Disaccharidase Activity In Children Undergoing Esophagogastroduodenoscopy: A Systematic Review

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**Abstract**

**Objectives:** Intestinal disaccharide analysis of duodenal biopsy specimens are often obtained during esophagogastroduodenoscopy (EGD) in children. We performed a systematic review of studies examining disaccharide activity from biopsy specimens in children undergoing EGD.

**Methods**: All full-length articles published in English during 1966-2014 were included if: (i) participants had small intestinal biopsy evaluation of disaccharide activity, (ii) levels of lactase, sucrase, maltase or palatinase were reported, (iii) age of participants was under 18 years.

**Results:** Thirty articles examining 34,753 disaccharide assays fulfilled the inclusion and exclusion criteria. All were observational and most (17) were prospective. Sixteen studies were performed in the United States and there were 9 European studies. The largest study examined about 30, 314 procedures and 13 studies examined less than 50 procedures. Eleven studies examined Caucasian subjects, 3 studies examined Asian subjects, and 6 examined African subjects. Only one Hispanic subject was included. In studies reporting disaccharide deficiency, the overall proportion of lactase deficiency was 39.2%, sucrase deficiency was 9.0%, maltase deficiency was 12.6% and palatinase deficiency was 9.1%. The prevalence of duodenal inflammatory changes ranged findings varied from 6% to 24% for non-specific histological gastrointestinal inflammatory lesions (e.g., duodenitis). 16 studies examined the association of histologic findings with disaccharide activities, and 12 studies reported an inverse association between degree of histologic inflammation and disaccharide levels.

**Conclusions:**  We reviewed 30 studies including 34,753 biopsy specimens with disaccharide analysis from children undergoing EGD. Our findings suggest that a large study is needed to further clarify the value of EGD with disaccharide analysis in children.

**Keywords**:

## [Disaccharidase](http://www.ncbi.nlm.nih.gov/pubmed/10067723), Endoscopy, ChildrenIntroduction

Intestinal disaccharide analysis of duodenal biopsy specimens are often obtained during esophagogastroduodenoscopy (EGD) in children. Options for disaccharide evaluation include stool analysis, hydrogen breath tests, and sugar tolerance testing. However, the “gold-standard” to achieve a definitive diagnosis is a small bowel biopsy and small bowel enzyme assay.(1) The four enzyme complexes commonly assessed for disaccharide hydrolysis (disaccharidases) are lactase, sucrase, maltase and palatinase. In pediatrics, disaccharide deficiency has a wide clinical presentation with symptoms possibly including diarrhea, bloating, flatulence, abdominal pain, borborygmi, and failure to thrive. Therefore, it can be challenging to select patients undergoing EGD to complete the additional disaccharide evaluation which generally requires at least two additional duodenal biopsy specimens.

Many studies and numerous reviews have attempted to define the prevalence of disaccharide deficiency and explore disaccharide activity in select pediatric populations. However, for most children with non-specific symptoms, clinical guidelines do not clearly express indications for disaccharide measurement during diagnostic EGD. Clear indications for disaccharide analysis might include chronic diarrhea and failure to thrive of unclear etiology. However, in patients with other clinical features such as abdominal pain, bloating, or gastroesophageal reflux it is not clear when disaccharide analysis should be pursued. For example, the diagnosis of functional gastrointestinal disease usually is made without evaluations of disaccharide activity, although symptoms from carbohydrate intolerance can overlap.

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We performed a systematic review of the literature to evaluate existing evidence regarding intestinal disaccharide activity reported in duodenal biopsy specimens from children undergoing EGD. We sought to review the effect of ethnicity, underlying conditions, presenting symptoms, histological findings, and region of origin on disaccharide activities in children. Finally, we searched for studies examining clinical outcomes (change in treatment, quality of life, improvement of symptoms, cost-effectiveness) following EGD with disaccharide analysis.

