



Vitamin D and malabsorptive gastrointestinal conditions: A bidirectional relationship?

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Abstract

This paper is one of the outcomes of the 5th International Conference "Controversies in Vitamin D" held in Stresa, Italy from 15 to 18 September 2021 as part of a series of annual meetings which was started in 2017. The scope of these meetings is to discuss controversial issues about vitamin D. Publication of the outcomes of the meeting in international journals allows a wide sharing of the most recent data with the medical and academic community. Vitamin D and malabsorptive gastrointestinal conditions was one of the topics discussed at the meeting and focus of this paper. Participants to the meeting were invited to review available literature on selected issues related to vitamin D and gastrointestinal system and to present their topic to all participants with the aim to initiate a discussion on the main outcomes of which are reported in this document. The presentations were focused on the possible bidirectional relationship between vitamin D and gastrointestinal malabsorptive conditions such as celiac disease, inflammatory bowel diseases (IBDs) and bariatric surgery. In fact, on one hand the impact of these conditions on vitamin D status was examined and on the other hand the possible role of hypovitaminosis D on pathophysiology and clinical course of these conditions was also evaluated. All examined malabsorptive conditions severely impair vitamin D status. Since vitamin D has known positive effects on bone this in turn may contribute to negative skeletal outcomes including reduced bone mineral density, and increased risk of fracture which may be mitigated by vitamin D supplementation. Due to the immune and metabolic extra-skeletal effects there is the possibility that low levels of vitamin D may negatively impact on the underlying gastrointestinal conditions worsening its clinical course or counteracting the effect of treatment. Therefore, vitamin D status assessment and supplementation should be routinely considered in all patients affected by these conditions. This concept is strengthened by the existence of a possible bidirectional relationship through which poor vitamin D status may negatively impact on clinical course of underlying disease. Sufficient elements are available to estimate the desired threshold vitamin D level above which a favourable impact on the skeleton in these conditions may be obtained. On the other hand, ad hoc controlled clinical trials are needed to better define this threshold for obtaining a positive effect of vitamin D supplementation on occurrence and clinical course of malabsorptive gastrointestinal diseases.

Keywords Vitamin D · Vitamin D deficiency · Vitamin D supplementation · Celiac disease · Inflammatory bowel disease · Bariatric surgery · Obesity

1 Introduction

The 5th International Conference "Controversies in Vitamin D" was held in Stresa, Italy, 15–18 September 2021 as part of this series that started in 2017 [1–8].

The objective of this conference, which featured international experts and leaders, was to review and discuss controversial topics regarding vitamin D. Besides the well-known benefits of vitamin D on skeletal health, new evidence highlights its role also in multiple conditions not specifically related to the skeleton often referred to as extra-skeletal actions. Examples include diabetes mellitus, obesity, kidney and neurological diseases, malignant disorders and infections including COVID-19 [9, 10]. Additionally, the gastrointestinal

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tract has been a topic of current interest [4]. During the conference, discrete sessions addressed aspects of vitamin D on aging [8], COVID-19 [11], and the gastrointestinal system. Participants prepared for these sessions by reviewing the available literature on their assigned topic. After each topic was covered by presentations, open sessions enabled full discussion to reach consensus. A separate document was prepared for each component of the conference.

This paper presents topics related to vitamin D and the gastrointestinal system.

2 Background

Vitamin D is a requirement for efficient intestinal calcium absorption. Any gastrointestinal disease, as well as any surgical gastrointestinal intervention such as bariatric surgery, can lead to impaired gastrointestinal function. One key

consequence, namely vitamin D malabsorption can reduce vitamin D and calcium levels leading to negative consequences on skeletal health [7] (Fig. 1).

The relationship between gastrointestinal diseases and vitamin D is classically considered unidirectional with the gastrointestinal diseases leading to hypovitaminosis D. Emerging evidence, however, has shown that hypovitaminosis D itself can negatively influence the clinical course of the gastrointestinal disease, whether it be disease activity or recurrence [7]. These newer concepts have been advanced because vitamin D receptors, which are highly expressed in intestinal epithelial cells, mediate the pleiotropic actions of vitamin D which include immunomodulatory actions. To this end, vitamin D has the potential to regulate gut mucosal immunity, a key pathophysiological aspect of inflammatory bowel diseases (IBDs), such as Crohn's disease (CsD) and ulcerative colitis (UC). Celiac disease (CD) is also potentially affected by the immunomodulatory actions of vitamin D. Thus, the current concept being advanced in this paper

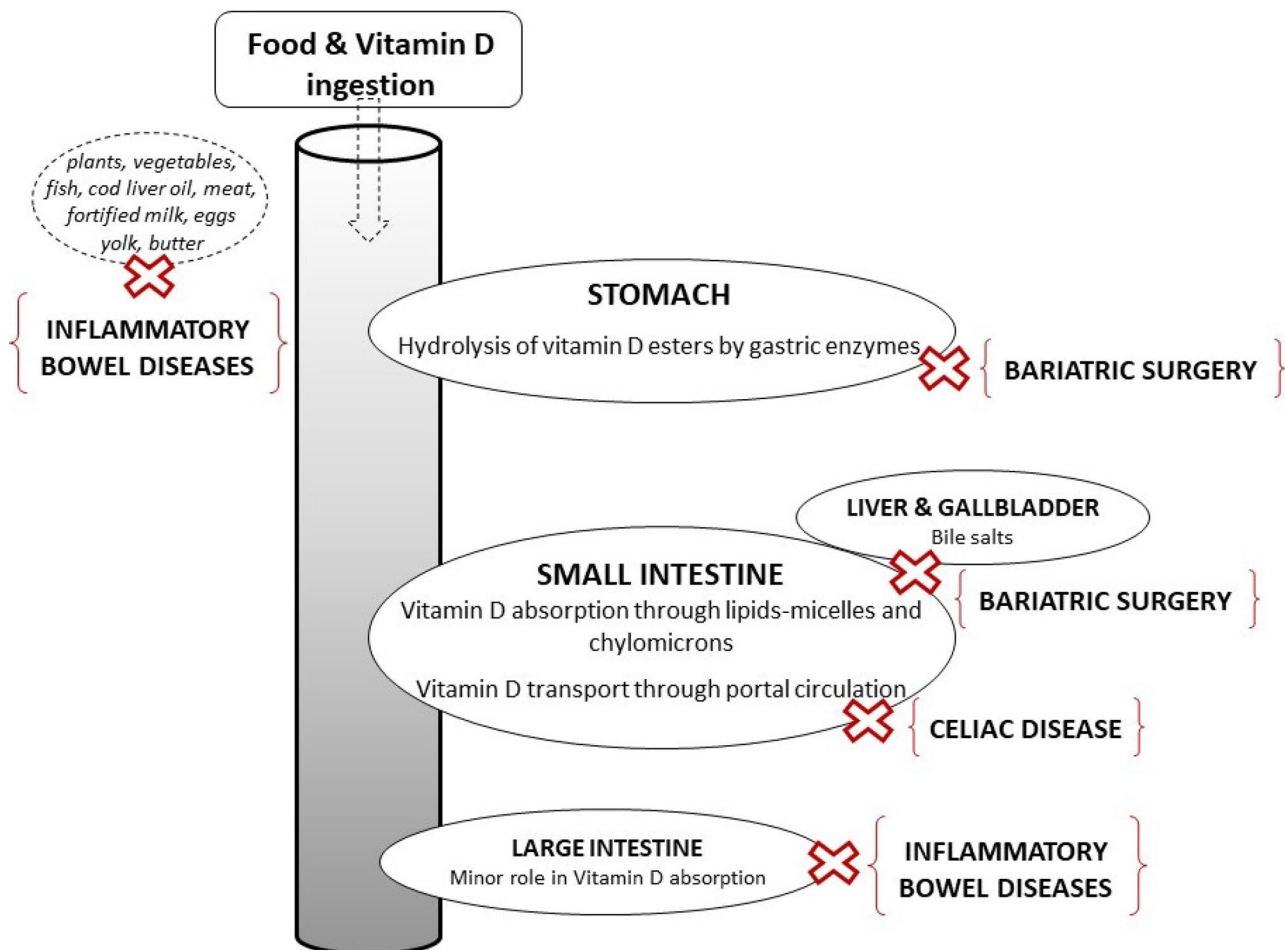


Fig. 1 Pathophysiology of Vitamin D malabsorption in Celiac Disease, Inflammatory Bowel Diseases and Bariatric Surgery

