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Intestinal absorption and vitamin levels: is a new focus needed?

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Abstract: Vitamins are micronutrient chemical compounds that cannot be synthesized by an organism but are essential for human metabolism and life. They act as required intermediaries, cofactors or coenzymes in many of the reactions of normal metabolism. In addition, anti-inflammatory effects have been reported for specific vitamins. In inflammatory bowel disease (IBD), vitamin deficiency is often due to malnutrition (due to a decreased food intake) or malabsorption (due to inflamed, malfunctioning mucosa and diarrhea) which results in anemia. Vitamin B(12) and folic acid supplementation may be necessary in IBD patients, especially those with Crohn's disease (CD) with either inflammation of the terminal ileum or after resection of the terminal ileum. It is also recommended during therapy with sulfasalazine as this compound inhibits the absorption of vitamin B(12). Patients with high or continuous inflammatory CD activity and frequent therapy with steroids have an increased risk of low bone mineral density and vitamin D deficiency. These should be monitored regularly and vitamin D should be supplemented. In a recent trial, a trend towards a reduced risk of relapses in CD patients treated with vitamin D was reported. Only limited studies and case reports exist on other vitamin deficiencies, e.g. vitamins A, B(1), B(2), niacin, B(6), C, E and K, found in IBD patients. These are summarized in this review. Regular nutritional monitoring in IBD patients is warranted and requires the special attention of treating physicians and dieticians.

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Intestinal absorption and vitamin levels: Is there need for a new focus?

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Key words: vitamin, intestinal absorption, IBD

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Abstract

Vitamins are micronutrient chemical compounds that cannot be synthesized by an organism but are essential for human metabolism and life. They act as required intermediaries, cofactors, or coenzymes in many reactions of normal metabolism. In addition anti-inflammatory effects have been reported for specific vitamins. In inflammatory bowel disease (IBD) vitamin deficiency is often due to malnutrition (due to decreased food intake) or malabsorption (due to inflamed, malfunctioning mucosa and diarrhea) which results in anemia. Vitamin B₁₂ and folic acid supplementation may be necessary in IBD patients, especially in Crohn's disease (CD) patients with inflammation of the terminal ileum or in CD patients after resection of the terminal ileum. It is furthermore recommended during therapy with sulfasalazine since this compound inhibits absorption of vitamin B₁₂. Patients with high or continuous inflammatory CD activity and frequent therapy with steroids have an increased risk of low bone mineral density and vitamin D deficiency. Vitamin D levels and bone mineral density should be regularly controlled in these patients and vitamin D should be supplemented. In a recent trial even a trend to a reduced risk of relapses in CD patients treated with vitamin D was reported.

Only limited studies and case reports exist on other vitamin deficiencies found in IBD patients such as deficiency of vitamins A, B1, B2, niacine, B6, C, E, and K. They are summarized in this review. Regular nutritional monitoring in IBD patients is warranted and requires special attention of treating physicians and dieticians.

Introduction

Vitamins play distinct roles in human physiology, metabolism and disease. The physiological role is not part of this overview which will concentrate on the role of vitamins during the course of inflammatory bowel disease (IBD) and for associated complications. Deficiencies of single vitamins are rarely endemic, even in developing nations, and are more likely to occur either in the context of general malnutrition or as a result of diseases with malabsorption and/or the need of total parenteral nutrition. IBD is frequently associated with vitamin deficiencies. The etiology of decreased vitamin levels in IBD is multifactorial and partly due to anorexia (such as pain-related decrease in food intake), or partly caused by malabsorption i.e. decreased absorption of vitamins by the inflamed mucosa. Furthermore intestinal losses caused by the disease (i.e. blood and haemoglobin during ulcerative colitis) may play a role. The most important mechanisms that lead to vitamin deficiencies in IBD are summarized in table 1 [1]. Table 2 summarizes current literature on prevalence of vitamin deficiencies in IBD patients and recommended daily allowances [2-14]. As supplementation of vitamins may significantly improve the health status and the quality of life in patients with IBD it is important to recognize nutritional deficiencies at an early stage and initiate appropriate treatment. Otherwise many patients may experience a further disease aggravation caused by deprivation of vitamins which could be easily avoided. Unfortunately the availability of highly effective treatment options has somewhat decreased the attention to the issues discussed here.

Water soluble vitamins

1. Thiamine (vitamin B1)

Thiamine is synthesized by a variety of plants and microorganisms but usually not by animals. Small amounts may be synthesized by microorganisms in the gastrointestinal tract. Thiamine is absorbed both by an active transport process and by passive diffusion. The capacity to absorb the vitamin in the human intestine is about 5 mg/d; approximately 25-30 mg is stored in the body. The recommended daily allowances for thiamine are given in Table 2. The vitamin has a widespread distribution in food and is absent only in oils, fats, and refined sugar. A substantial loss of the vitamin takes place during heating above 100°C.

