Disaccharidase activity in children with inflammatory bowel disease

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ABSTRACT

Background/Aims: The etiopathogenesis of inflammatory bowel disease (IBD) is multifactorial and not well explained. Environmental, genetic, and dietary factors play an important role. The aim of the study was the evaluation of lactase, saccharase, and maltase activity in patients with IBD.

Materials and Methods: The study comprised 65 children, aged 3-18 years. During a routine endoscopy, we took biopsies from the descending part of the duodenum. In these biopsies, we determined disaccharidase activity using Dahlquist’s method.

Results: Decreased lactase activity in the biopsies taken from the small intestine mucosa was most frequently observed in patients with Crohn’s disease (5/15-33%) and least frequently seen in children with lymphocytic colitis (in 1/10-10%). The lowest mean values of lactase activity were found in the children with Crohn’s disease and ulcerative colitis (1.7-2.5 U/1 g). Decreased saccharase activity in the biopsies obtained from the small intestine mucosa was most frequently observed in patients with lymphocytic colitis (in 5/10-50%) and ulcerative colitis (9/20-45%) and least frequently seen in children with non-specific undetermined colitis (in 7/20-35%). Decreased maltase activity in the small bowel mucosa was the most frequently observed in patients with Crohn’s disease (in 5/15-33%) and least frequently seen in children with ulcerative colitis (in 3/20-15%). The lowest mean values of maltase activity were found in the children with Crohn’s disease (5.4 U/1 g).

Conclusion: Therefore, it seems reasonable to perform diagnostic examinations aimed at lactose, saccharose, and maltose intolerance and to initiate a dietary regimen in children with IBD.

Keywords: Disaccharidases, inflammatory bowel disease, children

INTRODUCTION

The etiopathogenesis of inflammatory bowel disease is not still clear and includes environmental, genetic, and dietary factors.

The inflammatory process that develops in the course of inflammatory bowel disease may also involve the upper part of the alimentary tract and the small intestine. It seems that inflammatory bowel disease may promote the coexistence of decreased disaccharidase activity. Disaccharidases are present in the brush border on the top of small intestinal villi (1-3).

The greatest lactase activity is observed in the duodenum and the proximal section of the jejunum. Its activity appears in 12 week of fetal life and increases continuously, reaching the maximum in infancy. At this time, saccharase activity also reaches its maximum values. Saccharase is mainly located in the central part of intestinal villi, predominantly in the distal section of the jejunum and proximal section of the ileum. The greatest activity of maltase is observed in the distal part of the small intestine. Lactose, a disaccharide that is the principal carbohydrate of animal milk, requires the enzyme lactase to split it into glucose and galactose. Undigested disaccharide passes to the colon, where fermentation produces hydrogen and short-chain fatty acids that can cause abdominal symptoms. Clinical manifestations of disaccharidase deficiency may be very similar to the clinical symptoms of inflammatory bowel disease and/or may exacerbate
them. Clinical symptoms of disaccharidase deficiency can involve diarrhea, abdominal cramping, bloating, flatulence, or vomiting and may result in malnutrition and loss of water or electrolytes.

Malabsorption of carbohydrates can be:
- secondary to congenital defects of the intestinal brush border (the first symptoms are typically present at birth)
- secondary to iatrogenic injuries causing damage to the functional integrity of the small intestine (celiac disease, bacterial overgrowth, food allergy, giardiasis, chronic diarrhea, protein malnutrition, Crohn’s disease, short bowel syndrome, drug-induced)
- primarily related to genetically determined lactose intolerance (in Poland about 20%-30% of the population) (4,5).

In children with inflammatory bowel disease, the crucial issue is the proper diagnosis as well as determination of coexisting diseases. This allows the physician to introduce the proper pharmacotherapy and dietary regimen, which results in quicker improvement of a patient’s general condition and regression of symptoms.

The literature contains reports on the high incidence of lactose intolerance in patients with inflammatory bowel disease; however, there are no data regarding children.