is that there is a bidirectionality to vitamin D and the gastrointestinal tract. Gastrointestinal diseases associated with malabsorption can lead to variable degrees of vitamin D deficiency and its classical consequences on skeletal and extra-skeletal health (Fig. 2). Hypovitaminosis D can also lead to exacerbation or recurrence of diseases of the gastrointestinal tract, particularly in IBDs, and potentially also attenuate the efficacy of bariatric surgery (Fig. 2). This concept helps to underscore the guidelines that place vitamin D adequacy as a cornerstone of therapeutics for the examined gastrointestinal diseases [7].

This paper summarizes the evidence for this bidirectional relationship between vitamin D and the gastrointestinal tract as summarized by the deliberations at this international conference.

3 Calcium intestinal absorption in healthy individuals

The intestine is the first and best studied target for active vitamin D, 1,25-dihydroxyvitamin D [$1.25(\text{OH})_2\text{D}$]. The ratio of transcellular to paracellular calcium absorption directly follows from the levels of transcription of various genes, including those best known to be under regulation

by $1.25(\text{OH})_2\text{D}$, and in particular *Trpv6*, *S100g* (aka calbindin 9 k), *Atp2b1* (aka *Pmca1b*), highly expressed by both the duodenum and cecum [12–16]. The vitamin D receptor (VDR) and those genes involved in the paracellular pathway such as claudins 2, 12, 15 are more widely distributed throughout the intestine [17–19]. Moreover, the contribution of transcellular vs paracellular pathways likewise varies, and age modifies both this balance and the degree to which $1.25(\text{OH})_2\text{D}$ regulates overall absorption [20]. For example, in rodents prior to weaning, intestinal calcium absorption is not dependent on vitamin D and relies primarily on the paracellular pathway.

Another factor that contributes to calcium absorption is transit time. Although the efficiency of calcium absorption is highest in the duodenum, the transit time is short, around 3 min. Transit time is longest, 2 h or so, in the ileum which is the major site of calcium absorption (65–88% in adult rodents) while having the lowest ratio of transcellular to paracellular absorption [21]. Similar studies in human subjects also demonstrate that the ileum is the main site for calcium absorption [13].

The previous paradigm for transcellular calcium transport was incomplete, since blocking or deleting the proteins known to be involved in this process, such as either or both *Trpv6* and *CaBP9k*, as well as *myosin 1A*, do not completely

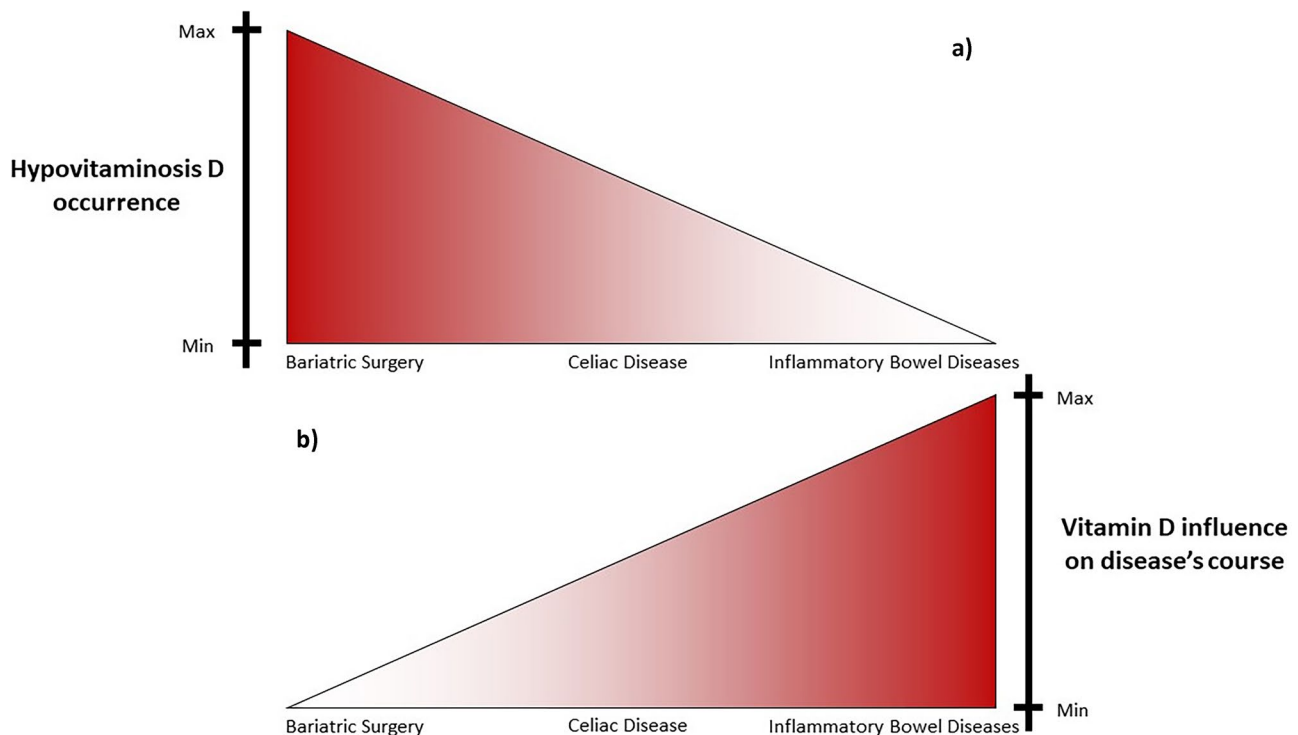


Fig. 2 The respective relative influence of **a)** Gastrointestinal conditions on hypovitaminosis D occurrence and **b)** Vitamin D influence on disease's course in Bariatric Surgery, Celiac Disease and

Inflammatory Bowel Diseases. Higher intensity of red corresponds to greater clinical role in the different malabsorptive gastrointestinal conditions

block it [22–24]. Other calcium binding proteins in the cytoplasm have been suggested, including CaM, parvalbumin, and sorcin (soluble-resistant calcium binding protein), but none of these has been carefully studied. On the other hand, deletion of *Pmca1b* does reduce calcium absorption and blocks $1.25(\text{OH})_2\text{D}$ action, resulting in reduction in growth and bone mineralization [15].

With regard to paracellular absorption, solvent drag plays a large part in moving calcium across the tight junctions between the epithelial cells. Solvent flow follows the osmotic gradient which is maintained distal to the tight junction by the Na/K ATPase and sodium glucose cotransporter of the basolateral membrane which may be stimulated by $1.25(\text{OH})_2\text{D}$, while the claudins and occludins contribute to charge selectivity [20, 21]. Claudin 2, 12, 15 are negatively charged and enable cations such as sodium and calcium to pass [17–19]. The expression of claudins 2 and 12 are stimulated by $1.25(\text{OH})_2\text{D}$ [17–19].