The two major manifestations of thiamine deficiency involve the cardiovascular (wet beriberi with edema, tachycardia, and a high-output state) and nervous system (dry beriberi with peripheral neuropathy and the Wernicke-Korsakoff syndrome). The typical patient has mixed symptoms involving both cardiovascular and nervous system. Wernicke's encephalopathy consists of vomiting, nystagmus (horizontal), ophthalmoplegia, fever, ataxia, and progressive mental deterioration that eventuate in a global confusion state. Korsakoff's syndrome consists of retrograde amnesia, impaired ability to learn, and (usually) confabulation. Development of thiamine deficiency occurs mainly in alcoholics due to low thiamine intake, and in patients with malabsorption or malnutrition. Several case reports have been published describing vitamin B1 deficiency in patients with CD [15-17]. Hahn and colleagues [15] describe a CD patient on TPN, where beriberi and Wernicke's encephalopathy developed because multivitamin infusions were switched to an oral multivitamin formula. Another case report emphasizes the dependence of thiamine on magnesium and

states, that if thiamine and magnesium are deficient at the same time, both should be substituted simultaneously [16].

2. Riboflavine (vitamin B2)

Riboflavin participates in a variety of oxidation-reduction reactions. In addition, riboflavin is essential to a variety of enzymes such as succinate dehydrogenase and monoamine oxidase. The vitamin is either passively absorbed from the gastrointestinal tract as free riboflavin or taken up by an active transport. The vitamin is excreted in urine predominantly in the free form, although a small fraction of the daily turnover is the result of catabolism by microorganisms in the gastrointestinal tract. Deficiency is characterized by sore throat, hyperemia and edema of the oral mucus membranes, cheilosis, angular stomatitis, glossitis, seborrheic dermatitis, and normochromic, normocytic anemia due to red cell hypoplasia of the bone marrow. No case reports have been published on vitamin B2 deficiency in IBD patients. Two publications report a decreased vitamin B2 intake in CD [18,19] and UC [19].

3. Niacin (vitamin B3)

Niacin is the generic name for nicotinic acid (pyridine-3-carboxylic acid) and derivatives that exhibit the nutritional activity of nicotinic acid. In some sense, niacin is not a “true” vitamin, since it can be synthesized from the essential amino acid tryptophan. In humans, an average of about 1 mg niacin is formed from 60 mg of dietary tryptophan. Once niacin is orally taken up, the vitamin is absorbed rapidly from the intestine by both active and passive transport mechanisms. A deficiency in niacin is called pellagra. Pellagra is a chronic wasting disease typically associated with dermatitis, dementia, and diarrhea. The dermatitis is bilateral symmetric, and present in sites exposed to sunlight (due to photosensitivity). The mental changes

comprise of fatigue, insomnia, and apathy, which may precede the development of an encephalopathy, characterized by confusion, disorientation, hallucination, loss of memory, and eventually, organic psychosis. Paresthesias and polyneuritis may be the results of coexisting deficiencies of other vitamins. Diarrhea, when present, results from widespread inflammation of the mucous surfaces. Further symptoms such as glossitis, stomatitis, proctitis, mental depression, abdominal pain, vaginitis, dysphagia, and amenorrhea are described.

Pellagra has seldom been described as a complication of CD. Only five case reports are published in the literature [4-7, 20]. The cause of nicotinic acid deficiency in IBD patients may reflect an inadequate intake, malabsorption, or increased demand. Suggested treatment regimens are parenteral administration of niacin at 100 mg/day.

4. Pyridoxine (vitamin B6)

Pyridoxine is widely distributed in different kinds of foods: muscle meats, liver, vegetables, and whole-grain cereals are among the best sources. More than for most vitamins, the demand is increased in pregnancy. The widespread occurrence of this vitamin in food is probably the reason that isolated pyridoxine deficiency is rare. However, some drugs act as pyridoxine antagonists and may cause a B6 deficiency. Among those drugs are isoniazid, and penicillamine. The prevalence of vitamin B6 deficiency in IBD patients was reported to be around 29-30% [8, 14, 21]. Low levels of vitamin B6 have been associated with hyperhomocysteinemia among IBD subjects [22]. However, the role of vitamin B6 deficiency for the etiology of hyperhomocysteinemia remains controversial. Several studies support hyperhomocysteinemia as risk factor of both arterial and venous thromboembolisms especially in IBD patients [23, 24]. There is a fourfold increased risk for the thromboembolic events in IBD patients, especially in patients with active disease. As

outlined above, IBD may be associated with deficiencies in vitamin B6 and B12 levels that in turn may promote increased homocysteine levels [14, 21, 22]. In contrast homocysteine levels were found to be normal in the majority of IBD patients and in IBD patients with low vitamin B 6 serum levels no elevated homocysteine levels were found [8]. This questions the role of vitamin B6 levels for the thromboembolic risk in IBD.