**Methods**

## *Literature Search*

A search of the medical literature was conducted for studies examining subjects undergoing EGD with small intestinal biopsy evaluation of disaccharide activity using MEDLINE (1966- March 2014), EMBASE (1995 – March 2014), and the Cochrane Database (March 2014). Articles were identified with the Medical Subject Heading [MeSH] and free text terms [*Disaccharidases/analysis*](http://www.ncbi.nlm.nih.gov/pubmed/10067723)*, Duodenum/enzymology,* [*Disaccharidases/deficiency*](http://www.ncbi.nlm.nih.gov/pubmed/100368)*, Disaccharidases/metabolism, Intestinal Mucosa/enzymology* (all MeSH heading and free text terms). *PubMed* was used to search MEDLINE and the following limits were applied: *Languages: English* and *Ages: All Child 0-18 years*. Bibliographies of pertinent articles were also reviewed for relevant articles (Figure 1).

Selection Criteria and Analysis

Studies were selected if they assessed disaccharide levels after EGD in pediatric patients. Only fully published articles in English were considered. The inclusion criteria (in addition to those mentioned above) for the studies were: (i) participants had small intestinal biopsy evaluation of disaccharide activity, (ii) levels of lactase, sucrase, maltase or palatinase were reported, (iii) age of participants was under 18 years. The exclusion criteria were: (i) participants were over 18 years of age; (ii) failure to report specific results (activity levels or deficiency) of disaccharide analysis of intestinal biopsy.

The primary data extracted from each article included: the year and country of enrollment, study design, number of participants, ethnicity, underlying conditions, presenting symptoms, disaccharide activity level, and result of the histology reports. Studies also were reviewed for: 1) association of alarm symptoms or signs to diagnostic yield 2) correlation of the nature of the abdominal pain (duration, location, severity) with organic pathology 3) patient outcomes (quality of life, improvement of symptoms), or cost-effectiveness 4) patient outcomes (quality of life, improvement of symptoms), or cost-effectiveness. The following quality criteria were identified in each study: whether (1) the subjects were recruited consecutively (2) the outcome was measured accurately (3) confounders were identified and adjusted for.

We determined overall prevalence estimates by pooling values from studies that met the selection criteria and calculating sample-size—weighted mean values. We calculated pooled means for disaccharide levels using the weighted means equation. The findings are presented in tabular form.

**Results**

Total retrieval was 2152 articles based on the general search strategy (Figure 1). Titles and abstracts were reviewed and 30 studies were found which fulfilled the inclusion and exclusion criteria (Tables 1, 2, 3). All of the identified articles were observational or cohort studies and most were prospective (17). The included studies were conducted between 1966 and 2012. The majority of the studies (n=23) were conducted in European or American populations. 11 studies examined Caucasian subjects, 3 studies examined Asian subjects, 6 examined African subjects, and one study examined Native Americans. Hispanic subjects were only included in one study which had only one Hispanic subject.(2) Only one study did not report histologic features of participating subjects.(3) None of the studies examined resource utilization, cost-effectiveness, or quality of life of disac analysis after EGD. The largest study examined about 30, 000 procedures and 10 studies examined less than 100 procedures.

One large study examined 30,314 biopsy specimens. A total of 4,439 patients were subjects in the remaining 29 studies. In studies reporting specific disaccharide deficiency, the overall proportion of lactase deficiency was 39.2%, sucrase deficiency was 9.0%, maltase deficiency was 12.6% and palatinase deficiency was 9.1%.

Twenty-nine studies included histological analysis. Among histologic findings, eight studies reported no histopathologic abnormalities and 21 studies reported abnormal histopathology. Patients categorized as “abnormal” generally had varying degrees of villous atrophy or histological mucosal inflammation. The prevalence of duodenal inflammatory changes ranged findings varied from 6% to 24% for non-specific histological gastrointestinal inflammatory lesions (e.g. duodenitis). The prevalence of villous atrophy ranged from 8.7% to 100%. Sixteen studies examined the association of histologic findings with disaccharide activities. Four studies reported no clear association between histopathology findings and disaccharide activity.(4) (5) (6) (7) However, 12 studies reported some degree of inverse association between degree of histologic inflammation and disaccharide levels. Among these 12 studies, 3 studies reported an association between all disaccharide levels and histologic findings. (8) (9) (10) Five studies reported correlation between lactase, sucrose, and malatase and histoligc inflammation. (11) (12) (13) (14) (15) Ogrady et al study reported association between lactase and sucrose with histology inflammation.(16) Hetlinger et al reported reported an inverse correlation with lactase and maltase with inflammatory changes.(17) Finally, two studies reported a correlation with lactase only.(18) (19)

