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## The Influence of Deficiencies of Essential Trace Elements and Vitamins on the Course of Crohn's Disease

### Wpływ niedoborów niezbędnych pierwiastków śladowych i witamin na przebieg choroby Crohna

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#### Abstract

In patients with Crohn's Disease (CD), malnutrition is frequently observed and is an important complication, frequently associated with nutritional deficiencies, especially vitamins (both water- and fat-soluble) and essential trace elements. It is often a result of the disease activity, poor oral intake and/or restrictive diets. Nutrition plays an important role in disease management and helps to maintain remission in CD patients. Deficiencies occur in patients with active Crohn's disease, and also in those in remission. Specific supplementation of vitamins and micro- and macronutrients might be helpful or even necessary in this group of patients. This review outlines the most frequent nutritional deficiencies and their complications in relation to the Crohn's Disease Activity Index, and provides an overview of therapeutic perspectives for CD patients in adult patients with inflammatory bowel disease (IBD). Biological therapy, which is being used with increasing frequency, seems not only to mitigate the inflammatory process in the gastrointestinal tract, but also has significant impact on the nutritional status of patients with Crohn's disease (*Adv Clin Exp Med* 2012, 21, 1, 5–11).

**Key words:** trace elements, vitamins, malnutrition, Crohn's disease, nutritional deficiencies.

#### Streszczenie

Niedożywienie jest często obserwowane u pacjentów z chorobą Crohna, stanowi poważne powikłanie i jest związane z niedoborem składników pokarmowych, zwłaszcza witamin (rozpuszczalnych zarówno w wodzie, jak i tłuszczach) oraz niezbędnych pierwiastków śladowych. Zazwyczaj stan taki jest rezultatem nasilonej aktywności choroby, niedostatecznej podaży pokarmu i restrykcyjnej diety. Odpowiednie odżywienie odgrywa kluczową rolę w leczeniu choroby i przyczynia się do uzyskania pełniejszej remisji. Niedobory te występują nie tylko u pacjentów z aktywną chorobą Crohna, ale także podczas remisji, dlatego też odpowiednia suplementacja witamin, mikro- i makroelementów powinna być pomocna, a nawet niezbędna w tej grupie chorych. W pracy omówiono najczęściej występujące niedobory pokarmowe i powikłania z nich wynikające w zależności od indeksu aktywności choroby oraz przedstawiono przegląd możliwości ich leczenia u dorosłych pacjentów z IBD. Coraz szerzej stosowane leczenie biologiczne wydaje się skuteczne nie tylko w aspekcie zahamowania procesu zapalnego w przewodzie pokarmowym, ale także wywierania znacznego wpływu na stan odżywienia u pacjentów z chorobą Crohna (*Adv Clin Exp Med* 2012, 21, 1, 5–11).

**Słowa kluczowe:** pierwiastki śladowe, witaminy, niedożywienie, choroba Crohna, niedobory pokarmowe.

As O'Sullivan wrote: "The exact aetiology of Crohn's disease [CD] remains unknown. The consensus is that the disease results from a complex interaction between genes, immunity and environmental factors" [1]. It has also been proposed that nutrition is an important etiological factor in the development of inflammatory bowel disease (IBD) [1]. As O'Sullivan also wrote: "The epidemiologi-

cal data... have failed to confirm a direct link between [pre-illness diet] and the development of Crohn's disease" [1], but the role of nutrition in the management of IBD is better understood. As O'Sullivan noted, "malnutrition, weight loss and suboptimal nutrition status... may be present at any stage of the disease... Malnutrition has been identified in approximately 40% of hospital ad-

missions with [CD] and is associated with higher mortality, longer hospitalization and higher healthcare costs” [1]. It has been noted that when the disease is in remission, some CD patients may be overweight, but they are at risk for micronutrient, macronutrient and vitamin deficiencies regardless of their body mass index (BMI) scores [1]. Currently, therapy involving 5-aminosalicylates, corticosteroids, azathiopyryne and nutrition continues to play a primary role in the management of IBS patients [2]. When the treatment fails it is usually connected with a lack of cooperation between dietitians and clinicians with regard to the type and duration of treatment [1, 2]. Numerous dietary components, such as sugar, fat, fiber, fruit and vegetables, protein, fast foods, preservatives, etc., have been examined as possible causative agents for CD [3]. Sakamoto et al. conducted an evaluation of the role of dietary factors in patients with Crohn’s disease in the Japanese population as a multicenter hospital-based case-control study in which “a semi-quantitative food frequency questionnaire was used to estimate pre-illness intakes of food groups and nutrients... The consumption of [sugars and sweeteners, sweets, fats and oils, fish and shellfish, monosaturated fatty acids and polyunsaturated fatty acids] were positively associated with CD risk”. These findings suggest the importance of dietary factors in IBD prevention [3].

