loss. Indeed, a recent RCT trial comparing usual follow-up (without any supplementation) to the effects of 1000mg daily citrate calcium, vitamin D and protein supplementation (adjusted to BMI and body resting energy expenditure) associated with an aerobic exercise program, demonstrated subnormal systemic vitamin levels, reduced BMD loss and bone turnover in the intervention group. More importantly, although participants were of pre-menopausal age, atraumatic fractures only occurred in the non-intervention group [55]. Finally, a recent RCT comparing the addition of exercise training to usual follow-up post-RYGB, showed a reduced loss, yet no improvement, of BMD in the exercise group. However, fractures were not evaluated in this cohort composed mostly of pre-menopausal women [56].

Importantly, the authors point at a very low compliance of vitamin and mineral supplementation during post-BS follow-up. Indeed, 16% of patients drop out of the RCT [55] and only one third of the patients reported regular calcium and vitamin D intake in retrospective studies [34]. Furthermore, the prevalence of patients undergoing systematic vitamin dosage dropped dramatically at one year post-BS which confirms previous findings of a decreased compliance to follow-up after the first years [57]. Overall, adherence to vitamin intake and compliance to follow-up are major issues post-BS.

Functional food, health outcomes and bariatric surgery: perspectives

The European commission defines functional food as “a food that beneficially affects one or more target functions in the body, beyond adequate nutritional effects, in a way that is relevant to either an improved state of health and well-being and/or reduction of risk of disease. It is part of a normal food pattern” [22]. Functional food can include dietary intake compounds or physiologically active nutrients (i.e. antioxidant vitamins, fibers for example) or non-nutrients (i.e. flavonoids for

examples) with proven health benefits. Some pieces of evidence show that intervention programs using functional food are beneficial to improve T2D control [9,58] (i.e. Mediterranean diet component or polyphenols), or some obesity related traits [59,60] (using flavonoid). Nevertheless further larger studies using precision nutrition should be undertaken before recommending a wide use in routine care [9]. However, the use of these specific functional food (for example flavonoid, polyphenols or Mediterranean diet) after bariatric surgery has not yet been evaluated. Importantly, defining the targeted patients who will mostly benefit from such add-on therapies is also mandatory (i.e. whether in all patients undergoing BS or in selected patients predicted to have a poor clinical response post-BS as defined earlier). Even though BS is effective in inducing weight loss, results display, in fact, major inter-individual variability both in the first year [61] as well as in the longer-term [62], with some patients even regaining weight. The same is observed for metabolic improvement. Indeed, while some patients undergo diabetes remission post-BS (i.e. normalization of glycemic parameters in the absence of glucose lowering drugs) [63], others remain diabetic and still need treatments despite major improvement in Hba1c target. Finally, some patients even relapse their diabetes in the mid-term [64]. Whether interventions proposed on top of BS could enhance its clinical benefice is an open question, specifically using functional food.

Nevertheless, studies evaluating whether functional food could be added to bariatric surgery in order to further improve its outcomes have not yet been performed to our knowledge. Retrospective studies have observed that patients maintaining their weight post-BS compared to those regaining weight after 18 months were those consuming more fibers and having a global healthier behavioral lifestyle [65]. Some studies have further tested whether dietary interventions associated to BS would decrease weight regain in unselected patients undergoing BS. A recent RCT [66] where patients were randomized post-BS to usual follow-up or to a lifestyle intervention program (i.e. increasing healthy food such as fruits and vegetables and improving food choices and quantities) did not evidence any difference

in weight regain between groups. However, at the end of the study period, both groups displayed similar food pattern. Likewise, another recent RCT comparing protein supplementation with or without resistance training to usual follow-up in an unselected bariatric cohort did not evidence any difference in weight or body composition outcomes [67]. Overall, these data could suggest that synergic interventions post-BS should be proposed in selected individuals predicted to display a poor response (either poor weight-loss [61] or non-diabetes remission or diabetes relapse [64]) or at risk to display adverse surgery outcomes (bone fractures) to evaluate whether it improves further health outcomes.

Conclusion:

Bariatric surgery represents an effective therapeutic tool to treat obesity and its related diseases, yet with major inter-individual variability in clinical outcomes and secondary effects in particular due to vitamin deficiencies. The mechanisms involved in differential improvement between individuals remain incompletely understood and involve many factors. Among them, the gut microbiota might play a role. Current knowledge is growing regarding the implication of gut microbiota in health outcomes. Its role in vitamin biosynthesis and degradation has been shown but further studies are needed to evaluate whether microbiota changes post-BS could be linked to vitamin deficiencies and adverse medical outcomes. Indeed, despite systematically prescribed vitamin and mineral supplementation post-BS, nutritional deficiencies still occur. This underlines the need of close biological monitoring, systematic vitamin supplementation (which needs to be increased in more malabsorptive procedures). Some interventions using vitamin or nutrients have been performed to evaluate their beneficence in risk reduction. Nevertheless, to date, precision medicine proposing specific vitamin supplement to patients predicted at risk of vitamin deficiencies has not been evaluated. With increasing knowledge on gut microbiota and its interaction with the host, this field probably represents the future research perspective. Likewise, if functional food has demonstrated its beneficence in chronic metabolic

diseases, its use post-BS has not been tested to improve specific health outcomes and thus warrants clinical studies before its prescription in routine care.

- **Key points:**

- Bariatric surgery is commonly associated with vitamin deficiencies despite systematic vitamin and mineral supplementation.
- Bariatric surgery decreases bone mass density which can be attenuated by sufficient calcium and vitamin D supplementation associated with exercise training.
- Gut microbiota is largely disturbed in severe obesity and only partially recovers after bariatric surgery.
- The modified gut microbiota post-BS is involved in vitamin pathways and nutrient metabolism switch and could thus be involved in vitamin deficiencies post-BS.
- Functional food (such as flavonoid, polyphenols or Mediterranean diet component) improves certain health outcomes in metabolic diseases, yet their use has not been tested after BS to further improve clinical outcomes in poor responders.

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