Seven studies specifically examined patients with celiac disease and enumerated the results accordingly. (20) (16) (15) (21) (5) (13) (22) These studies examined a total of 269 EGDs in 224 patients were performed with celiac disease. Among these 269 procedures, 181 had significant microscopic inflammation/villious atrophy and 88 patients had no significant inflammation. Six studies reported mean disaccharide levels and found that mean lactase levels were 6.9 uM/min/g protein in patients with significant inflammation and 20.69 uM/min/g protein in patients without significant histologic changes. Mean sucrase levels were 18.3 uM/min/g protein in patients with significant inflammation and 45.14 uM/min/g protein in patients without significant histologic changes. mean maltase levels were reported in 5 studies, 49.6 uM/min/g protein in patients with significant inflammation and 102.4 uM/min/g protein in patients without significant histologic changes. Mean palatinase levels were reported in 2 studies 3.44 uM/min/g protein in patients with significant inflammation and 8.27 uM/min/g protein in patients without significant histologic changes. Among 4 studies reporting the proportion of subjects with lactase deficiency, lactase deficiency was found in 54/61 (88.5%) patients with untreated celiac disease as compared to 8/51 (15.7%) patients with treated celiac disease. Among 3 studies reporting the proportion of subjects with maltase deficiency, maltase deficiency was found in 54/61 (88.5%) patients with untreated celiac disease as compared to 2/6 (33.3%) patients with treated celiac disease. Among 3 studies reporting the proportion of subjects with sucrase deficiency, sucrase deficiency was found in 27/76 (35.5%) patients with untreated celiac disease as compared to patients with 2/6 (33.3%) treated celiac disease. Among 2 studies reporting the proportion of subjects with palatinase deficiency, palatinase deficiency was found in 27/31 (87.1%) patients with untreated celiac disease as compared to 2/6 (33.3%) patients with treated celiac disease.

Five studies specifically examined patients with chronic diarrhea and enumerated the results accordingly. (13) (8) (4) (23) (22) These studies examined a total of 214 patients were performed with chronic diarrhea undergoing EGD. All studies reported mean disach levels and found that mean lactase levels were 27.5 uM/min/g protein in patients with normal histology, 15.3 uM/min/g protein in patients with mild inflammatory changes , 8.7 uM/min/g protein in patients with moderate/severe inflammation. Mean sucrase levels were 59.7 uM/min/g protein in patients with normal histology, 44.2 uM/min/g protein in patients with mild inflammatory changes , 27.3 uM/min/g protein in patients with moderate/severe inflammation. mean maltase levels were 201.5 uM/min/g protein in patients with normal histology, 177.2 uM/min/g protein in patients with mild inflammatory changes, 110.3 uM/min/g protein in patients with moderate/severe inflammation. Two study reported palatinase levels and found mean palatinase levels were 12.1 uM/min/g protein in patients with normal histology, 5.8 uM/min/g protein in patients with mild inflammatory changes, 3.0 uM/min/g protein in patients with moderate/severe inflammation.(8) (22) Among two studies reporting the proportion of subjects with lactase deficiency in subjects with chronic diarrhea, lactase deficiency was found in 73/190 (38.4%). (13) (8) One study reported sucrose deficiency in subjects with chronic diarrhea and found 10/88 (11.4%). (13)

Two studies examining 7 patients reported disaccharide activities in subjects with failure to thrive. (23) (22) All studies reported mean disaccharide levels and found that mean lactase levels were 1.97 uM/min/g protein, mean sucrase levels were 4.6 uM/min/g protein, mean maltase levels were 15.5 uM/min/g protein. All 7 patients had pan disaccharide deficiency.

