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The Relationship between Disaccharidase Activity and Histopathology in Pediatric Patients Undergoing Endoscopy

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Abstract

Investigating disaccharidase (DS) inter-relationships and relationships between DS activity and mucosal disease may impact the understanding of disease pathogenesis and potentially alter dietary recommendations. The aim of this study was to assess relationships between DS activity levels, villous blunting/atrophy, and duodenal inflammation in pediatric patients undergoing endoscopy. This retrospective cross-sectional study assessed DS activity in patients, ages birth to 21 years, who underwent endoscopy with DS analysis from 2016-2019. A total of 1,868 unique patients were identified. Medical records were reviewed for DS deficiency, DS activity levels, primary indications for endoscopy, gastrointestinal diagnoses, and duodenal histology including villous blunting/atrophy and inflammation. Duodenitis was further characterized as chronic, acute, or eosinophilic. Lactase deficiency was identified in 47.2% and pan-deficiency in 10.4%. All DS activity levels were correlated with each other and deficiency in one DS was associated with an increased deficiency in each of the others. Villous blunting/atrophy was associated with DS deficiency. Duodenitis, specifically chronic inflammation, was associated with DS deficiency. In the absence of villous blunting/atrophy, chronic inflammation was associated with decreased sucrase and maltase activity. DS activity levels are inter-related which may have implications when considering specific dietary recommendations for treatment of DS deficiencies; however, it remains to be determined whether DS assays predict clinical response to DS restriction. DS deficiency is associated with duodenitis, even in the absence of villous blunting/atrophy, and this appears unique to chronic inflammation. Future studies are needed to assess whether treating inflammation restores DS activity.

Keywords: Lactase; Sucrase, Maltase, Palatinase, Duodenitis.

Abbreviations: DS: Disaccharidase

Introduction

Disaccharidase (DS) deficiency has been identified with some frequency in pediatric patients being evaluated for a variety of gastrointestinal symptoms [1-5]. Although the current rate of evaluating DS deficiency varies significantly from clinician to clinician, Opekin and colleagues suggest that dietary modification has an important role in pediatric gastrointestinal symptoms justifying more routine testing [6]. Given the current frequency of testing, and especially if it becomes more widespread, it is important to understand DS inter-relationships and relationships between DS activity and mucosal disease as these may impact our understanding of pathogenesis in individual patients and affect our dietary recommendations.

DS deficiencies may be primary (i.e. genetic) or secondary to mucosal injury. In most, but not all, pediatric studies, DS deficiencies are seen more

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frequently in patients with duodenal villous blunting or atrophy but have also been reported in a substantial portion of patients with normal histology presumably as a primary or genetic deficiency [1,3,7-10]. DS deficiency has also been associated with duodenal intraepithelial lymphocytes and with the degree of duodenal inflammation in general [1]. However, previous studies have not evaluated inflammation in the absence of blunting/atrophy to determine if inflammation can affect DS activity without inducing villous architectural changes [2].

The primary aims of the current study were,

1. To assess inter-relationships between DS activity levels and deficiencies, and,

2. To assess relationships between DS activity and villous blunting/atrophy and duodenitis. In addition, these relationships were assessed between gender and by age group.

Materials and Methods

Study design and participants

This study was a single site, retrospective chart review of patients who had evaluation of mucosal DS between 2016 and 2019 at Children's Mercy Kansas City. The study included all patients, ages 0-21 years, who had DS testing during this period of time. Patients were identified from a Department of Pathology database which includes all DS tests. Biopsies for histology and DS analysis were obtained from the second portion of the duodenum distal to the ampulla. The tissue samples for DS testing were immediately placed on ice and time stamped. The tissue was transferred to the lab within 30 minutes and then flash-frozen in the lab. The frozen tissue was sent to Mayo laboratories the same day from where the samples were forwarded to Joli Diagnostics, Inc. Laboratories for DS analysis. All disaccharidase analyses were performed utilizing the modified Dahlqvist method to determine enzyme activity levels. All biopsy assessments were performed by board certified pediatric pathologists as part of routine clinical care. This study was approved by the Institutional Review Board at Children's Mercy Kansas City which also waived consent and assent for this retrospective study.

Data collection

All charts were reviewed with collection of demographic data, co-morbid diagnoses, primary indication for the endoscopic evaluation as determined by the ordering provider, DS activity levels, and pathology findings. Pathology reports were reviewed for the presence of villous blunting/atrophy and the presence of inflammation in the duodenum.

Outcome measures

The primary outcome measures were actual DS activity levels and whether DS levels were normal or abnormal per laboratory standard values. Normal DS values include: lactase >15 umol/min/gram protein, sucrase >25 umol/min/gram protein; maltase >100 umol/min/gram protein; palatinase >5 umol/min/gram protein. The secondary outcome measure was duodenal inflammation as defined and reported by pathologists; acute (presence of neutrophils in addition to chronic inflammatory cells or alone), chronic (presence of increased lymphocytes and/or plasma cells), or eosinophilic (increased eosinophils >26 eosinophils/hpf).