Another factor that may help regulate calcium absorption is the calcium sensing receptor (CaSR), expressed on the membranes of the small intestine cell [25, 26]. Stimulation of the CaSR pharmacologically blocks $1.25(\text{OH})_2\text{D}$ -induced calcium absorption. In preliminary experiments with an intestinal specific deletion of CaSR, calcium absorption at higher calcium loads was increased. Although $1.25(\text{OH})_2\text{D}$ induces the CaSR in other tissues, this has not been tested in the intestine. Other regulators include estrogen, prolactin, growth hormone, and IGF1, but these remain little explored [27–29]. A number of other dietary (such as oxalate and phytate) or hormonal (e.g. estrogens) can interfere with calcium absorption [30].

4 Vitamin D and gut microbiome

Several studies showed that gut microbiota regulate intestinal vitamin D metabolism and circulating vitamin D levels were affected by probiotic supplements [31]. A study evaluating the association between the vitamin D metabolites and the gut microbiome indicated that serum $1.25(\text{OH})_2\text{D}$ level explained 5% of variance in α -diversity and, 2% of variance in β -diversity of intestinal microbiota. Higher levels of $1.25(\text{OH})_2\text{D}$ and higher hormone-to-prohormone [$1.25(\text{OH})_2\text{D}/25(\text{OH})\text{D}$] activation ratios, but not $25(\text{OH})\text{D}$ itself, were more likely to possess butyrate-producing bacteria that are associated with healthier gut microbiota [31]. The association of active vitamin D metabolites with more favorable gut microbial diversity provide promising targets for intervention [31]. Schaffler et al. reported that vitamin D_3 supplementation altered the gut microbiota composition only in CsD in remission, but not in vitamin D deficient healthy controls, [32] suggesting that administration of vitamin D has potential as an adjuvant therapy for CsD patients. In

another study, increased serum $25(\text{OH})\text{D}$ was associated with increased beneficial bacteria and decreased pathogenic bacteria. There was a dose-dependent increase in bacteria linked to decreased IBDs activity after vitamin D_3 supplementation [33]. Further experimental data demonstrated that probiotics stimulate VDR expression and activity. Besides the effect on VDR, some clinical and experimental data indicate that probiotic bacteria may increase vitamin D levels [34]. In the gut lumen, the mucus layer and the underlying epithelium serve to keep resident microbiota at bay [35, 36]. Vitamin D ensures an appropriate level of antimicrobial peptides in the mucus and maintains epithelial integrity by reinforcing intercellular junctions.

Gut microbiota and the metabolites they produce constitute an important part of the mucosal barrier, but the relationship between disturbance of the gut flora and the development of IBDs is not fully understood [33, 37–41].

In sum, serum vitamin D levels affect the distribution of fecal microbiota, and elevated vitamin D levels are generally associated with higher levels of beneficial bacteria and reduced levels of pathogenic bacteria [36, 41, 42]. Gut microbiota helps to maintain gut immunity and is essential for protection against pathogens. Vitamin D/VDR regulates functions of Paneth cells and modulates release of antimicrobial peptides in gut microbiota-host interactions. Meanwhile, beneficial microbial metabolites, e.g., butyrate, upregulate the VDR signaling.

5 Gastrointestinal malabsorptive conditions

The clinical gastrointestinal conditions that were discussed during the Conference were CD, IBDs and bariatric surgery. A common denominator of these diseases was the malabsorptive state leading to decreased circulating $25(\text{OH})\text{D}$ levels as the widely accepted biochemical marker of vitamin D status [2]. Additionally, vitamin D deficiency may have negative effects on the underlying gastrointestinal conditions due to some of its extraskelatal immunomodulatory and metabolic effects [4]. Vitamin D is increasingly viewed as an immune modulator capable of directly impacting both innate and adaptive immune responses [36, 41, 43–46] (Fig. 2). In innate immunity, vitamin D inhibits LPS-induced p38 activation and IL-6 and TNF- α production by monocytes and downregulates TLR-9 expression. Vitamin D also favors an anti-inflammatory phenotype of macrophages, inhibits the innate NF- κB and MAPK signaling in dendritic cells. The activation of NLRP3 inflammasome is downregulated by vitamin D. In adaptive immunity, vitamin D downregulates Th1/Th17 while it upregulates Treg and Th2. Vitamin D, through the VDR, inhibits the proliferation of B-cells and T-cells and the expression of pro-inflammatory cytokines, such as IL-2, IFN- γ , IL-12, IL-17 and TNF- α from T-cells

[43, 47–51]. Conversely, vitamin D enhances the production of anti-inflammatory cytokines, such as IL-4 and IL-10 [52–54] (Fig. 3).

6 Celiac disease

The most prevalent malabsorption condition, affecting about 0.7% of the world population, is CD. CD is characterized histologically by intestinal villus atrophy, crypt hyperplasia and lymphocytic infiltration. In the setting of long-standing CD, low bone mineral density (BMD) is a common finding, due to secondary hyperparathyroidism triggered by calcium and vitamin D malabsorption. Screening for CD among patients with

osteoporosis is a matter of debate unless there are concomitant clinical signs of malabsorption. In patients with CD the initiation of a gluten free diet improves BMD, controls the secondary hyperparathyroidism, reduces bone alkaline phosphatase activity and improves vitamin D status in more than 80% of patients. Time-course of improvement depends in part on duration and severity of the disease.

6.1 Vitamin D status in celiac disease

Lower vitamin D levels are commonly observed in patients affected by CD (Fig. 2). Pediatric retrospective studies report vitamin D deficiency in 9–52% of CD patients [55].