With regard to a high risk of malnutrition in the course of inflammatory bowel disease (IBD), nutritional support plays a crucial role in the management of this group of patients. In more than 60% of children with Crohn’s disease, malnutrition is observed as a result of insufficient food supply, coexisting malabsorption syndromes, and recurrent diarrhea, leading to intestinal loss and increased demand for nutrients. In the case of severe exacerbations, it is recommended to introduce no-residue, semi-elemental, or elemental diets. Elemental diet also shows immunological effects by increasing the supply of food and macromolecular antigens, changing intestinal bacterial flora, inhibiting intestinal loss of lymphocytes, and decreasing synthesis of inflammatory mediators. An adequate dietary regimen leads to improved protein and energetic balance, correction of micronutrient deficiency (vitamins, trace elements), and decreased intestinal loss of nutrients (6-9).

The aim of the study was to evaluate lactase, saccharase, and maltase activity in the small intestine mucosa and the prevalence of their decreased activity among patients with various types of inflammatory bowel disease (Crohn’s disease, ulcerative colitis, lymphocytic colitis, and non-specific undetermined colitis).

**MATERIALS AND METHODS**

The study included 65 children at the ages of 3-18 years (mean age: 14 years; 35/65 boys (54%) and 30/65 girls (46%)) in whom we diagnosed, following the Porto criteria (clinical manifestation, results of laboratory tests, endoscopic examination, histopathological evaluation of the obtained biopsies, and imaging examinations) (3), various forms of IBD:

- in 15 children - Crohn’s disease (mean age 14.5 years)
- in 20 children - ulcerative colitis (mean age 15 years)
- in 10 children - lymphocytic colitis (mean age 14 years)
- in 20 children - non-specific colitis (mean age 13.5 years)

The analysis included the following parameters: age, gender, nutritional status, disease activity, and atrophy of the small intestine villi.

For the assessment of nutritional status, the Cole’s index was used. The following subgroups were separated: malnutrition (Cole’s index <85), slight body mass deficiency (Cole’s index 85-90), and normal nutritional status (Cole’s index >90).

For the evaluation of disease severity in patients with Crohn’s disease, the PCDAI scale was used, and ulcerative colitis was assessed by means of the Truelove-Witts scale.

In all patients, upper gastrointestinal endoscopy was performed using the Olympus endoscope (in younger children GIV N30, GIV P140; in older children GIVV2).

During a routine endoscopic examination of the alimentary tract, we obtained biopsies from the descending part of the duodenum. In these samples, we determined lactase, saccharase, and maltase activity using Dahlquist’s method. The obtained biopsies were immediately frozen at -20°C in physiological saline solution. Disaccharidase activity was presented as micromoles of decomposed disaccharide in 1 minute of incubation per 1 g of mucosa. The following values were accepted as normal: lactase activity in the range 1.0-19.0 U/1 g tissue, saccharase over 6.0 U/1 g tissue, and maltase over 13 U/1 g tissue.

Additionally, diagnostics of lactose intolerance included hydrogen breath test performed by means of the Bedfont glyzer. The hydrogen breath test was performed by measuring the amount of exhaled hydrogen before and after 30, 60, 90, and 120 minutes administering an oral lactose dose of 1.75 g/kg body weight (max. 50 g). As a positive result, an increase in hydrogen content in exhaled air over 20 ppm after lactose load was accepted. Bacterial overgrowth of small intestine was diagnosed on the base of the result hydrogen breath test, using Gastrolizer of Bedford company.

All examined patients were informed about the method and purpose of the examination. In order to take additional biopsies, informed written consent was obtained from parents/legal guardians and the examined children, if they were older than 16 years old.
The authors gained the consent of the Bioethics Committee at the Medical University of Silesia in Katowice.

The obtained results were statistically analyzed, and a significance level of $p<0.05$ was accepted. For comparisons of feature incidence in the examined groups, chi$^2$ test was used, whereas the Kruskall-Wallis test was used for comparisons between groups.

**RESULTS**

The clinical picture of the analyzed patients was dominated by chronic or recurrent diarrhea in 60/65 patients (92%), blood in stool in 45/65 (69%), recurrent abdominal pain in 58/65 (89%), and bloating, flatulence, and rumbling stomach noises in 35/65 (53%) patients.

Activity of Crohn’s disease on the PCDAI scale was within the range of 35-65 points (mean 45 points), and the score for ulcerative colitis was between 5 and 10 points on the Truelove-Witts scale (mean 8 points).