Two studies examining 14 patients reported disaccharide activities in subjects with kwashiorkor. (24) (25) All studies reported mean disaccharide levels and found that mean lactase levels were 6.4 uM/min/g protein, mean sucrase levels were 52.9 uM/min/g protein, mean maltase levels were 190.9 uM/min/g protein. One article reported the specific proportion of disaccharide deficient patients and found 8/10 (80%) were lactase deficient, 2/10 were sucrose deficient, and 3/10 were maltase deficient. (25)

Three studies compared disaccharide activity across ethnic populations. (26) (27) (12) One study performed in the USA found that lactase deficiency is rare in Caucasian children as compared to native American and African populations as all 117 Caucasian children under age 5 had normal lactase levels. (26) Another study from Finland found that the mean activities of lactase, sucrose, and maltase were significantly higher in Finnish children as compared to African children. (27) The study further found that 31% (59/188) of Finnish children had low lactase as compared to 67% (18/27) of African children. The final study was performed in Belgium and compared Belgian children to non-Belgian Caucasian children and found that median values for lactase activities were lower in non-Belgian children (33 uM/g) as compared to Belgian children (40 uM/g) (p=.02).

11 studies examined Caucasian subjects, but only 4 focused on Caucasian subjects and enumerated results accordingly. Among these 4 studies, a total of 441 patients were included with variable underlying conditions including FTT, IBS, CF, immunologic deficits and giardiasis. (28) (29) (18) (6) All 4 studies reported the proportion of lactase deficiency in subgroup populations and the overall prevalence was 43/162 (26.5%). 2 studies report the proportion of sucrose and maltase deficiency and sucrose deficiency was reported in 12/39 (30.8%) and maltase deficiency was reported in 16/39 (41.0%). Combined mean disaccharide levels from studies examining Caucasian populations were: 30.6 uM/g for lactase, 61.0 uM/g for sucrose, 204.0 uM/g for maltase and 16.7 uM/g for palatinase. When stratified by histologic inflammation, Caucasian patients with normal histology had mean levels of 31.8 uM/g for lactase, 61.4 sucrase, 204.8 for maltase, and 16.8 for palatinase. Those with mild inflammation had levels of 17.9 lactase, 62.0 sucrase, 219.5 maltase, 17.3 for palatinase. Moderate severe inflammation was associated with levels of 7.3 lactase, 39.1 sucrase, 125.5 maltase, 11.3 palatinase.

One study focused on 100 Indian subjects with celiac or GERD and did not report the proportion of disaccharide deficiency in the cohort.(15) Overall levels were reported at 15.7 for lactase, 30.7 sucrase. 62.2 for maltase. When stratified by histologic inflammation, Caucasian patients with normal histology had mean levels of 23.3 uM/g for lactase, 39.9 sucrase, 72.8 for maltase, Those with mild inflammation had levels of 18.4 lactase, 28.7 sucrase, 64.3 maltase. Moderate severe inflammation was associated with levels of 11.0 lactase, 25.3 sucrase, 55.7 maltase.

Prinsloo et al reported disaccharide levels in an exclusively African cohort of 22 subjects with kwashiorkor or pellagra. (25) The proportion of patients who had disaccharide deficiency was only reported for lactase with 7/10 subjects with kwashiorkor

and 10/10 for pellagra for an overall prevalence of 17/20 (85%). For kwashiorkor, the levels were 8.4 for lactase, 50.1 for sucrose, 185.7 for maltase, 67.9 for palatinase. For pellagra, the levels were 2.73 lactase, 50.7 sucrase, 163.4 maltase and 70.0 for palatinase. Combined levels were 5.3 lactase, 50.4 sucrase, 173.5 maltase, 69.1 for palatinase.

3 studies examined Asian subjects, 6 examined African subjects, and one study examined Native Americans. studies focused on specific ethnic populations.

The largest study reported findings in 30,314 samples received over a 5 year period in a reference laboratory. (3) This study found that the most common deficiency was lactase occurring in 8963 (32%), followed by pandisaccharide deficiency in 2347 (8%). Congential sucrose-isomaltase deficiency was extremely rare, occurring in just 0.1% of the samples.

Only one study examined management changes as a result of intestinal disaccharide analysis. (8) Gupta et al conducted a questionnaire to assess the efficacy of diet changes in patients with lactase deficiency and found that 81.5% (22/27) of patients responded to dietary modification.