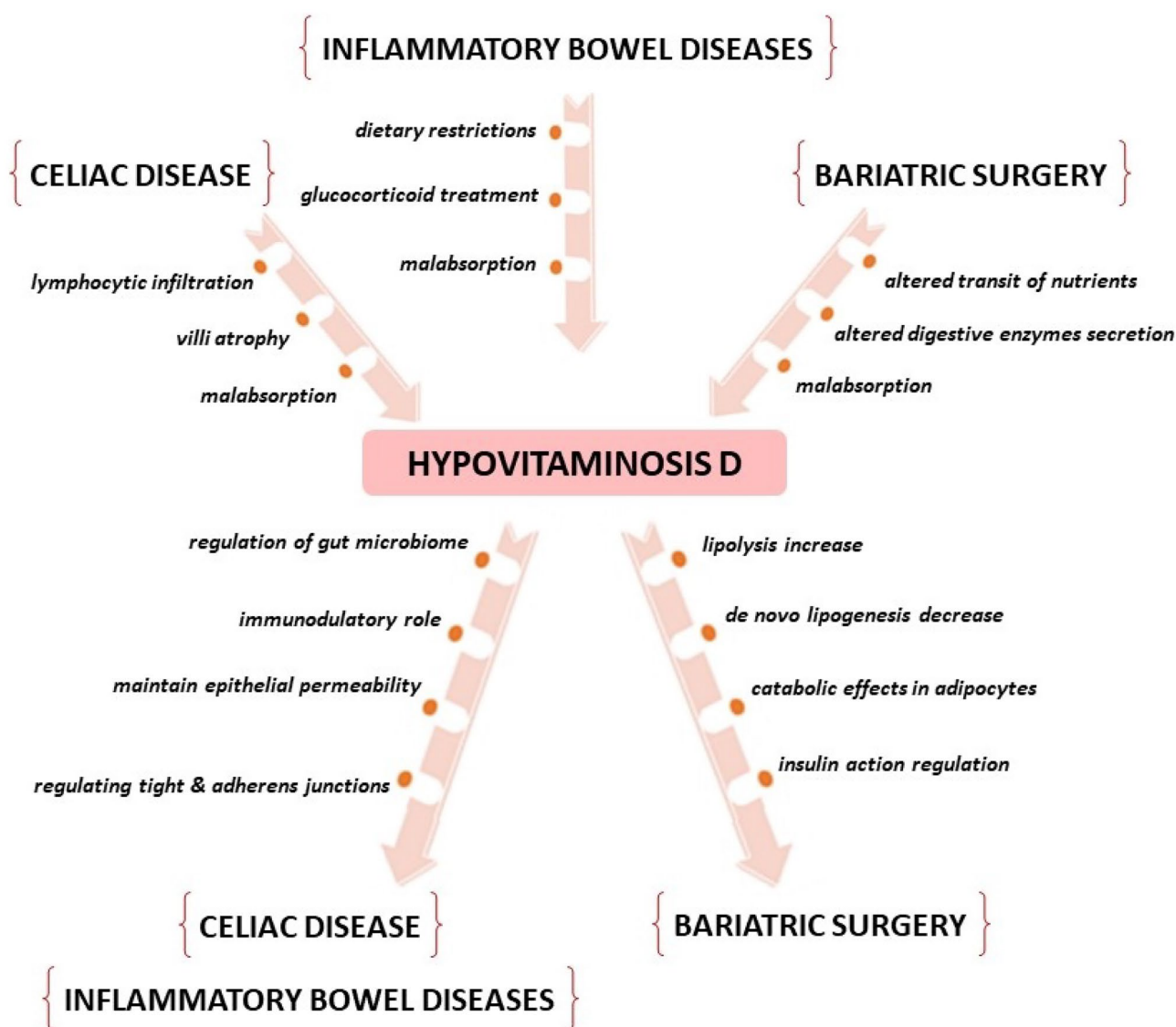


Fig. 3 The bidirectional pathophysiological relationships between the malabsorptive gastrointestinal diseases leading to the occurrence of hypovitaminosis D (upper part of the figure) and the different mecha-

nisms through which low vitamin D could influence the underlying gastrointestinal conditions (lower part of the figure)

In adult patients, older reports place the percentage of the vitamin D deficiency in CD between 20.3 and 59% [56]. A more recent published meta-analysis including 24 articles and 25 sets of data evaluating a total of 1137 CD patients and 2613 controls, showed that the average 25(OH)D level in CD patients was 3.34 ng/mL (8.36 nmol/L) lower than controls. Confirming the negative effect of chronic inflammation and intestinal damage of CD on the vitamin D intestinal absorption (Fig. 1), this meta-analysis reported that, after a gluten free diet, the average 25(OH)D level in treated patients was 6.24 ng/mL (15.6 nmol/L) higher than untreated patients [57]. Other prospective reports showed that the high prevalence of vitamin D deficiency observed in these patients at diagnosis, slightly decreased after starting and during the gluten free diet [56].

6.2 Skeletal impact of vitamin D status in celiac disease

Hypocalcemia and skeletal disease are frequent findings in CD and may even represent the presenting features of the disease [58]. In the setting of a long-standing CD, low BMD is a common finding due the concomitant presence of calcium and vitamin D malabsorption with secondary hyperparathyroidism, and higher levels of proinflammatory cytokines, including IL-1 beta, IL-2, IL-6, and tumor necrosis factor alpha. These factors help to account for accelerated bone turnover and skeletal demineralization. Markers of bone resorption including serum bone-specific alkaline phosphatase and urinary pyridinoline cross-links, and markers of bone formation including osteocalcin have been demonstrated to be higher in individuals with CD, newly diagnosed individuals with CD and those with refractory CD when compared to patients on a gluten free diet or healthy controls [59].

The few studies of pediatric patients affected by CD show either normal or low bone mineral content at the time of diagnosis [60]. Among newly diagnosed patients with CD, 43% to 63% has Z-scores that could be interpreted to be low (between -1.0 and -2.5) or 12–21% to be very low (< -2.5) [59]. Individuals with a subclinical CD demonstrate a higher BMD compared to those with a classic disease presentation, although still lower compared to healthy controls [59].

Worsened BMD correlates with earlier onset of disease, disease activity and higher anti-transglutaminase antibodies levels, as well as menopausal status, low serum vitamin D and low dietary calcium intake [59]. Several studies have shown that a gluten free diet can improve BMD parameters with a complete normalization of bone mass only when the diagnosis was made early and a strict diet was rigorously followed [60].

Beyond the conventional evaluation of bone health with quantitative assessment of BMD by dual energy X-ray absorptiometry (DXA), novel imaging methodology is also available to assess skeletal health. For example, high resolution peripheral quantitative computed tomography (HR-pQCT) is a non-invasive method to quantitate volumetric and microarchitectural features of several peripheral skeletal sites. In a prospective study enrolling 31 premenopausal women with newly diagnosed CD and 22 healthy women of similar age, HRpQCT analysis showed that patients with CD were significantly lower in total volumetric density mg/cm³, trabecular density mg/cm³, number of trabeculae 1/mm, trabecular thickness per mm, and in cortical volumetric density [61]. These skeletal microarchitectural deficits were observed more in symptomatic CD as compared to subclinical CD.

Alterations in nutrient absorption and chronic systemic inflammation both are responsible for quantitative and qualitative deficits of bone health in CD with increased fracture risk. In a meta-analysis of case-controlled prospective studies, CD at baseline was associated with a 30% increase in the risk of any fracture and a 69% increase in the risk of hip fracture [60]. Individuals with CD were 1.92 times more likely to have sustained any fracture at some point in their lives [62]. Two studies evaluated the relationship between unrecognized CD and fracture risk. Unrecognized CD cases were subjects with positive CD autoantibodies but no clinical diagnosis of the disease. In a study of Finnish men and women aged 50 and over, the authors reported that low-energy fractures were statistically more common among the seropositive participants than the seronegative ones [63]. In a cross-sectional study of Swedish women aged 50 years and over, seropositive participants (n=90, of whom 18.9% had fractures) were slightly but not statistically more likely to have fractures than the comparison group (n=390, of whom 12.5% had fractures). [64]. In these two studies, fractures were ascertained only from self-report or a diagnostic registry without a specific radiological morphometric evaluation. The limitation of these studies could be interpreted to be an underreporting of the actual incidence of fractures.

6.3 Skeletal impact of vitamin D supplementation in celiac disease

Since CD is a cause of secondary osteoporosis, screening for skeletal disease and adequate therapeutic management in the setting of CD is a priority. The therapeutic approach includes, thus, not only a gluten free diet, but also adequate vitamin D and calcium supplementation. In a 1-year follow-up study following the implementation of a gluten free diet and vitamin D supplementation in 26 newly

diagnosed patients with CD, improvements were demonstrated in trabecular bone with regard to volume, density, and thickness. With such a short follow-up, however, the values were still significantly lower compared to healthy controls [65]. A study evaluating CD patients treated with a gluten free diet and calcium (1.0 g/day) plus alfacalcidol (0.25–1 µg/day) supplementation for one year, showed a significantly increase in mean BMD, most definitively in the lumbar spine (mean 7.3%) [66]. Another study evaluating CD patients with low BMD treated with a gluten free diet and calcium (1.0 g/day) plus an annual injection of cholecalciferol (600,000 IU) (if vitamin 25(OH)D < 20 ng/ml) showed an improvement of 35.9% in the lumbar spine [67]. These studies have led to a general consensus that vitamin D levels should be measured at diagnosis and that supplementation be provided to restore levels to normal (Fig. 3). As for any condition associated with a metabolic disease, the normal level is considered by most experts to be > 30 ng/mL (> 75 nmol/l). Along with vitamin D and a strict gluten free diet, supplementation with calcium is also important [68].