The nutritional status of patients with CD is often very poor as a result of the disease activity, poor oral intake and/or bad dietary habits (for example excessive intake of fast foods, sweets, fats). A large number of ambulatory patients have sub-optimal dietary patterns despite a normal BMI and inactive disease [4]. In a study carried out in the Canadian population, based on the Canadian Dietary Reference Intake, ambulatory patients with CD and normal BMI scores completed a 7-day food record and a diary for the Crohn’s Disease Activity Index [4]. The results showed that the participants’ energy and protein intakes were within the recommended levels, but total carbohydrates, fat and saturated fat intakes exceeded the recommended levels. Essential trace elements intakes were sub-optimal, as were intakes of folate, vitamins C and E and calcium, and there were no substantial differences between patients with active and inactive CD. The conclusion was that dietary supplementation, dietitian counseling and changes in dietary habits may be warranted for these patients. [4]

Malnutrition is observed frequently in patients with CD and is a significant complication. The pathophysiology of that state in Crohn’s disease is multifactorial. According to the results of one study, 82.8% percent of the CD patients in the active phase of disease and 38.9% of those in

remission were malnourished [5]. In that study, four factors were assessed to estimate the patients’ nutritional status: body composition, dietary intake, biochemical indexes of nutrition and muscle strength (as a functional index). The study revealed a variety of nutritional and functional deficiencies in patients whose CD was in long-term remission. Mean daily intakes of fiber and phosphorus, and serum concentrations of beta-carotene, vitamin C, E, D, selenium, zinc, antioxidants and magnesium were significantly lower than in the control subjects, whereas muscle strength was preserved [6]. In another study, deficits of selected trace elements and a loss of body cell mass (BCM) and muscle strength was found in patients in remission [7]. It is probable that, as Fillipi et al. wrote: “In CD patients in remission, macronutrient needs are usually covered by food intake. However, micronutrient deficiencies are frequent” and need some supplementation [7–9]. Vitamin deficiencies are also prevalent and as Kuroki et al wrote, “concentrations of some vitamins, such as vitamin B2 and nicotinic acid, may reflect the severity of the disease” [10]. Fat-soluble vitamins such as A, D, E, K are significantly decreased in patients with IBD [11]. A study by Rumi et al. found that serum concentrations of vitamin A and carotenoids (lutein, zeaxanthin, alpha-, betacarotene, alpha-, betacryptoxanthin) were significantly lower in patients with CD than in the controls [11]. Imes et al monitored serum retinol and serum carotene concentrations over a six-month period. The results of that study indicated that “serum retinol concentrations were normal [in the studied group] of patients with Crohn’s disease and did not reflect a low dietary vitamin A intake” by a third of the studied population. Those authors also found that “serum carotene levels were frequently low in patients with Crohn’s disease, possibly due to the presence of steatorrhea”, but were not related to low dietary intakes of carotene or activity of CD; and that “a low serum level of carotene does not indicate that the patient is at risk of developing vitamin A deficiency” [12].

A study by Janczewska et al. found that in patients with the active phase of the disease, “serum retinol levels and retinol-binding protein were significantly lower than in controls. Concentrations of vitamin A did not depend on the localization of inflammatory bowel disease, previous ileal resections, duration of the disease or age and sex of the patients. The absorption of vitamins A and E in patients with IBD” [13] and normal vitamin A levels were observed in CD patients with an inactive phase of the disease. Janczewska et al. concluded that “serum retinol levels in patients with active inflammatory bowel disease are secondary to the

decreased serum retinol-binding protein concentrations, and probably depend on the increased protein catabolism in these disorders" [13].

A 2009 study by Kang et al. demonstrated that "retinoic acid plays a positive role in induction of FoxP3(+) T cells...[which] regulate intestinal inflammation" [14]. Those authors "investigated the impact of vitamin A status on the regulatory T cells and inflammation in the intestine... because retinoic acid is produced as a metabolite of vitamin A in the intestine." The results of the study "identify novel pathways of inducing highly suppressive FoxP3(+) regulatory T cells that can effectively control intestinal inflammation" and could have implications for the future treatment of IBD [14].

As Abreu et al. wrote in 2004, "Many patients with Crohn's disease (CD) have low bone mineral density (BMD) that may not be solely attributable to glucocorticoid use", but at the time CD is diagnosed, the patient's BMD is usually normal [15]. Those authors "hypothesised that low BMD in patients with CD is associated with elevated circulating levels of the active form of vitamin D, 1,25-dihydroxyvitamin D (1,25(OH)(2)D)" and that this is "secondary to increased synthesis of 1,25(OH)(2)D by inflammatory cells in the intestine... Treatment of the underlying inflammation may improve metabolic bone disease" in CD patients [15].

