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Nutritional concerns in pediatric inflammatory bowel disease

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The pathophysiology and fundamental etiologic mechanism of inflammatory bowel disease (IBD) is not well understood even though therapeutic regimens and drugs are rapidly evolutionary. IBD has complicated connections with genetic, immunologic, gut microbial, environmental, and nutritional factors. It is not clearly well known to the physicians how to feed, what nutrients are more helpful, and what food to be avoided. This review discusses the issues of growth and important nutritional concerns in the management of IBD in childhood.

Key words: Inflammatory bowel disease, Pediatrics, Nutritional management

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Introduction

All kinds of diseases may be related with what the people ingest. In Korea, most doctors had believed that inflammatory bowel disease (IBD) does not occur in this country for decades. However, the prevalence of IBD has jumped up during very short period as we have incurred quite westernized changes on our daily meal tables, although we cannot ignore that the evolution of the diagnostic approaches and the devices could have enabled the detection of IBD.

The development of pharmacologic therapeutic regimens are already well known to the doctors, but they feel a scarcity of knowledge concerning how to teach and guide the patient toward good nutritional care and supplementation. Few physicians can detect what foods induces the patient be suffered by the aggravated symptoms and how to educate the parents to feed those children well.

It was already required to let the physician be acknowledged about the nutritional therapy and care in the patients with IBD because these patients experience the relapse, aggravation, and serious delayed growth and pubertal development.

IBD and delayed growth and pubertal development

The main reasons why delayed linear growth is more common in IBD, especially Crohn disease (CD), are as follows; deficient meal intake due to fear of symptomatic aggravation, intestinal mucosal loss of nutrients, increased nutritional requirement and chronic catabolic status, pharmacologic treatment (corticosteroids) which can inhibit insulin-like growth factor-I (IGF-I), and disease activity producing cytokines which depress linear growth[1].

1. Cytokines

Retardation of growth and delayed pubertal development are one of the major nutri-

tional issues in the children and adolescents with IBD, especially with CD. The main factors inducing these problems are poor nutritional conditions, the severity of the disease itself, genotype and the most important things; various cytokines tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-1β[2]. The presence of pro-inflammatory cytokines, secreted from the inflammation sites, interferes linear growth of the patients. Among the numerous cytokines, TNF-α has a core role in the cytokine-associated growth retardation[3-5]. The effect upon growth is more aggressive as the severity of the disease itself is more fulminant and aggravated. It is documented when we see treatment with anti-TNFα improves patient's growth as well as clinical problems[6].

This problem is more noticeable in the patients of CD. The patients with CD already show decreased growth velocity far before the diagnosis of CD, and become large burden to their parents and their doctors.

2. Nutritional deficit

The symptoms of IBD between children and adults are all the same but the distinctive delayed growth. In the adults the growth is already completed and does not matter of linear growth, even though sometimes severe status accelerates weight loss. Contracting IBD before full growth let the patient have poor appetite due to gastrointestinal (GI) symptoms, avoid well-eating and suffer from nutritional loss through the GI mucosa despite enough nutrient intake. So pediatric IBD patients show delayed growth. Furthermore, their developmental velocities are also retarded, and make them look younger than their peers. During active stage of CD, protein-losing enteropathy, mucosal hemorrhage, fistula, and hepatopathy result in hypoproteinemia. Chronic mucosal hemorrhage causes iron deficiency, and severe diarrhea induces electrolyte (potassium, magnesium) loss, and zinc deficiency, which in a cascade incur another GI problems of aggravated diarrhea, decreased immunity, and decreased tissue integrity[7].

Patients with IBD showed increased energy requirements and decreased energy expenditure, especially in the active status. With these reasons, 85% of CD patients, and 65% of ulcerative colitis (UC) already have weight loss at the time of initial diagnosis[8].

Those nutrient-associating problems in CD children may result in growth hormone (GH) resistance. They show decreased lean body mass with circulating IGF-I decrease[9]. Poor oral intake and malnutrition are related with acquired GH resistance at the site of GH receptor, and deficient serum nutrients conduct a GH-independent stimulatory effect on the height growth[10].