Decreased lactase activity in biopsies from the small intestine mucosa was most frequently observed in patients with Crohn’s disease (in 5/15 - 33%) and least frequently seen in children with lymphocytic colitis (in 1/10 - 10%). However, this difference was not statistically significant.

In patients with ulcerative colitis and non-specific undetermined colitis, the incidence of decreased lactase activity in biopsies corresponded to the incidence of lactose intolerance in the population of Polish children (about 20%).

The lowest mean values of lactase activity were found in children with Crohn’s disease and ulcerative colitis (1.7-2.5 U/1 g tissue) (Table 1).

We found a statistically significant correlation between the higher occurrence of decreased lactase activity and atrophy of the small intestine villi ($p<0.005$). Atrophy of the small intestine villi was observed in 6/65 (9.2%) of the examined patients with IBD, in 4 children (26.6%) with Crohn’s disease, in 1 patient with ulcerative colitis, and in 1 patient with lymphocytic colitis.

Among 4 children suffering from Crohn’s disease and coexisting villi atrophy, lactase activity was decreased in 3 children, and in one limit values were observed (statistically significant difference, $p<0.005$).

We did not find any relationship between lactase activity in children with inflammatory bowel disease and sex, age, and degree of malnutrition. In patients with Crohn’s disease and ulcerative colitis characterized by a more active disease course, lower lactase activity was observed; however, this difference was not statistically significant.

Decreased saccharase activity in biopsies from the small intestine mucosa was most frequently observed in patients with lymphocytic colitis 5/10 (50%) and ulcerative colitis 9/20 (45%); however, this difference was not statistically significant. The lowest mean activities of saccharase were found in children with lymphocytic colitis and Crohn’s disease. Lack of correlation between saccharase activity or the frequency of abnormal saccharase levels and age, sex, and atrophy of the small intestine mucosa was revealed in all examined groups of patients.

The lowest mean values of saccharase were found in children with a considerable body mass deficiency, and the highest was seen in children with normal nutritional status (but not statistically significant) (Table 2).

Decreased maltase activity in biopsies obtained from the small intestine mucosa was most frequently observed in patients with Crohn’s disease (in 5/15-33%) and lymphocytic colitis (in

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<th>Lactase activity</th>
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<td>Crohn’s disease</td>
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<td>Ulcerative colitis</td>
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<td>Lymphocytic colitis</td>
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<td>Non-specific Undetermined Colitis</td>
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<td>Examined patients with IBD</td>
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IBD: inflammatory bowel disease

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**Table 1. Lactase activity in examined children with IBD**
3/10-30%) and least frequently seen in children with ulcerative colitis (3/20-15%) and non-specific undetermined colitis (3/20-15%). The lowest mean values of maltase activity were found in children with Crohn’s disease, too (5.4 U/1 g tissue) (Table 3). Statistically, maltase activity was significantly higher in older children (>10 years) (p<0.001).

We did not find any relationship between maltase activity and the incidence of decreased values in children with inflammatory bowel disease and gender, degree of malnutrition, and atrophy of the small intestine villi.

No correlation was found between the mean values of saccharase and maltase activity and disease activity in patients with ulcerative colitis and Crohn’s disease.

Bacterial overgrowth in the small intestine was observed in 6/65 (9.2%) analyzed patients with IBD: in 3/15 (20%) patients with Crohn’s disease, 1/20 patients with ulcerative colitis, 1/10 (10%) patients with lymphocytic colitis, and 1/20 (5%) patients with non-specific undetermined colitis. In 3 patients with bacterial overgrowth, decreased lactase activity was found in the small intestine mucosa biopsies.

Lactase activity was compared with the results of hydrogen breath test. In 83% (54/65) of subjects, results of the hydrogen breath test were consistent with lactase activity. In 8/65 (12%) patients, the hydrogen breath test produced positive results at normal lactase activity; in 6/65 of them, lactase activity values were at the lower limit of normal. In 3/65 (4.6%), normal results of the hydrogen breath test were observed at decreased lactase activity in the small intestine mucosa biopsies.