6.4 Impact of vitamin D status and supplementation on disease activity in celiac disease

While the evidence implicating CD in abnormalities of vitamin D absorption are clear, as summarized above, no human data are available on the possible direct or indirect effects of vitamin D status and supplementation on pathological features of CD. However, recent data on experimental animals on a possible favorable role of vitamin D on CD features are intriguing [69] (Fig. 2). While animal models do not reproduce all pathological features of CD pathology, they are nevertheless noteworthy. For example, Non-Obese Diabetic ShiLtJ (NOD/ShiLtJ) mice spontaneously develop autoimmune disorders and, in particular, a celiac-like disease when exposed to grains. Alterations at the level of small intestine are very similar to those seen in human subjects with CD, namely reduction of villi length, intraepithelial infiltration of CD3 + lymphocytes and villi atrophy. Cholecalciferol administration may activate intestinal mucosa regeneration by inducing a significant change in gene expression [69]. Nutritionally, NOD/ShiLtJ mice with this model of CD consumed 10 g on average less food/week as compared to healthy controls. When they were treated with 50 and 130 µg/kg of cholecalciferol, food intake was significantly improved compared to these mice who were not given vitamin D. While food intake was improved, there were no significant improvements in body weight or in levels of serum 25(OH)D. Nevertheless, only

the mice administered cholecalciferol showed regression of lesions to normal histological features (grade 0). With increasing doses of cholecalciferol, villi length, morphology, atrophy, and cell infiltration improved towards mucosal features similar to those seen in healthy control mice. The group receiving the higher dose of cholecalciferol (130 µg/kg) did not show the significantly increased expression of CD3, high expression of infiltrating lymphocytes, villus atrophy, crypt hyperplasia, or extensive ZO-1 expression.

6.5 Optimal vitamin D levels in celiac disease

Optimal care of patients with CD starts with referral to a specialist or Celiac Disease Center. An initial assessment of the patient's current nutritional and biochemical status, and potential risk factors for associated short- and long-term complications should be performed. Specific nutritional supplements, including vitamin D, may be necessary [70]. The amount of vitamin D will vary depending upon the activity of the disease ranging from a simple nutritional amount of vitamin D (600–800 IU per day) to in some cases pharmacological doses (4,000 IU per day or more) [68] (Fig. 4). Vitamin D-fortified milk/ plant-based alternatives and other natural sources of vitamin D can complement the dietary regimen [71].

No 'gold standard' for adequate 25(OH)D levels in CD exist but levels between 20 ng/mL and 50 ng/mL (50–125 nmol/L), the standard nutritional recommendation for healthy subjects without metabolic bone disease, may be adjusted upwards to > 30 ng/mL (> 75 nmol/l) [7]. In those with osteoporosis, the most important initial therapeutic approach is to make sure that the patient is on a gluten free diet with adequate vitamin D and calcium supplementation. Often, this intervention can be associated with marked gains in BMD. Only after the dietary and nutritional needs are met and the patient has been monitored for expected improvement, or in the case of incident clinical or morphometric fractures, bone protective pharmacological interventions can be considered [72].

7 Inflammatory bowel diseases

IBDs are categorized primarily as CsD and UC. Both IBDs display heterogeneity in inflammatory and symptomatic features between patients and within individuals over time. The etiology of IBDs has not been fully elucidated. The proposed underlying pathophysiological mechanism is the result of inappropriate activation of the immune system against environmental triggers in genetically predisposed individuals.

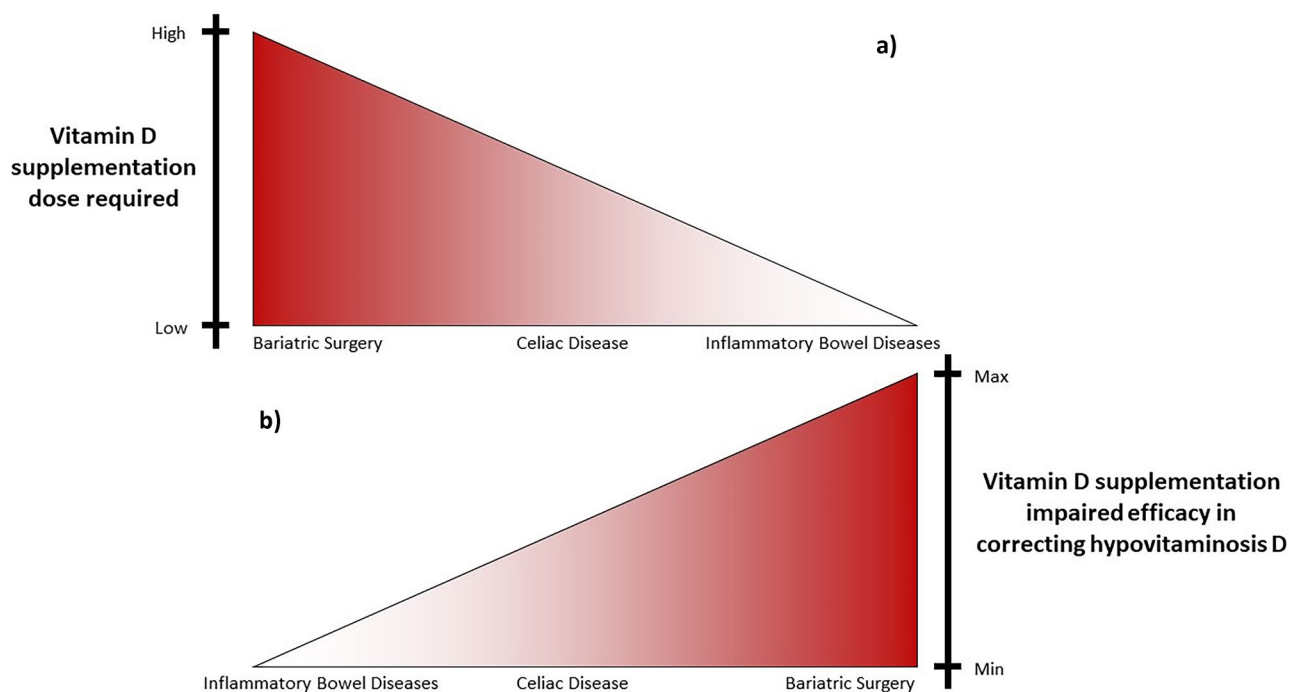


Fig. 4 The respective relative **a)** Vitamin D supplementation dose required and **b)** Vitamin D supplementation impaired efficacy in correcting hypovitaminosis D occurrence in Bariatric Surgery, Celiac

Disease and Inflammatory Bowel Diseases. Higher intensity of red corresponds to greater role in the different malabsorptive gastrointestinal conditions

Proposed risk factors associated with IBDs include altered intestinal flora, a diet rich in carbohydrates and fats, living in urban areas and a stressful lifestyle [73]. In this setting, an aberrant and hyperactivated innate immune response to intestinal luminal agents, possibly facilitated by an altered mucosal barrier function, results in the stimulation of dendritic cells with subsequent activation of the inflammatory response and a cascade, leading to active and chronic intestinal inflammation [73].

7.1 Vitamin D status in IBDs

Through its interaction with the VDR in gut cells, vitamin D exerts a spectrum of effects ranging from immune modulation and reduced Th1-driven inflammation to cell differentiation and intercellular adhesion, and increased colonic bacterial clearance to increased expression of intestinal epithelium tight junctions.

Patients affected by IBDs are quite often characterized by vitamin D deficiency (Fig. 2) due to multiple factors such as inadequate sun exposure, dietary restrictions, glucocorticoid treatment [74] and, in some instances, impaired absorption of nutrients (Fig. 1). Hypovitaminosis D is reported to be as high as 60% in IBD patients [74]. A systematic review with meta-analysis including 14 studies

and comprising 1891 participants (938 IBD cases and 953 controls) showed that IBD patients had 64% higher odds of vitamin D deficiency when compared with controls [73], and another recent review have reported an overall prevalence of hypovitaminosis D of 31.6% in UC and 38.1% in CsD, respectively [75].

