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REVIEW PAPER

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Macro and micronutrient deficiency in inflammatory bowel diseases

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ABSTRACT

Introduction. Inflammatory bowel disease (IBD) is group of global range inflammatory conditions. There has been a regular increase in the number of IBD cases. Patients exclude whole food groups from their diet fearing the emergence of disease symptoms or due to learning from unreliable sources. Doing so, they might deepen the already existing vitamin deficiencies which occur along with the shortage of many minerals. These deficiencies might intensify the disease process or cause a new one. The most common deficits pointed out by numerous researchers concern vitamin D, calcium, cobalamin, folic acid and iron. It is well worth introducing selenium, zinc and ascorbic acid into a diet because of their immunomodulating effect. Important aspect of the healing process is a personalized diet which is designed to compensate for, or prevent vitamin and mineral deficiencies.

Aim. The purpose of the study was to review the literature about vitamin and mineral deficiency in Inflammatory Bowel Diseases.

Materials and method. Analysis of literature

Key words. Crohn's disease, IBD, ulcerative colitis, vitamins

Introduction

Inflammatory bowel disease, such as ulcerative colitis and Crohn's disease, constitute chronic illnesses of global range. The gradual increase of newly diagnosed cases has been observed in the developed countries, whereas in newly industrialized countries, the incidence is rising rapidly.[1,2]

Crohn's disease (CD)

The disease process might occur in every part of the gastrointestinal tract, whether it is the oral cavity, stomach, intestines or rectum. Most often the symptoms occur in the last part of the small intestine and the initial part of the large intestine (the colon). The inflammatory process involves all the layers of the intestinal wall. The areas of intestine that are affected by the disease are sep-

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arated by normal, unaffected segments. The symptoms may be minor or acute, and they depend on the location of inflammation and the severity of the condition. The most common symptoms that patients mention include abdominal pain, diarrhea with visible blood, loss of appetite, ulceration of the oral cavity, nausea, vomiting and dysphagia. Approximately 40% of the patients are also diagnosed with fever during the relapse of the disease. CD often leads to weight loss which results both from the symptoms and the restriction of nutrient absorption.[3] The disease has periods of remission and recurrence.

Ulcerative colitis (UC)

The inflammation occurs in the large intestine and/or the rectum. What makes it different from CD is that only the intestinal mucosa structure is affected. The most common symptoms are abdominal pain, a sensation of urgent need to defecate and diarrhea with blood and mucus (which discriminates UC from irritable bowel syndrome). Similarly to CD, there can occur such symptoms as weight loss, fever and loss of appetite. The disease has periods of remission and recurrence.

Complications

In both CD and UC, there may be complications. The most common are osteopenia, osteoporosis, arthropathy, liver and bile ducts diseases, nephrolithiasis, eye and skin diseases and growth retardation in children.[3]

IBD Causes

Currently, a few factors influencing the occurrence of UC and CD can be distinguished.

Genetic factors

There are many genes which influence the body's immunological responses such as the intestinal barrier, the body's ability to fight against pathogens or the effects of oxidative stress.

First-degree relatives with positive family history of CD are more likely to develop the illness. In 2001, the NOD2 gene located on chromosome 16 was identified. It can be found in three polymorphisms and it has been associated with CD. NOD2 encodes a receptor for peptidoglycan which is found in bacterial cell walls. It is more common among patients of European origin rather than those of Asian or Afro-American descent. NOD2 polymorphism alone is not enough to trigger CD. Therefore, other factors are believed to be highly influential.[4] Genes ATG16L1 and IRGM also play crucial role. They are linked directly to autophagy, i.e. the removal of micro-organisms and dead cellular components. Approximately 160 genetic loci have been associated with susceptibility to IBD.[5,6]