3. Severity of disease

Even though their nutritional intake is enough, growth may be threatened by the disease severity, the loci of the active disease, pharmacologic agents. The usual activity index such as C-reactive protein (CRP) which reflects a short-term phenomenon does not give enough information concerning the severity itself in the chronic complicating diseases[11].

The severity of disease was documented to be the impactful indicator to predict retarded growth. The patients with higher pediatric CD's disease activity index (PCDAI) score[12] grow more slowly than those with lower score.

4. Pharmacologic agents

Corticosteroid therapy may be the direct cause of poor growth when it is used for long term. Glucocorticocoids directly inhibit the chondrocytes of bony growth plate. But short-term therapy is not directly related with growth retardation. The height of the patient is already low at the time of first diagnosis. And disease complications such as fistula also cannot be a reason of poor growth[13].

In the large study of Griffiths et al[14], the effect of corticosteroids on linear growth was weaker than the effect by disease severity, and they emphasized that major risk factor for growth retardation is disease severity.

These complicated problems of growth and development bother the patients even more than the clinical difficulties.

Nutrients and childhood IBD

The eventual purposes of nutritional concern in the children with IBD are (1) improvement of nutritional status, (2) improvement of disease activity, (3) diminution of surgery indications and prevention of postoperative complications, (4) correction of pubertal growth retardation

The major purposes of the nutritional care are to alleviate the clinical conditions and to improve growth and development of the patients. In some patients, avoiding of dairy foods and fiber-rich foods diminish the GI symptoms. In some other patients, their GI symptoms become milder after decreasing fatty meals. Responses to dietary changes are different in the individuals despite same diseases. Sometimes clinical dietician can be helpful to set up proper dietary plan for each patient. The patients experience which foods aggravate their symptoms and improve those. Most parents have wrong insight to some foods. Especially Korean traditionally have thought pork and chicken meal are not suitable for GI patients, but there is no evidence to support this claim.

Foods that aggravate the symptoms of acute stage of IBD are as follows; (1) grains such as soy, red bean, and sorghum, (2) uncooked vegetables and pickled veggie, (3) citrus fruits and juices, (4) spicy foods – hot, sour, salted, (5) fatty foods and trans fats especially in case of severe ileal disease, (6) sugar, (7) caffeinated foods, (8) dairy foods (milk fat, milk protein), and (9) meat and processed meats[15,16].

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Important nutritional concerns in pediatric IBD are (1) enteral nutrition (elemental nutrition), (2) total parenteral nutrition, (3) supplement of deficient nutrients-protein, vitamins (A, D, E, K, B_{12}, folate), minerals (iron, zinc, calcium, phosphorus, magnesium, kalium), (4) avoidance of symptom-aggravating foods[17-20].

Inflammation in the small intestine leads to poor digestion and absorption of food. As poorly digested food materials pass into the colon, diarrhea and loss of nutrient more progress. That is the reason why children with malnutrition and growth retardation are more common in CD than UC. The lesion site of UC is confined in the colon with normal mucosa of small intestine, so malnutrition is not severe as CD. But if the lesions are wider and more severe, diarrhea is more exaggerated as water is reabsorbed in the colon.

Symptoms can be aggravated by some foods, but it does not indicate worsening disease severity. On the other hand, food poisoning or acute infectious gastroenteritis may aggravate the severity and affect the clinical course. Special dietary therapy is not required in IBD, we need to consider the diverse effects of specific foods.

1. Protein in IBD

The indirect index of protein-energy efficiency is kidney function, increase of body weight, biochemistry laboratory data, and acute phase reactant. Weight-for height explains the acute condition, while height-for-age suggests chronic status. Weight velocity and height velocity are very efficient indices for body growth. The indices which explain the quantitative status of protein are total protein, albumin, prealbumin, transferrin, retinol-binding protein. The qualitative examinations to evaluate the disease activities of IBD are acute phase reactant proteins such as α1-, α2-macroglobulin, transferrin, CRP, complements, and erythrocyte sedimentation rate.