**DISCUSSION**

With regard to a possible location of IBD inflammatory lesions within the upper gastrointestinal tract and small intestine, a more frequent co-existence of insufficiency of disaccharidases may be suspected in this group of patients. On the other hand, symptoms of disaccharide intolerance may be very similar to the manifestations of IBD. Initiation of appropriate diet in these...
patients leads to general improvement in condition and resolution of the clinical symptoms.

In adults, the genetic background of primary hypolactasia has been established. In Poland, it affects approximately 30%-35% of the population. However, a relationship between C/C-13910 and G/G -22018 genotypes (characteristic for primary hypolactasia) and genetic background of Crohn’s disease has not been proven. Therefore, it seems that the pathomechanism of increased incidence of hypolactasia in Crohn’s disease patients is much more complex and still unclear (10,11). Among our patients with Crohn’s disease, decreased lactase activity in the small intestine mucosa biopsies was observed in more than 1/3 patients. However, when compared to the other groups of patients, the difference was not statistically significant. The mean values of lactase activity were also the lowest in this group of children. Buning, in his study, demonstrated the presence of genotype characteristics for primary hypolactasia in 21% of patients with diagnosed Crohn’s disease, which may correspond to the population incidence of primary hypolactasia. A similar incidence was observed for patients suffering from ulcerative colitis. Thus, it appears that increased incidence of hypolactasia in patients with IBD is not genetically determined (11). Lactose intolerance may be related to increased permeability of the intestinal mucosa, being a consequence of its damage and inflammatory processes. In our study, we have demonstrated a statistically significant correlation between more frequent decreased lactase activity and atrophy of the small intestine villi. Welsh, in his studies, demonstrated a correlation between decreased activity of lactase, saccharase, and maltase and villi atrophy, especially in the course of celiac disease. At complete villi atrophy, lactase and saccharase deficiency was observed in nearly 100% of patients, and in over half of the subjects, maltase deficiency was found. Following a dietary regimen and villi recovery, normal activity of these disaccharidas was observed in most patients (12). We have not observed such a correlation for maltase and saccharase. Park, after analyzing patients with Crohn’s disease and irritable bowel syndrome, demonstrated lack of differences in disaccharidase activity between these two groups. Only in 2/62 patients with Crohn’s disease did the author observe decreased lactase activity and limit values of saccharidase in 2 patients. In all of the patients, he observed normal maltase activity. Thus, decreased disaccharidase activity was less frequent than in the general population. Patients analyzed by Park very rarely manifested lesions within the upper gastrointestinal tract; only 4/62 patients had lesions within the jejunum (13). Approximately 4% of patients suffering from Crohn’s disease have lesions located in the upper gastrointestinal tract, most often in the form of gastric mucosa ulceration. Some authors believe that upper gastrointestinal tract lesions can also be secondary to drug administration. In patients with Crohn’s disease located within the upper gastrointestinal tract, body mass deficiency and hypoproteinemia are most frequently observed. It may be assumed that in this group of patients, disaccharidase deficiency may be more frequent. In 4/15 of our Crohn’s disease patients, we observed villi atrophy; however, in the upper gastrointestinal tract, we did not find any granulomas characteristic for this disease.

Mishkin claimed that in patients at low ethnic risk, there is a statistically significant increase in the prevalence of lactose malabsorption in Crohn’s disease patients and a decreased prevalence in ulcerative colitis, when compared with controls. In his study, Mishkin also demonstrated that decreased lactase activity is more frequent in patients with Crohn’s disease involving the small intestine than the large intestine, which was consistent with our observations (14).

In over 1/3 pediatric patients with Crohn’s disease, Pfefferkorn observed lactase deficiency that did not correlate with atrophy of the small intestine villi (15).

It has been established that NOD2/CARD15 mutation affects immune responses and is related to mucosal barrier damage and increased antigen penetration, leading to villi damage and secondary hypolactasia (1).

Terpitz, in his studies, observed the symptoms of lactose intolerance, confirmed by diagnostic tests, in almost 50% of Crohn’s disease patients. The author demonstrated a relationship between more frequent lactose intolerance and disease activity and duration of the inflammatory process, which was not confirmed by our own studies (16).