Disturbed intestinal microflora

Microorganisms that live in the intestines constitute a complex ecosystem. More than one thousand species of bacteria living in the gastrointestinal tract have been identified. The environment they inhabit changes dynamically. Normal microflora helps the digestive process, synthesis of some vitamins and supports the development and functioning of the immune system. Composition of gut microflora develops throughout life. It can be influenced by environmental factors, dietary habits and lifestyle. Intestinal dysbiosis, i.e. a condition when the beneficial bacteria in the GI tract are outnumbered by the pathogenic ones, can also influence the development of IBD.[7,8] The main role is attributed to *Proteobacteria*, precisely to *Escherichia coli* (AIEC). It is more often found in patients suffering from CD than in healthy parts of the population. Some researchers suggest that AIEC plays an important role especially in the development of UC.[9] It has been shown that the number of *Clostridium leptum* and *Clostridium coccoides* is lower in patients with IBD. Both of them contribute to the production of butyrate which is the main source of energy for colon cells. Butyrate also inhibits the production of proinflammatory cytokines.[8,10]

Environmental factors

Chronic stress, trauma in the early life and depression have an impact on the condition of the immune system. Acute stress is one of the factors that may contribute to the relapse of IBD or intensification of the symptoms in its active form. Low mood and strong emotional tension are most often related to every-day school or work responsibilities or financial problems. Stress-related recurrence of the disease depends on individual characteristics of a patient, their experience and stress coping strategies. [11] A change in the intestinal microflora appears when a body reacts to strong, chronic stressors. It becomes less favorable. An increase in IL-6 concentration is also noted. [3,12]

Both in prevention and during various periods of IBD, it is important to stay physically active and maintain proper length and quality of sleep. Introducing low-intensity exercises reduces the symptoms of depression and improves the quality of life. It also lowers the disease activity.[13,14] Ineffective sleep hinders the efficiency of immune system. Both prolonged sleep (more than 9 hours) as well as shortened sleep (less than 6 hours) increases the risk of UC recurrence.[15] Patients with an active form of the disease often experience sleep disorders which might lower their mood and quality of life. [12]

Environmental factors also include a poor nutrition. Inadequate diet influences the change of intestinal microflora which in turn contributes to the recurrence or incidence of UC and CD. An infant's GI tract is colonized by bacteria beginning from the very first days after birth. For

this reason, it is worthwhile to breastfeed as it enhances the baby's immune system. The most important components of human milk include immunoglobulin A, growth factors and large number of oligosaccharides which contribute to the concentration of lactic acid bacteria in the intestines. However, it is just as important to select proper food later in life. It has been shown that the Western diet, which is rich in saturated fatty acids and trans fatty acids, and contains many high energy and processed foods, with little amount of vegetables and fruit, may influence the development and exacerbation of IBD. It has been proven that high dietary intake of myristic acid, which is one of the saturated fatty acids, may contribute to the occurrence and exacerbation of UC. Above all, it can be found in palm and coconut oil. Further study is essential to show its influence on IBD. [16-18] The dietary ratio of (n-6) to (n-3) polyunsaturated fatty acids is also crucial. High n-6 and low n-3 dietary intake may increase the risk of UC and CD. N-6 fatty acids demonstrate proinflammatory activity. The predominant *n*-6 fatty acid is arachidonic acid. It undergoes a lot of changes caused by COX-2 which lead to the development of prostaglandins (PGD2) in the mast cells and the initiation of inflammation. [19] Food additives also influence the exacerbation of IBD. Researchers point out that some of them may change the intestinal microflora and thus lead to inflammatory response. [20] However, it is essential to conduct some more research on the matter. Yet another factor predisposing to the development of IBD is the low intake of dietary fiber. Its high consumption lowers the risk of CD incidence. Soluble fibre is frequently mentioned by the authors as its most important fraction. The main sources of soluble fiber are vegetables and fruit. It is beneficial to the body as it is food for gut bacteria. It also shortens gastrointestinal transit time which limits the incidence of diarrhea. Researchers pay attention specifically to the fruit which may significantly reduce the risk of IBD. [21]

Causes of vitamin and mineral deficiencies in IBD

The cause of macro- and microelement deficiencies in patients with CD and UC is a multifaceted issue. It can result from an inflammatory process, medications, surgeries or an unbalanced diet.

Dose adjustment in IBD depends on the activity of the disease and localization of inflammatory condition. Nonsteroidal anti-inflammatory drugs are most commonly used, e.g. sulfasalazine and mesalazine. Other drug classes are corticosteroids and immunosuppressive drugs including cyclosporine and methotrexate. Folic acid deficiency is often observed after drugs administration, especially after methotrexate and sulphonamides which are the acid's antagonists.[22] Medications may also inhibit calcium absorption and contribute to the development of hemolytic anemia.