Statistical analysis

Statistical analyses were performed using SPSS version 23 (SPSS Inc., Chicago, IL). Mean DS activity levels were compared between females and males and between patient age groups: 0-3 years, 4-7 years, and 8-21 years, by the student's t test and by one-way ANOVA, as appropriate. Frequencies of DS deficiency were compared for these same groups by chi square analysis. Pearson correlation coefficients were determined for each pair of DS. Frequencies of normal and abnormal DS levels were assessed for each pair of DS by chi square analysis. Mean DS activity levels were compared between patients with atrophy/blunting and those without by the student's t test. Frequencies of DS deficiency were compared for these same groups by chi square analysis. For all patients and for those without atrophy/blunting, Mean DS activity levels were compared between patients with duodenitis and those without by the student's t test. Frequencies of DS deficiency were compared for these same groups under both conditions by chi square analysis. Pearson correlation coefficients were determined for each pair of DS in patients without atrophy. Frequencies of DS deficiency were compared for these same groups by chi square analysis. Pearson correlation coefficients were determined for each pair of DS in patients without atrophy. For all patients and for those without atrophy/blunting, Mean DS activity levels were compared between types of duodenal inflammation (chronic vs. acute vs. eosinophilic) by one-way ANOVA with post-hoc comparisons utilizing the Tukey HSD test.

Results

During the study time period, DS analysis was performed in 1,868 unique patients who represent approximately 13.8% of all EGDs performed. Females accounted for 57.3% of the patients. Patients ranged in age from 3 months to 21 years with a mean of 10.9 ± 5.0 years. The most common primary indications for endoscopy were abdominal pain (60.0%), diarrhea (7.9%), inflammatory bowel disease (7.3%), eosinophilic esophagitis (7.0%), and gastroesophageal reflux or dysphagia (5.6%).

Lactase deficiency was identified in 47.2%, sucrase deficiency in 11.3%, maltase deficiency in 15.6%, palatinase deficiency in 11.3%, and pan-DS deficiency in 10.4%. Actual DS activity levels were significantly correlated for each pair of DS (Table 1).

Patients with lactase deficiency were more likely to have sucrase deficiency (22% vs. 1.8%, p<.001), maltase deficiency (30.0% vs. 2.7%, p<.001), and palatinase deficiency (22.0% vs.

	Sucrase	Maltase	Palatinase
Lactase	r= .544; p<.001	r= .554; p<.001	r= .332; p<0.001
Sucrase		r= .936; p.001	r= .655; p<0.001
Maltase			r= .663; p<0.001

Table 1: Correlation coefficients (and p values) for disaccharidase activity for each pair of disaccharidases.

1.8%, p<.001), respectively, than were patients with normal lactase activity. Patients with sucrase deficiency were more likely to have maltase deficiency (100% vs. 4.8%, p<.001) and palatinase deficiency (100% vs. 0%, p<.001), respectively, than were patients with normal sucrase activity. Patients with maltase deficiency were more likely to have palatinase deficiency (72.9% vs. 0%, p<.001) than were patients with normal maltase activity. Females exhibited lower levels for lactase (17.4 ± 14.7 umol/min/gram protein vs. 19.7 ± 16.1 umol/min/gram protein; p=.001), sucrase (48.1 ± 23.6 umol/min/gram protein vs. 51.6 ± 24.7 umol/min/gram protein; p=.002), and maltase (145.1 ± 56.9 umol/min/gram protein vs. 152.5 ± 58.1 umol/min/gram protein; p=.006), but not palatinase (9.5 ± 6.9 umol/min/gram protein vs. 9.9 ± 6.0 umol/min/gram protein; p=.157). Females were more likely to exhibit lactase deficiency (43.7% vs. 51.8%; p=.001) and maltase deficiency (13.8% vs. 17.9%; p=.015), but not sucrase or palatinase deficiency. The frequencies of DS deficiencies were noted to be significantly different among the 3 age groups for all disaccharidases except maltase (Table 2).

Villous blunting or atrophy was present in 5.6% of patients. The main diagnosis associated with villous blunting was Celiac disease (n=104). The prevalence in patients with Celiac disease was 1.2%. Mean activity levels were significantly decreased in patients with blunting/atrophy as compared to those with normal villi for each of the DS (Table 3).

Patients with blunting/atrophy were more likely to demonstrate lactase deficiency (86.8% vs. 45.2%; p<.001), sucrase deficiency (54.8% vs. 8.8%; p<.001), maltase deficiency (62.5% vs. 14.7%; p<.001), palatinase deficiency (54.8% vs. 8.8%; p<.001), and pan-DS deficiency (52.9% vs. 7.9%; p<.001), when compared to patients without blunting/atrophy.