Physicians need to measure weight, height, and monitor the above mentioned laboratory tests to assess the current disease activity and nutritional status.

2. Fat intake in IBD

The patient who suffers from IBD in the ileum or has undergone operation ileectomy requires low fat diet. Medium-chain triglyceride is helpful for the patient with steatorrhea. Fish oil is also effective for the prevention of relapse. A research performed in high risk patients of CD showed that supplementation of enteric-coated fish oil for one year prevented relapses in 59%, compared with 26% in the placebo group (P=0.003)[21]. The effect of fish oil on UC is still controversial[22].

It is an important concern to know what oil is more helpful. High-fat meals rich in n-6 polyunsaturated fatty acids (PUFA) reportedly accelerate bacterial overgrowth but deplete microbes from *Bacteroidetes* and *Firmicutes phyla*. Fish oil supplementation (n-3 PUFA) recovered microbiota and inflammatory cell infiltration and accentuated regulatory T-cell recruitment. These findings suggest that n-6 PUFA-rich diet may induce dysbiosis and gut inflammation in aged mice, while fish oil supplementation together with an n-6 PUFA diet can down-regulate dysbiosis[23,24].

Trans fatty acids (TFA), known as major causes of metabolic syndrome, negatively affect IBD development and aggravation. Cytokine expression from the lesion sites is higher in lipopolysaccharide-stimulated cells exposed to TFA. It exacerbates colonic inflammation by inducing Th_{17} polarization and by up-regulating the pro-inflammatory cytokines from the affected mucosa[25,26]. Accordingly, patients with IBD should avoid TFA-containing foods such as fried and instant foods.

3. Micronutrients and minerals in IBD

IBD patients are prone to be deficient in water-soluble vitamins as well as lipid-soluble vitamins. They are on low-fiber, low-residue diet during active stage. In that case water-soluble vitamins are deficient. If the lesion is within the ileum, a vitamin B_{12} deficiency follows. After small intestine surgery or if a small intestinal lesion is severe, vitamin D, calcium, magnesium, phosphorus, and iron are more likely to become deficient.

Micronutrient deficiency are caused by insufficient intake due to the disease itself, acute or chronic GI mucosal loss, and as a side effect of some drugs. Sulfasalazine (SSZ) inhibits the absorption of folate, corticosteroids suppress the absorption of calcium, and cholestyramine interrupt the absorption of lipids and lipid-soluble vitamins.

As such, physicians recommend the use of elemental formula rather than a general diet to patients with severe disease or acute-onset status.

Folate is absorbed in the small intestine and stored in the liver. The storage period is several months, so folate-rich food intake is recommended. Patients with small intestine diseases are prone to folate deficiency, which may also be induced by drugs as SSZ and methotrexate (MTX). SSZ is a potent inhibitor of reduced folate carrier, the dominant cell membrane transporter for natural folate[27]. MTX is predominantly in its polyglutamated form with scarce of hepatic folate storage[28]. Folate is important in human body because it synthesizes DNA, repairs DNA, methylates DNA , and acts as a cofactor in certain biological reactions; accordingly, it prevents the development of colon cancer in patients with UC[29]. Daily requirement of folate in normal adult is 50 μg per day, while patients with IBD require 6-8 times that amount.

Vitamin B_{12} is synthesized in the ileum. Deficiencies occur in approximately 20% of patients with CD[30]. If the lesion is in the ileum or the patient underwent ileectomy, deficiency is more likely to occur. Periodic intramuscular injections are required if the patient is too severely affected to acquire sufficient nutrition via oral intake[31].

Vitamin B_6 may become deficient in patients with CD, followed

by deficiencies of vitamin B_1, vitamin B_2, and pantothenic acid.