Some cases require surgical intervention. Depending on the clinical situation of a patient, surgical treatment can be emergency, urgent or elective.[23] Malabsorption syndrome can be caused, among others, by partial bowel resection in patients with complicated disease as it influences malnutrition as well as vitamin and mineral deficiencies.

Another cause of deficits is inadequate nutrition. Patients exclude whole food groups from their diet for fear of causing the relapse of the disease. Most often, it is a matter of ignorance in the subject of nutrition in IBD. Such behavior may come from the fact that many people gather information from social media where they can exchange remarks concerning their condition. [24,25] Most often, knowledge acquired in this way, i.e. from other patients or from the Internet, is not verified in terms of reliability. Such restriction in food may lead to serious vitamin and mineral deficiencies. [26]

The most important vitamins and minerals in IBD

Vitamin D and calcium

The basic function of vitamin D is to maintain adequate calcium and phosphate homeostasis. It promotes calcium and phosphate absorption in the gut. The most active form of vitamin D is D - 1,25 (OX)2D3. It influences calcium absorption the most. Vitamin D stimulates the immune system. Intracellular vitamin D receptor binds to 1,25 (OH)2D3 and supports monocyte division. Moreover, it lowers the risk of autoimmunization. Calcium, on the other hand, is indispensable to maintain bone and teeth health. It controls many enzymes, and it takes part in nerve conduction and normal muscle contraction. Vitamin D mediates the maintenance of acid-base balance.

Vitamin D deficiency may be one of the environmental factors predisposing to autoimmune diseases. Recent studies prove that this deficit leads to higher incidence of IBD and aggravation of its symptoms. More importantly, the deficiency is also present in CD patients even in the periods of remission and irrespective of the disease localization. According to this, proper dose of vitamin D may lower the frequency of incidence of these diseases.[27] Insufficient vitamin D reduces calcium absorption which in turn contributes to decreased bone mineral density and more frequent fractures.[27,28] Patients with IBD are more at risk of developing osteoporosis than the overall population which may have several causes. One of the most significant factors is the disease activity, especially its severity and duration. The next factor concerns the medications. Treatment used in IBD may negatively influence the regrowth of bone tissue. Finally, calcium and vitamin D deficiency is most often mentioned by the researchers as the contributing factor. [29,30]

Both in support therapy and prevention of osteoporosis in inflammatory bowel disease, it is crucial to provide proper amounts of these nutrients in diet. Vitamin D can be found, above all, in fatty fish and eggs. Many researches imply that its supplementation is advisable in IBD. It is especially important in patients who take steroids. Diets rich in vitamin D prevents bone mass loss in IBD.[31] Much of it is synthesized in the skin under the influence of sunlight rays. It is worth mentioning that there is no medical history of vitamin D toxicity when it is obtained from sun exposure. The skin is incapable of producing excessive amounts of it which would lead to hypervitaminosis D. [32] However, it is advisable not to expose the skin to solar radiation for too long. It might lead to sunburns which can initiate skin cancer.[33]

It is worth to enrich the diet in calcium which can be found mainly in dairy products such as kefir, cottage cheese, natural yoghurt, and also leaf vegetables and eggs. Milk is not suggested to patients with IBD because of its high lactose concentration. Patients often exclude dairy products from their diet for fear of emergence of the disease symptoms. It is lactose that may be the cause of flatulence and diarrhea after eating dairy products. Despite a number of lactose free products available on the market, people choose not to consume them as they are afraid to experience these ailments.

Vitamin D levels should be monitored in patients with IBD. In case of deficiency, supplements should be introduced.

Vitamin C

Ascorbic acid influences the body in a variety of ways. It is an immunomodulatory compound present in leukocytes. This is one of the reasons why its amount drastically decreases during an infection and demand for it increases. Vitamin C is a strong antioxidant. It neutralizes reactive oxygen species through the process of hydrogenation. Ascorbic acid causes an influx of neutrophils into the localization of infection and thus enhances the antibacterial response.[34] Moreover, it plays important role in carbohydrate metabolism, melanin synthesis and the improvement of the capillary endothelial barrier.