Duodenitis was present in 18.8% of the patients. Inflammation was chronic in 42.0%, acute in 13.7%, and eosinophilic in 44.3% of patients with duodenitis. Duodenitis was present in 99.0% of patients with blunting/atrophy and in 14.1% of patients with normal villi. Mean activity levels were significantly decreased in patients with duodenitis as compared to those without inflammation for each of the DS (Table 4).

Patients with duodenitis were more likely to demonstrate lactase deficiency (59.3 % vs. 44.4%; p<.001), sucrase deficiency (26.2% vs. 7.9%; p<.001), maltase deficiency (32.2% vs. 11.7%; p<.001), palatinase deficiency (26.2% vs. 7.9%; p<.001), and pan-DS deficiency (25.1% vs. 7.0%; p<.001), respectively. DS activity differed by duodenitis type (chronic vs. acute vs. eosinophilic vs. normal) for lactase (F=15.167, p<.001), sucrase (F=39.037, p<.001), maltase (F=44.082, p<.001), and palatinase (F=14.374, p<.001). Post hoc analysis demonstrated that differences were driven by chronic inflammation as compared to normal and both the acute and chronic inflammation groups for each of the DS. DS activity did not differ between normal and either acute or eosinophilic inflammation.

To evaluate the effect of inflammation independent of atrophy, all patients with blunting/atrophy were excluded. The evaluation of DS correlations and relationships between deficiencies all remained significant (Table 5).

Differences in DS activity differed for sucrase and maltase but were no longer significant for lactase and palatinase. (Table 6) Post hoc analysis demonstrated that differences were driven by chronic inflammation as compared to normal and eosinophilic groups for both sucrase and maltase.

Discussion

In the current study, we assessed for the presence of DS deficiencies utilizing the measurement of enzyme activity on mucosal samples which is considered the gold standard for diagnosis [1-2,11,12]. Consistent with previous studies, we found that DS deficiencies are relatively common in pediatric patients being evaluated for a variety of symptoms or conditions such as abdominal pain, diarrhea, gastroesophageal reflux, inflammatory bowel disease, and eosinophilic esophagitis [1-5]. DS values were all significantly correlated with each other. This would be expected for sucrase with maltase and palatinase, however, the mild to moderate correlations between lactase activity and sucrase, maltase, and palatinase activity, respectively, was not necessarily expected. Cohen and colleagues previously found sucrase activity to correlate with maltase and palatinase but not

Age Group (years)	Lactase	Sucrase	Maltase	Palatinase
0-3	35.4%	18.0%	20.4%	18.0%
4-7	42.1%	9.7%	12.8%	9.7%
8-21	50.0%	10.7%	15.5%	10.7%
p value	<0.001	0.006	0.067	0.006

Table 2: Frequencies of disaccharidase deficiencies by age group.

	Blunting/Atrophy	Normal Villi	P value
Lactase	8.0 ± 8.4	19.3 ± 15.7	<0.001
Sucrase	24.9 ± 18.2	51.6 ± 23.8	<0.001
Maltase	85.2 ± 49.1	153.1 ± 55.9	<0.001
Palatinase	4.7 ± 3.6	10.1 ± 6.4	<0.001

Table 3: Mean (± SD) disaccharidase activities (*umol/min/gram protein)* in patients with blunting/atrophy vs. those with normal villi.

	Duodenitis	No Duodenitis	P value
Lactase	15.0 ± 15.2	19.5 ± 15.5	<0.001
Sucrase	40.6 ± 24.2	52.3 ± 23.7	<0.001
Maltase	126.0 ± 61.9	154.7 ± 55.3	<0.001
Palatinase	8.4 ± 8.6	10.1 ± 5.8	0.001

Table 4: Mean (± SD) disaccharidase activities (*umol/min/gram protein)* in patients with duodenitis vs. those with no duodenitis.

	Sucrase	Maltase	Palatinase
Lactase	.524 (<.001)	.534 (<.001)	.305 (<0.001)
Sucrase		.930 (<.001)	.632 (<0.001)
Maltase			.640 (<0.001)

Table 5: Disaccharidase correlations and relationships between deficiencies (excluding blunting/atrophy).