Crohn's disease is more commonly associated with hypocalcemia caused by poor calcium intake and decreased intestinal calcium absorption related to vitamin D deficiency as a complication of malabsorption, but elevated 1,25-dihydroxyvitamin D level may produce hypercalcemia during the active phase of the disease. It is usually connected with inflammatory process in the intestines [16]. Poorer vitamin D status correlates with lower BMD and serum 25-hydroxyvitamin levels should be assessed in patients with CD who have had the disease for over 15 years and who have been in the active stage of the disease for long periods [17, 18]. A study by Gilman et al. found that Crohn's disease patients had significantly lower serum total osteocalcin and 25-hydroxyvitamin D than the healthy control group, while their serum parathyroid hormone levels were similar to the controls. This means that osteopenia is also related to pathological rates of bone turnover [19]. However, as Schoon et al. noted, the pathogenesis of osteopenia reported in CD patients is probably multifactorial and is poorly understood. Deficiencies of fat-soluble vitamins, including vitamin K, could be another etiological factor in CD-related osteopenia. Schoon et al. wrote: "Vitamin K is a cofactor in the carboxylation of osteocalcin, a protein essential for calcium binding to bone. A high level of circulating uncarboxylated osteocalcin is a sensi-

tive marker of vitamin K deficiency" [20]. Their study findings indicated "a poor vitamin K status is associated with low bone mineral density in longstanding Crohn's disease, [which] may have implications for the prevention and treatment of osteoporosis in this disorder" [20, 21].

Among the water-soluble vitamins, Imes et al. noted that "low serum or leukocyte ascorbate levels are relatively common in patients with... Crohn's disease... due in part to reduced intake of dietary vitamin C; and... may be normalized by improving the dietary intake of vitamin C" [22]. Pettit et al. noted in 1989 that ascorbic acid absorption is normal in CD patients both with fistulas and without them, so "routine supplements of vitamin C are not necessary unless oral ascorbic acid intake is low" [23]. Ascorbate is an important factor in collagen production. When Pettit and Irving performed ascorbate analysis on samples of normal and diseased intestine from patients with CD with and without fistulas, the diseased tissues from both groups of CD patients contained significantly more ascorbate than the normal tissues. The study showed that "whereas diseased intestine from patients without fistulas contained 47 percent more ascorbate than their normal intestine... the diseased intestine from patients with fistulas contained only 23 percent more ascorbate than their normal intestine... Patients with fistulas appear unable to concentrate as much ascorbate in their diseased intestine as patients without fistulas. This difference may be a factor in the pathogenesis of fistula formation in Crohn's disease because of the importance of ascorbate in collagen production" [24].

A study by Aghdassi et al. found that patients with Crohn's disease had increased oxidative stress and lower levels of antioxidant vitamins (C, E) compared to healthy subjects. During supplementation with those vitamins, the patients' serum level increased, and all indices of oxidative stress (breath pentane and ethane output, plasma lipid peroxides, F2-isoprostone) decreased significantly, but their Crohn's Disease Activity Index (CDAI) scores remained stable. The authors noted that "vitamin E and C supplementation resulted in a significant reduction in oxidative stress. This suggests that patients with inactive or mildly active CD can be oxidatively stressed and have increased requirement in antioxidant vitamins" [25]. The fatty acid profile in CD patients is strongly associated with disease activity and serum antioxidant concentration. This observation is another argument in favor of considering antioxidants in treating inflammation in CD [25].

As Steger et al wrote: "Folate is postulated to protect against cell injury and long-term risk of