Levels of vitamin C are lower in people with IBD, both in its active form and in the periods of remission. [35] It may influence the reaction of immune system during infection.

Patients resign from fruit and vegetables out of fear of emergence of the IBD symptoms. This may lead to ascorbic acid deficiency which causes scurvy. Although it is rare nowadays, strict diet without vitamin C supplements increases the risk of developing this condition. It is most often observed in children, elderly people and those suffering from malabsorption syndrome. It is not easy to diagnose scurvy in its early stage. If not treated, the disease may have serious consequences, such as heart failure. Supplements are available to restore optimal vitamin C levels quickly.[36]

It is advisable to introduce parsley, berries (without the seeds), potatoes and citrus fruit in the diet of IBD patients as they are good sources of vitamin C. It is worth noticing that vitamin C is unstable. Its amount can be decreased by such factors as oxidation process, high temperature and a basic pH environment. Fruit and vegetables should be stored properly not to decrease vitamin C levels.

Vitamin B12 and folic acid

Vitamin B12 (also called cobalamin) and folic acid are indispensable to form blood morphotic elements such as erythrocytes and leukocytes. Cobalamin takes part in fatty acid and carbohydrate metabolism, whereas folic acid is involved in amino acid metabolism. Their deficits may lead to hematopoiesis disorders – megaloblastic anemia. These deficiencies may also cause alterations in the intestinal mucosa structure and nervous system disorders.

Insufficient concentration of cobalamin is one of the most often diagnosed deficits in IBD. Vitamin B12 is absorbed along small intestine which is one of the reasons why its deficiency is more common in patients with CD than those with UC. Patients after ileum resection are especially prone to it. Additionally, lower concentrations of vitamin B12 and folic acid are related to the active form of the disease when compared to the patients in remission.[44,45] Folic acid deficiency is observed in patients treated with sulfasalazine.[46,47] Researchers indicate that this deficit is more often diagnosed than vitamin B12 deficiency.[48,35] Furthermore, folate insufficiency may increase the risk of colorectal cancer in patients with IBD.[49,50] Researchers suggest screening for vitamin B12 and folate deficiency. Healthy nutrition should aid treatment of the deficits. The best source of cobalamin recommended for patients with IBD is meat (rabbit, lean beef, veal), fish, poultry and chicken egg yolk. Folate-rich foods are, above all, green leafy vegetables such as lettuce, parsley, and also citrus fruit, meat, kefir and whole grain cereal products. About 50% of folate present in food is bioavailable. Folic acid is sensitive to high temperature and sunlight.

Iron

The main role of iron concerns oxygen transport. It is indispensable for oxidase formation which regulates cellular respiration processes, and for catalase activity in erythrocytes, leukocytes and liver. Iron is absorbed in duodenum and the initial part of the small intestine. For this reason, its deficits may significantly worsen in patients with CD after the resection of those parts of the GI tract. The main iron deficiency symptoms are pallor

of skin, fatigue, impaired concentration and weakened immune system. The mineral possesses immunomodulatory properties which is highly important for patients with IBD. It reduces the risk of infection because of its antibacterial activity. It also influences lymphocyte proliferation. [34,37] IBD patients are often diagnosed with microcytic anemia. [38] The deficit may result from prolonged bleeding, malabsorption syndrome and unhealthy dietary choices.[39] The accompanying anemia may negatively affect the patients' quality of life and their job. [40]

Patients often exclude red meat from their diet. It may result from previous experiences and symptoms caused by it as well as from other patients advice. [25] Researchers often point out that such dietary modifications (exclusion of heme iron) are usually not consulted with any doctors or dieticians.[41] It is worth while to follow an iron-rich diet in order to support oral or intravenous supplementation. A well-balanced meal may enhance iron absorption. It has been proven that drinking orange juice after the meal facilitates this process, whereas tea or coffee can inhibit it.[42] Iron absorption may be reduced, among others, by phytic acids and phosphates. On the other hand, vitamin C and amino acids, such as histidine and lysine, enhance its intake. Many products eaten on a daily basis contain nonheme iron (from plant products) which show better resorption than heme iron (from animal products). In order to enhance iron absorption it is advisable to combine food products such as meat, fish, poultry and yolk together with ascorbic-acid-rich foods. [43] It can be found in parsley, berries (without the seeds), kale and citrus fruit.