Lactose intolerance symptoms, such as diarrhea, abdominal pain, or stomach rumbling, may be consistent with the symptoms of IBD. In everyday clinical practice, it is very important to differentiate symptoms of the underlying condition-Crohn’s disease-and manifestations of disaccharide intolerance. Initiation of a dietary regimen will improve a patient’s general condition and symptoms. On the other hand, a diet must be adequately adjusted to the patient and provide animal protein and calcium, since it has been established that in patients with Crohn’s disease and coexisting lactose intolerance, statistically, osteoporosis is significantly more frequent (6,16).

From a historical perspective, the concept of ‘milk allergy’ was introduced in the early part of this century, when it was believed that food and eating habits were involved in the pathogenesis of IBD. Today, the only recognized value of these studies is the evidence that lack of breast-feeding and increased prevalence of hypersensitivity to cow’s milk may be risk factors for the development of IBD in the future (14).

Food sensitivities, in particular to dairy products, are occasionally relevant to Crohn’s disease and probably even less often to ulcerative colitis patients.

In our patients with coexisting disaccharidase deficiency, we did not observe an increased incidence of food allergy.
A theory indicating a relationship between the immunological impact of cow’s milk proteins and manifestation of inflammatory bowel disease has not been fully proven. On the other hand, undigested and unabsorbed lactose leads to increased osmolarity in the intestinal lumen; as a result of bacterial flora activity, an increased amount of gas is produced, leading to aggravation of clinical manifestations of the underlying disease.

In the course of ulcerative colitis, the jejunum is not damaged; therefore, it seems that the incidence of hypolactasia should not be higher than that observed in the general population. In our patients with ulcerative colitis, the incidence of decreased lactase activity was consistent with the population incidence in this age group. Girard, in his study, did not demonstrate any statistically significant differences in incidence of lactose intolerance between patients with ulcerative colitis and controls. The author claims that routine initiation of a low-lactose diet is a mistake, and it can lead to protein and calcium deficiency (17). Park observed saccharase deficiency in only 2/62 patients with Crohn’s disease and did not find maltase deficiency in any subjects (13).

Rana et al. (8) demonstrated that severe malnutrition is related to decreased disaccharide activity and consequently affects digestion and absorption of disaccharides, especially lactose. It is probably connected with considerable protein deficiency. In our studies, no relationship between malnutrition and lactase/maltase activity was observed. We found such a correlation for saccharase. However, in our patients, we very rarely observed considerable protein deficiency, which was believed to be secondary to atrophy of the small intestine villi. In the literature, there are numerous reports on more frequent decreased lactase activity in patients with severe malnutrition than in the general population (18).

The literature data emphasize the problem of increased sugar consumption, especially saccharose, in patients with Crohn’s disease (9,19,20). The question is whether it is a factor promoting manifestation of IBD, particularly Crohn’s disease. The links between nutrition and Crohn’s disease have now become strong, and the role of fat may be the most exciting of all.

Additional factors that may affect disaccharidase activity are overgrowth of small intestine bacterial flora and duration of intestinal passage. A huge role is played by changes of the intestinal flora in the course of inflammatory bowel disease – methanogenic bacteria that frequently occur during IBD (20,21).

In patients with lymphocytic colitis, coexistence of disaccharidase deficiency may be connected with increased coexistence of celiac disease (22,23). However, in our patients with lymphocytic colitis, only one patient suffered from celiac disease. In this patient, we observed lactase, saccharase, and maltase deficiency in the small intestine mucosa.

In most studies, lactose intolerance is evaluated by means of the hydrogen breath test. This test is characterized by high sensitivity and specificity. However, its results may be affected by bacterial overgrowth in the small intestine, antibiotic therapy, and disturbances of intestinal passage. In our analysis, this test produced results of high sensitivity and specificity. In 83% (54/65) of subjects, the results of the hydrogen breath test were consistent with lactase activity. Thus, the question is whether disaccharidase activity assessment in the small intestine mucosa biopsies is more reliable.

In conclusion, it seems reasonable to perform diagnostic examinations aimed at lactose, saccharose, and maltose intolerance and to initiate dietary regimens in children with IBD. In patients with Crohn’s disease, we observed a higher incidence of decreased lactase activity than is observed for the general population. Therefore, it seems reasonable to perform diagnostic examinations aimed at lactose intolerance and to initiate dietary regimens in children with inflammatory bowel disease. In other groups of patients, disaccharide intolerance should be considered in the case of treatment failure.

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