cancer. Folate deficiency has been shown to be associated with inflammatory bowel disease... Abnormal folate absorption was not correlated with disease extent or activity... [and for] about 10% of all patients with CD, parenteral folate supplementation could be considered" [26, 27] Folate levels are especially low during and after total parenteral nutrition (TPN), so 800 micrograms per day folic acid should be administered to patients with CD who have undergone TPN [27]. Erzin et al. noted: "Homocysteine is a sulfur-containing amino acid formed during the demethylation of methionine and high levels of this amino acid is a known risk factor for both arterial and also venous thromboembolic complications. Deficiencies of cobalamin, folate, and pyridoxine may predispose subjects to hyperhomocysteinemia, a common phenomenon in inflammatory bowel disease (IBD) patients.... IBD patients have a higher prevalence of hyperhomocysteinemia than do healthy controls and elevated homocysteine levels are independently associated with lower serum cobalamin, albumin levels and elevated erythrocyte sedimentation rate, and platelet count. There is no correlation between hyperhomocysteinemia and a history of prior thromboembolic events" [28]. Folate deficiency turned out to be a more important factor than low cobalamin levels, because low B12 levels depend on the involvement of the terminal ileum. A study by Duerksen et al. showed that "patients with Crohn's disease and terminal ileal resections < 20 cm are not at risk of developing vitamin B12 deficiency" but that those with resections of 20–60 cm may be at a high risk of developing such a deficiency [29]. In patients with CD, homocysteine levels are elevated and are inversely correlated with folate levels, which is why folate supplementation is important in Crohn's disease [30–32]. Zepeda-Gómez et al. pointed out that "Patients with hyperhomocysteinemia and normal fasting homocysteine levels can be identified with an oral methionine load" [33], which avoids the risk of thromboembolic complications in IBD patients. A low plasma level of vitamin B6 is also an independent risk factor for thrombosis, especially in patients in the active stage of the disease, so supplementation is necessary for CD patients [34].

Imes et al. wrote: "Iron, folate, vitamin B12 status was found to be poor in a substantial proportion of outpatients with generally inactive Crohn's disease", and noted that the participants in their study "appeared to be at low risk of developing a zinc or copper deficiency" [35]. Lorner et al. found that "Dietary iron intakes are low in CD patients, which may contribute to an increased risk of ID and anaemia. Changing dietary advice may compromise perceived symptoms of the dis-

ease so the need for iron supplementation should be carefully considered" [36].

Sturnilo et al noted that the low serum concentrations of zinc, copper and selenium in patients with CD are "probably a result of inadequate intake, reduced absorption, increased intestinal loss due to impairment of the absorption as a result of inflammatory process... [and] may contribute to the continuation of inflammatory process of IBD". Sturnilo et al wrote: "A highly significant correlation between plasma zinc and albumin suggests a possible role of plasma-binding alterations in the depressed plasma zinc levels in patients with CD" [37]. Griffin et al found that "adolescents with CD have significantly reduced zinc absorption. Despite this, they were unable to reduce endogenous fecal zinc excretion to restore normal zinc balance" [37, 38]. Decreased serum concentrations of zinc and vitamin A are frequently seen in active Crohn's disease, and Schoelmerich et al. noted that "there was a marked correlation between zinc and vitamin A and the activity of the disease" [39, 40]. Fernández-Bañares et al. found that serum selenium levels are lower and serum copper levels are higher in patients with Crohn's disease [41]. Reimund et al. have concluded that "in CD patients low selenium concentration may participate in reduced erythrocyte glutathione peroxidase activity (GSHPx) activity facilitating inflammatory and immune activation" [42].

As Sturniolo et al. wrote: "Small intestinal permeability is often increased in patients with Crohn's disease and may be pathogenic for clinical relapses [but] no effective prophylactic treatment is available for these patients" [43]. Their findings indicated that "zinc supplementation can resolve permeability alterations in patients with Crohn's disease in remission [and that] improving intestinal barrier function may contribute to reduce the risk of relapse" [43]. According to Kruis et al., zinc deficiency is particularly pronounced in CD patients with skin lesions and fistulas, and "may play a role in the formation and clinical course of fistulas. Therefore... determination of serum zinc concentration in patients with CD and fistulas appears to be of value" [44]. El-Tawil investigated low serum concentrations of zinc as a possible reason for subfertility among males CD patients [45]. Myung et al. have suggested that acrodermatitis enteropathica and retinal dysfunction may also be manifestations of zinc deficiency in CD and "may be correctable with zinc supplementation" [46].

In the era of biological therapy, the most effective treatment of patients with Crohn's disease is the use of antibodies against tumor necrotic factor-alpha (TNF-alpha). TNF-alpha seems to contrib-

ute to inflammation and malnutrition in CD [47], but little is known about the nutritional impact of anti-TNF alpha treatment [48]. Diamanti et al. found that “infliximab seems to impact positively on the nutritional status as demonstrated by the improvement in weight and BMI [and] amelioration of disease activity” [47]. In a study by Weise et al., CD patients treated with infliximab showed “improvements on [the Prognostic Inflammatory and Nutritional Index (PINI)] index that measures both inflammation and nutrition. Increases

in plasma folate suggest improvement in enterocyte function and/or increased oral intake. The increase in respiratory quotient suggests decreased lipolysis and the lack of a starvation state” [48]. The results of a study by Sousa et al. showed that among CD patients undergoing immunomodulating therapies, “the most prevalent form of malnutrition... was an excess of body weight, which was concomitant with an inadequate dietary intake, namely micronutrients, clearly related to dietary exclusion of certain foods” [49].

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