7.2 Skeletal impact of vitamin D status in IBDs

The highly reported prevalence of hypovitaminosis D, in addition to poor nutrition, chronic low-grade inflammation and the frequent corticosteroid use, is thought to impair skeletal health and lead to a high risk of bone fragility and fractures.

The association between IBDs, low BMD and fractures has been examined in several studies. A higher risk of fracture in IBDs [76] was followed by a prevalence of osteopenia ranging from 22 to 77%, and of fragility fractures from 17 to 41% [77]. A meta-analysis evaluating 16 studies including 1338 patients with IBDs and 808 controls has been published [78]. The mean ages (30–47) and gender distribution (49–53% women) were similar between the two groups. Along with a significantly lower mean BMD and Z-scores for IBD patients versus controls at all sites (femoral neck, total femur and lumbar spine), there was a significant 38%

increase in global risk of fractures. These significant differences in bone density and fracture risk were maintained when stratified for the type of IBD, UC vs CsD.

Recent findings have also pointed out an impairment of bone quality in subjects with IBDs using the trabecular bone score (TBS), a texture analysis of the lumbar spine image from DXA. Utilizing TBS in a case–control study, CsD was associated with a significantly lower TBS, but not lumbar BMD when these patients were subclassified with stricture or penetrating disease as compared with those with only luminal disease. Thus, bone quality but not bone density was worse among those with more advanced CsD [79]. A cross-sectional study of 81 IBD patients (48 with CsD and 33 with UC) and 81 healthy controls reported that, compared with the healthy controls, IBD was associated with lower lumbar spine BMD, hip BMD and TBS. The patients with advanced CsD had lower TBS and lumbar spine BMD values compared with those with less severe disease [80]. Furthermore, in CsD, a low TBS was proposed to be an early negative prognostic feature [81]. Another non-invasive approach, using HR-pQCT, compared 49 young adult male patients with childhood-onset IBD and 245 matched young adult male controls. In IBD, median cortical area, median total vBMD, median cortical vBMD, median trabecular volume fraction were all lower than the control subjects [82].

7.3 Skeletal impact of vitamin D supplementation in IBDs

Vitamin D supplementation has been demonstrated to prevent bone loss in patients with CsD. Seventy-five non-hospitalized patients with CsD were randomly assigned to receive either an oral supplement of 1000 IU/day vitamin D for 1 year or no supplementation. BMD decreased significantly in controls but not in patients who received supplementation. Furthermore, BMD increased among patients who reached according to authors adequate serum levels of vitamin D with the supplementation (68%) versus BMD increases in only 18% of patients with hypovitaminosis D [83]. Also, an increase of volumetric bone density after vitamin D supplementation was prospectively observed even in paediatric patients with IBDs [84]. Fifty-five patients (aged 5–19 years) with IBDs were assessed using peripheral quantitative computed tomography after a median of 13.8 months of daily use of 2000 IU of cholecalciferol. The Z-scores of trabecular BMD and cortical bone cross-sectional area improved significantly during the follow-up period, and cholecalciferol supplementation was positively associated with trabecular BMD.

7.4 Impact of vitamin D status and supplementation on disease activity in IBDs

Low 25(OH)D has also been proposed as a biomarker for disease activity and as a predictor of poor clinical outcomes [85–88].

Vitamin D exerts its biological effects on the intestine in IBDs by maintaining mucosal barrier integrity, modulating the immune system and the composition of the gut microbiota [5, 35, 36, 86, 89–93]. Vitamin D deficiency or impaired VDR signaling could worsen colitis through multiple effects, including effects on bacterial diversity reducing butyrate-producing microbiota, the main substrate of intestinal epithelial cell and one of the factors regulating local immune response (Fig. 1).

A cross-sectional study observed an inverse association between serum vitamin D and disease activity in 182 patients with CsD reporting that subjects characterized by a CsD Activity Index (CAI) levels below 150 (i.e. quiescent disease), had a median serum level of vitamin D higher than patients with mild or moderate disease [94]. A subsequent study also revealed that vitamin D levels inversely correlated with activity scores in 37 patients with CsD [95]. A study exclusively performed on 50 patients with UC supported the association between lower levels of vitamin D and disease activity observing a significantly higher concentration of serum vitamin D in the group with mild disease activity as compared to the moderate disease activity group [96]. Furthermore, lower vitamin D, negatively influencing disease activity in patients with CsD, was also independently associated with lower health-related quality of life (HRQOL) of patients affected [97]. The negative impact of poor vitamin D status on the clinical course of IBDs (Fig. 2) was also recently confirmed by a study enrolling 711 patients with CsD and 764 with UC who had not undergone surgery before vitamin D was assessed [98]. Both in CsD and in UC patients, lower vitamin D levels were associated with higher disease activity scores and C-reactive protein (CRP) levels. Severe hypovitaminosis D (< 10 ng/mL) was associated with ileocolonic disease and complicated behavior in CsD and was relevant to the disease extent in UC. Moreover, in multivariable analysis, severe deficiency of vitamin D (< 10 ng/mL) was an independent risk factor for surgery in both CsD and UC.

Different meta-analyses have investigated the correlation between vitamin D supplementation and IBDs disease activity (Fig. 4) [99–101]. In the first meta-analysis including 18 randomized clinical trials (RCTs) and involved 908 IBD patients, vitamin D improved 25(OH)D levels more significantly than the control group (placebo group) (ng/

mL, weighted mean deviation = 7.85, 95% CI (5.52, 10.18), $p < 0.001$ [99] (Fig. 4). Vitamin D reduced the relapse rate more significantly than the control group (Fig. 4), but there were no significant differences between the low-dose and high-dose vitamin D treatment. The erythrocyte sedimentation rate (ESR) and CRP of patients treated with vitamin D and the control group showed no statistically significant difference. In a large meta-analysis including 27 studies comprising 8316 IBD patients (3115 UC, 5201 CsD), the association of vitamin D status with clinical outcomes was evaluated [100]. Low 25(OH)D status, mostly defined with a serum level < 20 ng/mL (19 studies) (in 5 studies < 30 ng/mL, in 1 < 10 ng/mL, in 1 < 12 ng/mL, in 1 < 35 ng/mL) was associated with increased risk of disease activity: OR 1.53 (95% CI 1.32–1.77), mucosal inflammation: OR 1.25 (95% CI 1.06–1.47); low quality of life (QOL) scores: OR 1.30 (95% CI 1.06–1.60); and future clinical relapse: OR 1.23 (95% CI 1.03–1.47). In another pooled analysis of 17 trials with 1127 IBD patients, oral vitamin D supplementation effectively increased the concentration of serum 25(OH)D and decreased serum CRP levels, but it did not decrease ESR, disease activity index, and relapse rate [101]. In another recent systematic review with meta-analysis including 12 RCTs, the risk of clinical relapse and disease activity in IBD patients treated with vitamin D supplementation compared with placebo was evaluated [102]. Vitamin D supplementation reduced the overall risk of clinical relapse in IBD patients (ITT: RR, 0.64; CI 0.46–0.89; $I^2 = 25\%$ and PP: RR, 0.62; CI 0.41–0.92; $I^2 = 18\%$), especially in CsD patients in clinical remission (RR, 0.47; 95% CI, 0.27 to 0.82; $I^2 = 0\%$). Concerning the impact of vitamin D supplementation on the alteration of disease activity score, this meta-analysis showed a slight, although not statistically significant, effect on CsD patients and no effect in UC patients (SMD, -0.29; 95% CI, -0.71 to 0.14; and SMD, 0.24; 95% CI, -0.61 to 1.10, respectively).