5. Cobalamin (vitamin B 12)

As most other B-vitamins cobalamin is a water-soluble vitamin. The only dietary source is from animal products such as meat and dairy food. During gastric digestion, cobalamin in food is cleaved from its binding protein by acid and pepsin in the stomach and binds to R factor which is produced in saliva and stomach. On entering the duodenum, the cobalamin-R binder complex is digested, releasing the cobalamin, which then binds to intrinsic factor (IF) (produced by the parietal cells of the stomach). The cobalamin-IF complex is resistant to proteolytic digestion and travels to the distal ileum, where specific receptors on the mucosal brush borders bind the cobalamin-IF complex, thereby enabling the vitamin to be absorbed. Once absorbed, cobalamin is bound to transcobalamin II, and then transported to the liver, bone marrow and other cells. Normally, about 2 mg cobalamin is stored in the liver, and another 2-3 mg is stored elsewhere in the body. In view of the minimum daily requirement (1-3 µg/d), and a body store of about 5 mg, about 3-6 years would be required for a normal individual to become deficient in cobalamin if absorption would cease abruptly. Vitamin B12 deficiency typically results in ineffective erythropoiesis and megaloblastic anemia as well as sometimes irreversible neurologic and psychiatric abnormalities including personality changes, neuropsychiatric deficits, paresthesias, ataxia, and a shuffling gait. Patients with CD may be at a particular risk

for vitamin B12 deficiency due to ileal inflammation or surgical resection of the ileum leading to an impaired absorption of vitamin B12 [25]. A good review on prevalence of impaired vitamin B12 absorption and vitamin B12 deficiency in CD patients has been published by Kulnigg et al. [26]. It has been reported that ileal resections < 20cm are not a risk factor for developing vitamin B12 deficiency. For patients with resections of 20-60cm, a routine monitoring or empiric therapy with vitamin B12 is mandatory [27]. An association with gastric CD had also been recognized [28].

Therefore, vitamin B12 supplementation often is necessary in patients with chronic active CD or resection of the terminal ileum and during therapy with sulfasalazine since this inhibits absorption of vitamin B12. Unfortunately, supplementation therapy with vitamin B12 and folic acid is only performed in 40 % of anemic IBD patients in gastroenterological practices in Switzerland as compared to 43% in tertiary referral centres [29]. More than 50% in need of supplementation do not receive the therapy.

6. Folic Acid (vitamin B9)

Folate is synthesized by many different plants and bacteria. Fruits and vegetables constitute the primary source of the vitamin. Some forms of dietary folic acid are labile and may be destroyed by cooking. Folate is absorbed in the duodenum and jejunum and deficiency may be due to inadequate diet, malabsorption, or drug interactions (sulphasalazine, methotrexate). Clinical manifestations occur earlier as in vitamin B12 deficiency as folate stores last only for 1-2 months. Patients with folic acid deficiency are more apt to be malnourished than those with cobalamin deficiency. The gastrointestinal manifestations of folic acid deficiency consist of diarrhea, cheilosis, and glossitis. In contrast to cobalamin deficiency, neurologic symptoms do not occur. The causes of folate deficiencies especially in IBD patients are undoubtedly often multifactorial: anorexia, malabsorption, increased disease

activity, and drug-induced hemolysis from sulphasalazine are all important mechanisms in CD. It has been proposed that oral folate supplementation should be recommended for patients with IBD as an anti-neoplastic and anti-thrombotic agent [30, 31]. Two retrospective publications have identified a folate-induced protective effect against dysplasia and colorectal cancer in patients with ulcerative colitis [30, 31]. Despite those studies, linking folate deficiency to increased cancer risk in IBD there are currently no prospective studies providing evidence for a reduced cancer risk in colitis following supplementation.