Zinc

Zinc is an essential mineral that plays a great role in the immune function of the body. It strengthens the monocyte endothelial adhesion which facilitates the immune system. Zinc also influences the NK cells function and phagocytic activity of macrophages. It affects the biological membrane stability which may limit infections and reduce the risk of IBD recurrence. Serum zinc levels decrease during infection which suggests its direct influence on the immune system.[8,11] Many enzymes which participate in protein synthesis, contain this mineral. Its deficiency weakens the immune system and may cause skin lesions, appetite impairment and growth retardation in children. In order to modulate the immune system, zinc dosage should be adjusted individually, depending on its current blood serum levels. The levels should be regulated, although it is important not to excess the recommended daily amount as it may negatively influence the lymphocyte activity.[37] It is crucial in IBD since it affects the immune efficiency. Because of the increased requirement of zinc in UC and CD, its levels may be lower, especially in the active forms of the diseases. The main sources of zinc include vegetables and fruit, although its accumulation depends on the amounts of this mineral in the soil. It can also be found in wholemeal bread, buckwheat groats, meat and dairy products. Animal protein enhances dietary zinc absorption.[12,37]

Selenium

Selenium functions as an immunomodulator. It has strong antioxidant properties as it is a component of glutathione peroxidase which neutralizes hydrogen peroxide. Selenium influences proper immune response to infection. It supports macrophage function and augments NK cells and T-lymphocytes functions. [34,37] It also takes part in systemic protein synthesis.

Selenium deficiency weakens the immune system and leads to impaired cell regeneration. It can also speed up the aging process and increase the risk of poorer mood which may result in depression.

Selenium can be found in grains and cereal products, nuts (especially Brazil nuts), fish and dairy products. Unfortunately, the human body absorbs only half of selenium from food. Its bioavailability is increased by methionine, ascorbic acid and vitamin E.[34,37]

Recommendations for vitamin, macro and microelement supplementation

According to the latest guidelines and recommendations of *European Crohn's and Colitis Organization (ECCO)*, patients with inflammatory bowel disease should supplement 500-1000 mg a day of calcium and 800-1000 IU of vitamin D if the T-score in the densitometry examination is -1.5. It increases the bone density in IBD patients, although further studies are needed to confirm that it reduces frequency of fractures. Irrespective of the densitometry examination results, *ECCO* recommends calcium and vitamin D supplementation in patients treated with corticosteroids and postmenopausal women.[51,52] On the other hand, in its guidelines from 2010, the *American College of Gastroenterology* recommends that the patients who take corticosteroids for longer than three months should supplement 800 IU of vitamin D and 1000-1500 mg of calcium a day.[53]

ECCO guidelines from 2015 indicate two recommended ways of iron administration in case of severe anemia. Intravenous iron administration is advised as both effective and well-tolerated by the patients. Depending on the preparation used, the Organization recommends: 20 mg/kg body weight of intravenous ferric carboxymaltose infusion lasting 15 minutes (maximum dose 500-1000 mg), 7mg/kg body weight of ferrous sulfate (maximum dose 200-300 mg).

In case of mild anemia (defined by the *World Health Organization - WHO* as a hemoglobin level 11.0-11.9 g/dL in women and 11.0-12.9 g/dL in men) and if patients

tolerate the preparation well, iron can be administered orally. Then, the maximum dose is up to 1000 mg per 24 hours.[54]

ECCO recommends regular tests of cobalamin and folic acid levels (more often than once a year) as their deficits also occur frequently. In case of deficiencies, it suggests supplementation according to the generally applicable standards.

Conclusions

Vitamins and minerals constitute important nutrients. Balanced diet may reduce the risk of IBD and its recurrence. Proper nutrition has a positive impact on a patient's quality of life. Dietary information should be scientifically proven and reliable. It is worth to check the levels of vitamins and minerals, especially knowing the most common deficiencies. It is also recommended to include in the diet products containing calcium, vitamin D, cobalamin, iron and folic acid. Many researches also mention zinc, selenium, magnesium, vitamins K and A, and the B-group vitamins deficiencies.[46] For this reason, diet should be varied, balanced and personalized.

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