	Normal (N) (N=1509)	Chronic (C) (N=61)	Acute (N=42)	Eosinophilic (E) (N=152)	ANOVA	*PostHoc*
Lactase	19.6 ± 15.6	14.5 ± 13.1	20.4 ± 18.1	18.7 ± 16.7	F=2.195 (p=0.087)	
Sucrase	52.3 ± 23.8	40.6 ± 19.4	46.7 ± 22.4	50.2 ± 24.5	F=5.607 (p=0.001)	*N vs. C (p=0.001)* *C vs. E (p=0.038)*
Maltase	154.8 ± 55.4	127.1 ± 46.7	138.8 ± 52.2	151.2 ± 62.7	F=5.872 (p=0.001)	*N vs. C (p=0.001)* *C vs. E (p=0.022)*
Palatinase	10.1 ± 5.8	9.6 ± 13.5	10.7 ± 13.4	10.0 ± 5.2	F=0.276 (p=0.843)	

Table 6: Mean (± SD) disaccharidase activities (*umol/min/gram protein)* in patients with duodenitis vs. those with no duodenitis in patients with normal villi (excluding blunting or atrophy).

lactase activity [3]. We also found that deficiency in one DS predicts (to varying degrees) a deficiency in each of the others. The modified Dahlqvist assay measures DS enzyme activity and sucrase-isomaltase accounts for nearly all palatinase (isomaltase) activity and approximately 80% of maltase activity [11,12].

Pan-deficiency warrants specific comment as concerns that these are the result of improper biopsy procedures or processing has made the significance unclear. Chumpitazi and colleagues previously evaluated disaccharidase activity prospectively with great care to ensure proper biopsy location and meticulous processing [13]. Even under these conditions, pan-deficiency was not uncommon. In the setting of atrophy or inflammation (discussed below), there is an increase in the rate of pan-defficiency suggesting that findings are not merely the result of processing. In the absence of inflammation, it has been suggested that pan-deficiency may result from lactase deficiency and un-recognized congenital sucrase-isomaltase deficiency (which would be expected to lower sucrase, maltase, and palatinase activity) [14].

We found that duodenal atrophy to be associated with a decrease in DS levels and an increase in the frequency of DS deficiency. Atrophy has been associated with disaccharidase deficiency in nearly all pediatric studies assessing the relationship with the one conflicting study being an evaluation of infants with diarrhea [1,7,8-10]. Heitinger and colleagues found that in patients older than 24 months, atrophy was associated with maltase deficiency and to a lesser degree with lactase deficiency [9]. Despite the association with atrophy, in the current study, lactase deficiency still occurred in >40% with normal villi and sucrase deficiency was noted in nearly 8% with normal villi. DS deficiency has been reported in 39.8% of pediatric patients with normal histology [1]. Overall, 91.5% of patients in this study with sucrase deficiency also had pan-deficiency and in patients with normal biopsies, 88.3% of the sucrase deficiencies had pan-deficiencies. These data suggest that DS deficiency is often not the result of villous blunting/atrophy but may be genetic or congenital deficiencies.

We found that duodenitis was associated with a decrease in DS levels and an increase in the frequency of DS deficiency. An inverse relationship between the degree of histologic inflammation and DS levels has been reported in children; however, in previous studies, severity has been largely defined by architectural changes (e.g. blunting/atrophy) [2]. Reed and colleagues reported that DS deficiencies were more common in patients with increased duodenal intraepithelial lymphocytes, active inflammation, or eosinophilic infiltration [1]. In the current study, differences in DS deficiencies for duodenitis were driven by chronic inflammation and not associated with acute or eosinophilic inflammation. Inflammatory cytokines have specific and selective effects on brush border sucrase-isomaltase in tissue culture and *in vivo* which may provide the mechanism for DS deficiency in association with intestinal inflammation [15].

The strengths of the current study include the large sample size, all DS samples were measured in a single commercial lab, and DS activity levels were analyzed as mean levels and as dichotomous variables (normal vs. abnormal). The study is not without weaknesses. Due to the retrospective nature of the study, all patients were pre-selected and evaluated in a tertiary care center and the decision to obtain disaccharidase analysis was based on individual clinician preference and practice and is not standardized.

Conclusion

DS activities are inter-related to each other, not only in terms of normal vs. abnormal but also in terms of actual activity levels. These findings suggest that dietary recommendations may often need to be broader, rather than restriction of a single DS. While villous atrophy/blunting is associated with DS deficiency and reduced activity levels, deficiency occurs in a substantial portion of patients with normal villi. Duodenal inflammation, separate from atrophy/blunting, is associated with DS deficiency and this appears to be driven by chronic inflammation rather than acute or eosinophilic inflammation. Prospective studies are needed to determine if DS activity assays predict response to dietary restriction or enzyme replacement. Additionally, prospective studies are needed to assess whether treatment of underlying inflammation results in restoration of DS activity.

Authors Contribution

Conceptualization, J.C., U.G, and W.S.; methodology, J.C., C.F, U.G, and W.S.; investigation, J.C., C.F, U.G, and W.S; data curation, J.C., C.F, U.G, and W.S.; validation, J.C., C.F, U.G, and W.S.; writing—original draft preparation, C.F.; writing—review and editing, J.C., C.F, U.G, and W.S.; All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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