**Discussion**

Our systematic review of 30 studies of intestinal disaccharide analysis, including over 30,000 samples, found that lactase deficiency was most common (39.2%), followed by maltase deficiency (12.6%), palatinase deficiency (9.1%), and sucrase deficiency (9.0%). Histopathology was reported in most studies and the primary findings included duodenal inflammation (6% to 24%) or villious atropy(9% to 100%). A large multi-center study including 30,314 disaccharide analysis was performed in 2012, however, this study did not include information on the underlying conditions, histology, or ethnicity of its subjects.

In the articles reviewed, many did not specifically enumerate the indication or underlying condition for the EGD with disaccharide analysis. The most common conditions examined included celiac disease, chronic diarrhea, and malnutrition. In clinical practice, chronic diarrhea and malnutrition are common indications for disaccharide analysis. However, generally enzyme levels are not routinely measured in patients with celiac disease, as intestinal function usually normalizes with a gluten free diet. The most common indications for EGD in children include abdominal pain, vomiting, and reflux symptoms. (30) (31) However, subjects with abdominal pain, reflux symptoms or vomiting were specifically examined in just 2 studies. Karnaskul et al. examined 33 children with abdominal pain, 11 with vomiting, and with reflux. Overall, half of all enrolled children had low activity of one or more disaccharidases.(2) The study also found that vomiting was related to low lactase, but no other associations between symptoms and disaccharide levels were found. Prasad et al enrolled 29 children with GERD symptoms and found normal disaccharide levels in this small cohort.(15) Four remaining studies include patients with abdominal pain, vomiting, and reflux but did not specifically analyze the relationship between disaccharide activity and these indications for EGD.

The majority of studies (29/30) included analysis of histopathology. Histology is critical to examine because it can be a factor leading to differentiation of primary from secondary disaccharidase deficiencies. The majority of studies (12/16) examining the association between enzyme levels and histopathology found that inflammatory changes were associated with enzyme deficiencies. It has been argued that specimens should be considered unsatisfactory when all the enzymes assayed are low and the histology appears normal. However, four studies included in this review reported no clear association between histopathology findings and disaccharide activity. Additionally, data in adult patients suggests that the disaccharidase deficiency is not confined to patients with abnormal histology.(32) Therefore, we conclude that although enzymes levels are lower in the majority of patients with duodenal inflammation, enzyme levels may be affected even with normal histopathology.

While ethnicity was reported in many studies, only three studies compared disaccharide activity between ethnic cohorts. The primary finding was lower levels of disacharidase activity in children of African descent.(27) (26) Although current studies includes over 30,000 biopsy specimens, only 1 Hispanic subject was included.

Change in clinical management after EGD with disaccharide anlysis was reported only in relation to dietary treatment low lactase levels*.*  No studies explored management changes after the discovery of low sucrase, maltase or palatinase. Studies also did not report on the use of enzyme or dietary supplements.

In summary, the current literature examining the utility of disaccharide analysis during EGD for children is limited primarily by inadequate investigation of clinical presentation to disaccharide levels. The prevalence and outcomes of disaccharide deficiency in children presenting with abdominal pain, reflux, vomiting has not been well-studied. Also, the majority of clinical outcomes after EGD with disaccharide analysis (e.g. change in patient management, improvement in quality of life, improvement in symptoms, cost-effectiveness) are not well described in the current literature. Previous studies do not adequately include all Hispanic subjects. We recommend large studies examining the association between clinical factors and disaccharide levels with adequate interpretation of biopsy reports to clarify the use of disaccharide analysis in children undergoing EGD. Future studies should include a robust sample size and examine the value of specific management options after low disaccharide levels are discovered by small intestinal biopsies.

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**Figure 1.**

Database Search (PUBMED, EMBASE, Cochrane)

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2152 Studies Identified In Medical Literature Search

2117 excluded (Titles/Abstracts Suggested Articles Not Appropriate)

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4 Excluded

• 1 case report

• 3 with findings of disaccharidases not enumerated

30 Total Articles With Extractable Data

34 Eligible Articles

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