Vitamin C deficiency is common in IBD. Vitamin C is a strong antioxidant. During the initial severe clinical stage, patients are recommended to follow low-residue diet and eat fewer vegetables and fruits, making them prone to vitamin C deficiency. Vitamin C protects intestinal mucosa from inflammation. Vitamin C deficiency is suspicious in patients with ano-enteral fistula[32].

Vitamin A deficiency is uncommon, but may occur if the lesion site is within the small intestine. Vitamin A deficiency leads to impairment of night vision. Beta carotene, precursor of vitamin A is a representative antioxidant.

Vitamin D deficiency is common in patients with CD. Poor absorption of lipids, deficiency of bile juice, and ileal surgery in patients with CD even more cause the deficiency. In this case, growth retardation and osteoporosis are noticed especially in CD rather than UC. Bone fractures sometimes occur in pediatric patients with CD treated with corticosteroid therapy[33].

Vitamin E also may be deficient in patients with IBD, which delays healing of the mucosal lesions.

Vitamin K, which is produced in the small intestine, is commonly deficient in patients with CD as well as those with UC. The major causes of this deficiency are impaired absorption and antibiotic therapy[34].

Zinc deficiency, caused by poor absorption or hypoalbuminemia is sometimes recognized in patients with CD. This deficiency is responsible for some disease manifestations such as malaise, poor wound healing and rashes inducing anorexia, decreased GI absorption or increased GI loss[35]. A research report showed that there is a correlation between zinc and vitamin A and the disease activity score (PCDAI), and a weaker correlation with serum proteins to this score. No correlation was found with vitamin B_{12} absorption, disease localization, or previous ileal resection[36].

Calcium supplementation is required as well. Deficiency is caused by not only decreased dietary intake but also hypoalbuminemia induced by the disease itself or medication like MTX. Calcium deficiency is not apparent at the early stage of diagnosis, but as the disease progress, the deficiency can develop. Vitamin D enhances calcium absorption in the intestine, so the intake of these two nutrients is helpful. The daily requirements for patients with IBD are 1,200 mg of calcium, and 1,000 IU of vitamin D, which are beyond the daily requirements of average normal adults[37].

Magnesium may also be deficient, symptoms of which include muscle spasm and bone pain. In IBD, magnesium deficiency is caused by small intestine surgery, malabsorption, and mucosal loss.

4. Micronutrient to be alert

Iron deficiency, the most common micronutrient deficiency in patients with IBD, caused by mucosal hemorrhage, anorexia, and malabsorption. A recent study showed that the oral supplementation of iron increases oxidative stress and aggravates the mucosal inflammation[38]. Iron deficiency prevents CD-like ileitis by altering the gut microbiota[39]. As such, supplementation via intravenous route with decreased oral dose amount is desirable in the very acute stage.

Choline and carnitine, which are sufficient in red meat and eggs, comprise major components of cell membrane and have a pivotal role in synthesizing very low density cholesterol in the liver. If their levels become depleted in an obese person, fatty liver disease can easily develop[40]. In a patient of acute ulcerative colitis the intraepithelial choline level is lower than that of remission state patients[41]. However, it is still to be determined whether choline deficiency plays a role in the development of experimental colitis and human IBD. It is believed that red meat can alter or aggravate ulcerative colitis. Until now there is no evidence to resist this opinion. Intestinal microbial choline metabolism may be linked with IBD. Germ-free mice do not produce increased timethylamine-*N*-oxide (TMA) when on a high-choline diet. Interestingly, IBD patients are tend to be at increased risk of cardiovascular disease. Recent study showed that IBD is associated with increased levels of urinary TMA, which is indicative of enhanced choline metabolism and decreased choline bio-availability[42]. So these patients are recommended to be monitor their intake of this nutrient.

Conclusions

There is still specific food of choice to treat IBD. However, it would be very helpful and efficient if physicians encourage patients with IBD to limit foods that may aggravate the disease. With sufficient information about nutritional issues in addition to traditional treatments, clinicians can promote improved growth and quality of life in children with IBD.

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