7. Ascorbic acid (vitamin C)

In most animals, ascorbic acid can be synthesized from glucose. However, humans are unable to synthesize vitamin C and therefore require it in their diet. Vitamin C has a key role as a redox agent for biologic oxidation and is essential in the synthesis of collagen. Many features of vitamin C deficiency (scurvy) result from these defects in collagen synthesis including capillary fragility that underlies the hemorrhagic features, the poor healing of wounds, and the bone abnormalities of children. Other features of scurvy include hyperkeratotic papules in which hairs become fragmented and buried, perifollicular haemorrhages, and purpura beginning on the backs of the lower extremities coalescing to become ecchymoses, gum involvement that include swelling, friability, bleeding, loosening of teeth, and emotional changes. Normochromic, normocytic anemia is common and is due to bleeding into tissue. The first case of scurvy in CD and confirmatory low leucocyte ascorbic acid level was reported in 1979 [32]. Gerson found that in patients with CD fistula formation might be related to local ascorbate deficiency [33]. Those old findings however never have been confirmed in larger studies. Aghdassi et al [34] conducted a randomized, controlled study in which patients with CD in remission and proven oxidative stress

received a vitamin C and vitamin E supplementation or placebo for 1 month. The supplementation significantly decreased all indexes of oxidative stress and increased vitamin C and E plasma concentrations. These results indicate that patients with CD supplemented with antioxidant vitamins E and C reduce their oxidative stress. However, whether there would be any long-term clinical benefit from antioxidant supplementation remains to be determined.

Fat-soluble vitamins

8. Vitamin A

Vitamin A (retinol) can either be directly ingested or synthesized within the body from plant carotenes. The best sources of preformed vitamin A are liver, milk, and kidney, where it occurs largely in the form of fatty acid esters. Retinol is stored as retinyl esters in the liver. The normal body pool is 300 to 900 mg.

The best-defined function of vitamin A is its role in vision. Deficiencies usually result from inadequate amounts of the vitamin and provitamins in the diet and occur in conjunction with deficiency of other nutrients. In some developing countries, vitamin A deficiency is a major cause of blindness in the young. In developed countries, vitamin A deficiency is usually due either to intestinal malabsorption (as in sprue or after intestinal bypass surgery), abnormal storage (liver disease), or enhanced destruction or excretion of the vitamin (proteinuria). Typical symptoms of vitamin A deficiency consist of night blindness, dry conjunctiva (xerosis), and ulceration and necrosis of the cornea (keratomalacia). Some case reports described CD patients with low plasma levels of vitamin A [35-37]. During acute flares of IBD decreased serum-vitamin A levels have been found [38]. Serum concentrations of vitamin A did not depend on the localization of disease, previous surgery, duration of IBD or age

and sex of the patients [38]. In IBD patients in remission normalization of serum retinol levels without substitution of vitamin A was observed [38].

Newer studies report that vitamin A is an important regulator of the human immune system, especially in the digestive tract. In fact, vitamin A deficiency induces increased blood interferon gamma and chronic diarrhea [39-41]. Furthermore vitamin A also has anti-inflammatory properties [42-45]. The cellular effects of vitamin A and derivatives have been studied in multiple in vitro settings and the molecular effects are well described [46]. Among the effects observed for vitamin A is an inhibition of pro-inflammatory IL-17 producing Th17 cells and an induction of anti-inflammatory Treg cells: When colonic biopsies from patients with UC were cultured and treated with vitamin A derivatives upregulation of FOXP3 expression (regulatory, anti-inflammatory T-cells) and downregulation of IL-17 expression was observed [47]. In animal models of colitis which were treated with vitamin derivatives lower levels of proinflammatory cytokines (TNF-alpha, IL-1beta, IL-17) and higher levels of regulatory cytokines (IL-10, TGF-beta) as compared with that of untreated mice were detected [47]. Colitis was less severe in the vitamin A derivative treated animals [42, 47].

These findings suggest that vitamin A might be a new therapeutic target for the treatment of inflammatory bowel disease. On the other hand two studies and some case reports have proposed an association between vitamin A derivative-treatment and IBD [48, 49]. This is in contrast to other epidemiological studies that could not find any association between retinoids and onset of IBD.

9. Vitamin D

Vitamin D is a hormone rather than a vitamin. Humans get vitamin D from exposure to sunlight, from their diet, and from dietary supplements [50]. With adequate