The conflicting results of these meta-analyses derive from the different primary outcomes of the studies, the small number of patients included in the studies and the high prevalence of observational studies over the RCTs included in the meta-analysis. Only a few RCTs have examined the effects of vitamin D supplementation on outcome of IBDs. However, there is substantial heterogeneity in the cut-off values defining the degree of vitamin D deficiency, the dosage regimens, and duration of treatment with vitamin D, as well as the disease subtypes and comorbidities.

Emerging evidence suggests that vitamin D deficiency may unfavorably affect response to biological therapy, being associated with an increased risk of both primary non-response and secondary loss of response to the drugs. Normal vitamin D levels (vitamin D level was classified as low or normal based on the reference lab's normal range: the lower cut-off for normal vitamin D levels ranged from

9 to 33 ng/ml depending on the assay) at induction with anti-TNF- α were associated with 2.64 increased odds of remission at 3 months compared to patients with low vitamin D levels (OR 2.64, 95% CI 1.31–5.32, $p = 0.0067$) [103] and serum vitamin D level ≤ 25 ng/mL identified patients losing response to biological drugs [104]. The same holds for an increased risk of primary non-response to vedolizumab (OR 26.10, 95% CI 14.30–48.90, $p < 0.001$) and failure at 1-year follow-up (OR 6.10, 95% CI 3.06–12.17, $p < 0.001$) [105]. Furthermore, vitamin D deficiency may worsen corticosteroid-related osteopenia/osteoporosis and increase the risk of immunomodulator-related infections, relevant complications possibly observed in patients with IBDs.

7.5 Optimal vitamin D levels in IBDs

No 'gold standard' for adequate 25(OH)D levels in IBDs exist, but most data suggest that a 25(OH)D level > 75 nmol/L (> 30 ng/mL) is beneficial compared with IBD patients with 25(OH)D < 50 nmol/L (< 20 ng/mL) in terms of inflammatory markers and clinical scores. In IBD patients, many experts have challenged the standard nutritional guidelines as in other diseases associated with skeletal damage. The doses required to reach recommended levels of > 30 ng/mL may exceed the nutritional guidelines for supplementation such as 600–800 IU/day because of reduced absorption. Simply put, patients should be given as much vitamin D as they need to achieve satisfactory levels of circulating 25(OH)D. In a recent meta-analysis, an attempt was made to define a daily vitamin D dosage that is most likely to yield significant results, assuming its effectiveness as adjuvant therapy. Meta-regression suggested that vitamin D dose may indeed influence treatment effectiveness, and it is to be expected to observe this effect with high dose vitamin D regimens [102].

8 Bariatric surgery

Bariatric surgery is typically associated with substantial weight loss in morbidly obese patients who commonly are characterized by low pre-surgical vitamin D levels [6]. The long-term positive effects on weight and diabetes prevention after bariatric surgery can be offset, at least in part, by bone loss and higher fracture risk. These latter consequences are thought to be related to altered bone metabolism through mechanical unloading, hormonal and bone marrow fat modifications, low vitamin D, as well as nutritional and calcium deficiencies. Due to the increasing prevalence of obesity and type 2 diabetes, indication and use of bariatric surgery have progressively and rapidly expanded. The most widely used bariatric surgery procedures are the laparoscopy

sleeve gastrectomy (LSG) and the laparoscopic Roux-en Y gastric bypass (LRYGB) that are characterized by variable degrees of malabsorption. Endoscopic bariatric and metabolic therapies (EBMT) represent another progressive alternative that offers higher efficacy than pharmacotherapy and at the same time is less invasive and has a lower incidence of complications than classical surgical treatment. In some procedures, the cost of endoscopic treatments may be lower than those of bariatric surgery [106].

8.1 Vitamin D status in bariatric surgery

Several epidemiological studies demonstrate a close relationship between obesity and hypovitaminosis D. The mechanisms underlying this association are still uncertain and undoubtedly multifactorial [107]. Among these factors, lower vitamin D intake and sun exposure, as well as sequestration and volumetric dilution of vitamin D into a larger than normal adipose tissue reservoirs are relevant [108, 109]. Lower expression levels of vitamin D activating enzymes (25-hydroxylase and 1 α -hydroxylase) in adipose tissue may also contribute to vitamin D insufficiency in obesity [110].

Patients undergoing bariatric surgery as a therapeutic choice to lose weight and to reduce long-term complications related to obesity are almost invariably characterized, nevertheless, by lower vitamin D levels (Figs. 1, 2, and 3), as reported by previous different studies. In a prospective follow-up study, which included data from 164 morbidly obese patients undergoing bariatric surgery, 96 (58.5%) underwent LSG and 68 (41.5%) LRYGB, a normal vitamin D level (> 30 ng/mL) was preoperatively found in only 5.7% of patients. The prevalence of vitamin D insufficiency (> 20 and < 30 ng/mL), deficiency (> 10 and < 20 ng/mL) and severe deficiency (< 10 ng/mL), was reported in the 15.1%, 59.1% and 20.1% of patients, respectively [111]. Similar findings were observed in a retrospective study including 211 patients presenting for bariatric surgery and evaluated preoperatively for nutritional deficiencies, reporting a rate of vitamin D insufficiency (> 20 and < 30 ng/mL) and deficiency (< 20 ng/mL) of 20% and 80%, respectively [112]. In a single-blind, parallel clinical trial, evaluating different vitamin D supplementation therapeutic options after bariatric surgery, patients included were characterized by a preoperative rate of normal (> 30 ng/mL), insufficient (> 20 and < 30 ng/mL) and deficient (< 20 ng/mL) vitamin D status of 22.48%, 15.5% and 62.01%, respectively [113].

In LSG, characterized by a restrictive surgical procedure, more than 80% of the stomach is transected, causing a rapid transit of nutrients through the gastric lumen. Results on the prevalence of vitamin D deficiency after

LSG are inconsistent. According to some studies it ranges from 14 to 72% 1-year post-surgery [6].

LRYGB has both restrictive and malabsorptive features. It is likely that the malabsorption induced by the surgical bypass procedure modifies the delivery of pancreatic secretions and bile salts leading to reduced vitamin D absorption. Moreover, intestinal fractional calcium absorption decreases from about 33% to about 7%, 6 months after surgery [114]. Daily supplementation with relatively low dose of vitamin D (800 IU) had a limited effect on preventing deficiency [6].

A less common surgical procedure is the biliopancreatic diversion (BPD) which causes massive malabsorption of minerals and fat-soluble vitamins. Vitamin D deficiency and increased PTH levels are common findings in patients undergoing BPD (ranging from 60 to 100% according to different studies) despite replacement with high oral doses of vitamin D [6].

8.2 Skeletal consequences of vitamin D status in bariatric surgery

During the last decade, bariatric procedures characterized by poor vitamin D status have been associated with likely multifactorial bone loss and skeletal fragility with higher risk of fractures. Prospective studies have shown that the magnitude of skeletal changes varies by skeletal region and surgical procedure [115]. DXA-measured bone loss at the femoral neck and total hip ranges from 5 to 11% 1 year after BPD and LRYGB surgery, while the BMD loss after restrictive procedures ranges from no change to 14%. Spine BMD changes are inconsistent with studies reporting 12-month reductions of 3–8% after BPD and LRYGB, but no change or even slight gains after restrictive procedures. Based on observational studies, bariatric surgery is also associated with a 21–44% higher risk of all fractures [116]. Fracture risk is reported to be time-dependent and increases approximately 3 years after bariatric surgery. The bariatric procedures that have a malabsorptive component (LRYGB and BPD) have clearly been associated with the highest risk of fracture compared to the restrictive procedures.

8.3 Skeletal effects of vitamin D supplementation in bariatric surgery

A prospective open-label study was conducted in a single bariatric surgical center, to assess the safety and effectiveness of once-yearly intramuscular high-dose vitamin D injection (600,000 IU: currently discouraged due to possible side effects) followed by a regular oral intake of vitamin D

supplements (total oral dose of 1.280 IU daily). In the year following injection in BPD patients, BMD was assessed at baseline and 12 months post-injection. A slight, but not significant, reduction at both femoral neck and lumbar spine BMD across the study period was reported [117]. Other non-controlled studies, however, have reported significant postoperative BMD reductions despite both high-dose (> 2.000 IU daily) and low-dose (< 2.000 IU daily) oral vitamin D supplementations [118, 119] (Fig. 4).

Postoperative maintenance of vitamin D through vitamin D supplementation and, perhaps, intramuscular administration are important considerations to prevent bone loss and to maintain bone mass. Furthermore, the demonstrated positive influence of vitamin D adequacy on body composition should also be considered in the postoperative period (Fig. 4) [10]. Unfortunately, clinical guidelines are lacking on presurgical vitamin D assessment and normalization as well as on how to monitor and manage vitamin D deficiency following bariatric surgery.

8.4 Impact of vitamin D status and supplementation on metabolic outcomes in bariatric surgery

Adipose tissue is a direct target of vitamin D, which plays a role in modulating its development, distribution, and metabolic and endocrine functions [120]. The VDR in pre-adipocytes and adipocytes, in both subcutaneous and visceral adipose tissue [121] is clearly the mediator of these properties. Moreover, due to its lipophilic structure, vitamin D accumulates in adipose tissues, the major site of vitamin D storage.

The role of vitamin D in adipocyte metabolism is still relatively unknown. Recent studies conducted *in vitro* on mouse adipocytes showed that $1.25(\text{OH})_2\text{D}$ increases basal and adrenergically stimulated lipolysis and decreases *de novo* lipogenesis [122], suggesting that active vitamin D has catabolic effects in adipocytes by decreasing lipid and triglycerides accumulation. Adipocyte size could be reduced, as a result. Moreover, vitamin D is known to affect insulin actions and glucose metabolism in adipose tissue, by increasing glucose transport in adipocytes through enhanced GLUT4 translocation [123].

The well-known anti-inflammatory actions of vitamin D reduce inflammation in adipose tissue. In both preadipocytes and adipocytes, $1.25(\text{OH})_2\text{D}$ suppresses expression of multiple cytokines, including IL-6, IL-1 β , IL-8 [124].

It follows, therefore, that vitamin D supplementation could represent a possibly additional pre- and post-operative measure to maintain weight loss in patients after bariatric surgery (Fig. 4). In fact, some but not all interventional studies, RCTs and meta-analyses have highlighted possible

vitamin D anti-obesity properties which however need confirmation through solid evidences. A meta-analysis focused on vitamin D supplementation in overweight and obese individuals with different conditions evaluated 11 RCTs with a total of 947 subjects, with a mean time of the follow-up from 1 to 12 months and different vitamin D interventions (from 25.000 to 600.000 IU/monthly of cholecalciferol). This meta-analysis reported that cholecalciferol supplementation decreased BMI by -0.32 kg/m^2 and waist circumference by -1.42 cm , but did not statistically affect weight loss [125].

A meta-analysis analyzed RCTs of oral vitamin D supplementation in obese individuals without weight loss, in obese subjects on medical weight loss regimens, and in those following bariatric surgery [126]. The latter group included specifically 6 RCTs (2 study duration < 12 months, 4 > 12 months) with a total of 615 patients evaluated. Treatment with vitamin D daily equivalent to between 800 and 7142 IU did not affect weight loss in any of the studies. However, weakened statistical power considerations limited any conclusions that could be drawn [126]. Additionally, it should be noted that vitamin D has been consistently shown to have relevant positive effects on muscle structure and function [127] and a role for vitamin D has been advocated in sarcopenic obesity [10]. Therefore, although no specific data are available on the adjuvant effect of vitamin D supplementation in weight reduction following bariatric surgery it can be hypothesized that ensuring vitamin D adequacy may help patients lose weight and/or improve body composition.

8.5 Optimal levels of vitamin D before and after bariatric surgery

Currently, there are no specific guidelines and no consensus on goals for adequate vitamin D supplementation in bariatric patients, pre- and post-surgery.

A very recent published meta-analysis was conducted to examine the effect of vitamin D supplements on serum level of $25(\text{OH})\text{D}$ in the patients undergoing bariatric surgery [128]. Nine clinical trials were included in the meta-analysis. Vitamin D supplementation in patients undergoing bariatric surgery modestly improves vitamin D status particularly, in the doses above 2850 IU/day and in the patients with BMI greater than 50 kg/m^2 .

In the meta-analyses conducted by Bassatne et al., including 6 RCTs, four conducted in patients following LSGB, one in LSG, and another one combining both LRYGB and LSG patients, only vitamin D doses $\geq 2000 \text{ IU/d}$ led consistently to mean $25(\text{OH})\text{D}$ concentration $> 30 \text{ ng/ml}$ [126]. The average increment in $25(\text{OH})\text{D}$ concentration per 100 IU/day of vitamin D dose in this population ranged between 0.4 and 1.1 ng/ml with doses of 600–3500 IU/day, and 0.2–0.4 ng/ml at doses exceeding 3500 IU/day [126].

LSG consisting in a stomach transection is considered to promote weight loss mainly, but not totally, with a restrictive effect leading to a minor, but not insignificant, malabsorptive impact on nutrients and vitamin D absorption. Daily doses of at least 3.000 IU of vitamin D have been required in these patients to reach the recommended threshold of 28 ng/mL [6]. On the other hand, RYGB has both restrictive and malabsorptive features to promote substantial weight loss, leading to a greater impact on nutrient malabsorption. Doses up to 5.000 IU per day have stabilized levels in these subjects whereas supplementation with usual doses of vitamin D (800 IU daily) had a limited effect on preventing vitamin D deficiency [6].

The consensus is that high doses of vitamin D supplementation and, perhaps, intramuscular vitamin D administration should be considered in all patients before and after bariatric surgery (Fig. 4).

9 Conclusions

Malabsorptive gastrointestinal conditions such as celiac disease, IBDs and bariatric surgery negatively affect through multiple mechanisms vitamin D absorption and metabolism (Figs. 1, 2, and 3) leading to hypovitaminosis D the severity of which depends on the different underlying conditions (Fig. 2) and on the severity of each condition with consequent higher risk of skeletal complications including hypocalcemia, impaired BMD and increased risk of fractures. Therefore, vitamin D status assessment and supplementation should be routinely considered in all patients affected by these malabsorptive gastrointestinal conditions. This concept is strengthened by the existence of a possible bidirectional relationship through which poor vitamin D status may negatively impact on clinical course of underlying disease (Figs. 2 and 3) particularly in IBDs (Fig. 2). Sufficient elements are available to estimate the desired threshold vitamin D level above which a favourable impact on the skeleton may be obtained and available data suggest variable efficacy and needs in dose and route of administration of vitamin D in order to reach target levels (Fig. 4) according to the different conditions. On the other hand, ad hoc controlled clinical trials are needed to better define this threshold for obtaining a positive effect of vitamin D supplementation on occurrence and clinical course of malabsorptive gastrointestinal diseases with the final goal of a possibly personalized supplementation of vitamin D which should also consider the specific genetic and epigenetic background of the affected patients.

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Declarations

Conflict of interest A.G. is consultant for Abiogen and Takeda and received research grant to Institution from Takeda. S.M. served as speaker for Abiogen, Bruno Farmaceutici, Diasorin, Geopharma, Sandoz, UCB. He also served in advisory board of Abiogen, Eli Lilly, Kyowa Kirin, Novo Nordisk, UCB. The other authors have no conflicts of interest to declare.

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