exposure to sunlight, no dietary supplements are needed. Solar ultraviolet B radiation penetrates the skin and converts 7-dehydrocholesterol to vitamin D₃ (cholecalciferol). Vitamin D from the skin and diet is metabolized in the liver to 25-hydroxyvitamin D (calcidiol), which is used to determine a patient's vitamin D status. 25-hydroxyvitamin D is then metabolized in the kidney to the active form 1,25-dihydroxyvitamin D (calcitriol). This renal production of calcitriol is tightly regulated by plasma parathyroid hormone, serum calcium and phosphorous levels. The active hormone is then transported through the blood to its target tissue (the small intestine and bone), where it regulates calcium homeostasis [51]. Vitamin D deficiency is found in 22-70% of patients with CD and has been proposed to play an important role in its pathogenesis [52]. Several lines of evidence support vitamin D as a promising environmental factor that substantially may influence the risk of developing IBD: (i) ecologic studies have suggested that the north-south gradient seen in the incidence of IBD patients (with increased incidences of IBD at higher latitudes) might be associated with reduced solar ultraviolet-B radiation exposure and consecutive low vitamin D levels [53]; (ii) studies have linked single-nucleotide polymorphisms in the vitamin D receptor to increased susceptibilities to CD and UC [54, 55]; (iii) deficiency of 1,25 dihydroxivitamin D and vitamin D receptor knock-out in mice increases the severity of a DSS colitis and administration of vitamin D suppresses the expression of several proinflammatory genes [56, 57]; and (iv) higher predicted plasma levels of 25-hydroxyvitamin D significantly reduces the risk for incident CD in women [58].

Vitamin D appears to have several important actions beyond the maintenance of bone health, including various effects on the immune system [59]. Vitamin D may play a role in the treatment of IBD-specific complications such as osteopenia, colorectal neoplasia, and depression [for a review see 51].

To date, only one randomized placebo-controlled trial has been reported assessing the benefits of oral vitamin D3 treatment in CD patients [60]. In total, 108 CD patients in remission were included in this trial and patients were randomized to receive either 1200 IU vitamin D3 or placebo once daily during 12 months. The number of relapses during 12 months of therapy was lower among patients treated with vitamin D3 and calcium (13%) than among patients treated with calcium alone (29%), but the difference did not reach statistical significance.

10. Vitamin E

Vitamin E is absorbed from the gastrointestinal tract and enters the circulation via the lymph. The vitamin is stored in all tissues, and the tissue stores can protect against vitamin deficiency for long periods. The recommended daily allowance is 10mg/d (see table 2). The vitamin is widely distributed in food, so a primary deficiency state has never been recognized in otherwise healthy children or adults. Vitamin E deficiency may be associated with a discrete syndrome especially in intestinal fat malabsorption. The manifestations of deficiency include areflexia, gait disturbance, decreased proprioceptive and vibratory sensation, and paresis of gaze. To the present date no case reports on isolated vitamin E deficiency in IBD have been published. In a cohort of children with IBD, serum levels of vitamin E were within normal values and not significantly different compared with controls without IBD [61]. These results are different from other studies, where low intake or low serum concentrations of vitamin E in IBD patients were described [14, 21, 62, 63]. As previously described, vitamin E supplementation in patients with IBD significantly decreases all indexes of oxidative stress and increases vitamin E plasma concentrations indicating the antioxidative properties of vitamin E [34].

11. Vitamin K

Vitamin K (vitamin K₁) is present in most edible vegetables, particularly in green leaves. Another form of vitamin K (vitamin K₂) is produced by intestinal bacteria but not in sufficient amounts to supply daily requirements. Under ordinary circumstances, about 80% of vitamin K is absorbed from the small bowel into the intestinal lymph. Deficiency can occur in association with diseases that interfere with fat absorption. In addition, long-term treatment with oral antibiotics may temporarily eliminate intestinal bacteria as a source for vitamin K and promote deficiency when the diet is marginal.

Vitamin K deficiency leads to low plasma levels of several coagulation factors in the prothrombin complex. Different case reports of CD patients with haemorrhagic problems have been reported in the literature [35, 64, 65]. Malabsorption is probably the most important cause of vitamin K deficiency either from extensive disease or resection that is severe enough to interfere with bile salt absorption. An interesting observation was published recently: a significant correlation of vitamin K deficiency and clinical disease activity was observed in patients with CD [66]. Also with this vitamin, further prospective studies are needed to clarify the role of vitamin K in patients with IBD.

Conclusion

Vitamins play important roles for metabolism but also for functions of innate adaptive immunity. Important anti-inflammatory roles of vitamin A, D and E have been described so far. Vitamin D substitution may have a role during maintenance therapy in IBD. Vitamin deficiencies are frequently observed in patients with IBD. Consequently, these patients should be considered as potentially being malnourished. Therefore, a regular assessment of the vitamin status should be recommended which could lead to a specific management, such as suggestions about food choices or vitamin supplementation in severe cases. Diet counselling is important and has proved to be effective in correcting low nutrient intake in CD patients, and even to improve the course of CD [67, 68].

As described for vitamin A, and D, vitamins may be used in future not only for substitution of deficiencies in IBD patients but also as treatment of active inflammation or maintenance of remission.

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