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The Impact of Acid Suppression Medications and Non-steroidal Anti-Inflammatory Drugs on Clinical and Histologic Features in Celiac Disease

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Abstract

Introduction—The prevalence of celiac disease (CD) in the US has increased in past decades, as has use of proton pump inhibitors (PPIs), histamine-2-receptor antagonists (H2RAs), aspirin (ASA) and nonsteroidal anti-inflammatory drugs (NSAIDs). We aimed to measure the association between medication use and distribution of villous flattening (VF) among newly diagnosed CD patients.

Methods—We performed a cross-sectional study of adult patients with newly-diagnosed CD at two institutions. We collected data on regular use of these medications, clinical presentation, CD serologic status, and distribution of VF. We compared current ASA/NSAID users to non-users, and current PPI/H2RA users to non-users, with regard to these clinical characteristics.

Results—Of 148 patients with newly-diagnosed CD, current users of ASA/NSAIDs were older than non-users (47 vs 39 years, p=0.003) and users of PPI/H2RAs were older than non-users (48 vs 39 years, p=0.004). PPI/H2RA users comprised 12% of seropositive patients, compared to 55% of seronegative patients (p<0.01). Patient gender and distribution of villous flattening in the bulb and distal duodenum did not differ by PPI/H2RA or ASA/NSAID use.

Conclusions—PPI/H2RA use was associated with seronegative CD. Given the effect of these medications on gastric milieu, the impact of these drugs on presentation and course of CD deserves further investigation.

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Disclosures:

All authors declare that they have no conflicts of interest and nothing to declare.

Keywords

Celiac Disease; Proton Pump Inhibitors; Non-Steroidal Anti-Inflammatory Agents

Introduction

Celiac disease (CD) is an autoimmune disorder triggered by ingestion of dietary gluten in those with genetic predisposition [1, 2]. The prevalence of CD in the United States (US) has increased over time [3], with prevalence estimates at 0.71% in a screening study in 2009–2010 [4]. Serologic testing for CD is typically performed based on a range of symptoms including diarrhea, weight loss, iron deficiency anemia, metabolic bone disease, and infertility, among others; the diagnosis is confirmed via duodenal biopsy showing villous flattening. The distribution of villous flattening in association with CD has been documented to be patchy, but little research has examined factors associated with the location of villous flattening in the duodenum.

Nonsteroidal anti-inflammatory drugs (NSAIDs) and acetylsalicylic acid (aspirin, ASA) are common medications used to treat inflammatory conditions, and prevalence of ASA and NSAID use in the US greatly increased during the previous decade [5]. Proton pump inhibitors (PPIs) and Histamine-2 receptor antagonists (H2RA) are acid secretion inhibitors. Use of PPIs and H2RAs have increased in the last two decades, with PPI overuse becoming a potential problem in US [6–8]. Previous studies have shown that acid suppression medication has been associated with an increased risk of subsequent development of CD in adults [8], and some NSAIDs have been associated with increased risk of villous flattening in mice [9].

Using a multi-institutional population, we aimed to determine if use of these medication class, NSAIDs/ASA or PPI/H2RAs, were associated with clinical characteristics and the distribution of villous flattening in newly diagnosed adult CD patients.

Methods

We performed a cross-sectional study of adult patients with newly-diagnosed CD via duodenal biopsy performed at Columbia University Medical Center (CUMC) in New York City and Beth Israel Deaconess Medical Center (BIDMC) in Boston. Both endoscopy suites are located at academic medical centers with a referral center specializing in CD. We identified patients with newly diagnosed CD from each institution during the time periods spanning January 2007 through March 2014 (New York) and September 2012 through February 2015 (Boston); we used these two time spans so as to identify an approximately equal number of newly-diagnosed patients from each institution. Celiac disease required the presence of duodenal villous flattening for inclusion in this analysis; patients with duodenal histology showing changes corresponding to a Marsh score of less than 3 (normal duodenal mucosa or intraepithelial lymphocytosis/crypt hyperplasia with normal villous architecture) were not included, due to the lower specificity of Marsh lesions <3 for CD. [10] In both institutions, duodenal biopsy was performed at the discretion of the endoscopist, and may be done if serologies were negative or not known/not performed at the time of endoscopy, or if

the clinical suspicion for celiac disease was high. Patients at CUMC were diagnosed by one of four gastroenterologists, and patients at BIDMC were diagnosed by one of 12 gastroenterologists.

Variable Collection and Coding

We searched the electronic medical record (EMR) for regular ASA/NSAID and PPI/H2RA use at the time of endoscopy. This information was abstracted from the pre-procedure interview that is routinely conducted by a nurse on the day of the procedure (CUMC) or the most recent office visit preceding the procedure (BIDMC). We also collected information from the electronic medical record regarding the mode of presentation, CD serologic status, and degree and distribution of villous flattening. Serologic values queried included tissue transglutaminase (TTG) IgA, deamidated gliadin peptide (DGP) IgA/IgG, and anti-endomysial antibodies (EMA). Patients were classified as having seronegative CD if they 1) had negative TTG IgA, DGP, and/or EMA values; and 2) exhibited clinical and/or histologic recovery while on a GFD in the context of a compatible HLA type. Only patients with Marsh scores of 3 were considered as having CD. When available, Marsh scores for the duodenal bulb and second part of the duodenum (D2) were collected and compared to determine which was more severe.

Mode of presentation was classified as classical or non-classical. Classical presentation was defined as diarrhea or weight loss. For the purposes of this analysis, non-classical and asymptomatic presentations were grouped together. Use of ASA/NSAIDs was categorized into groups based on whether patients were taking neither, one, or both medication. The same was done for PPI/H2RAs.

Statistical analysis

The primary outcomes of interest were clinical features and distribution of villous flattening. We compared current ASA/NSAID users to non-users, and current PPI/H2RA users to non-users, with regard to these outcomes. We used the Pearson χ^2 and Fisher exact tests to compare proportions and the student's t-test to compare continuous variables. For the purpose of these analyses, we defined PPI/H2RA users as anyone using either a PPI, an H2RA, or both; those without any PPI or H2RA use were deemed non-users. Similarly, we defined ASA/NSAID users as anyone using either ASA, NSAIDs, or both; all others were deemed non-users. We performed a post-hoc multivariable analysis to assess for independent associations between seronegative status and PPI/H2RA use, adjusting for age and severity of villous flattening.

All reported p-values are 2-sided. Two-sided p values of <0.05 were considered statistically significant. We used SAS 9.3 (Cary, NC) for all analyses. This study was approved by the Institutional Review Boards of Columbia University and Beth Israel Deaconess Medical Center.

Results

Of 148 patients with newly-diagnosed CD, 73 were diagnosed at CUMC and 75 were diagnosed at BIDMC (see Table 1). A minority (n=46, corresponding to 31%) were male,

and the median age was 40 years (range 18–77). A classical presentation was noted in 62 patients (42%) while the remaining 86 (58%) had non-classical (45%) or a screen-detected (13%) presentation. Elevated antibodies (TTG IgA, DGP IgA, or EMA IgA) were present in 136 (93%), whereas the remaining 12 patients (7%) were seronegative at the time of diagnosis. Duodenal bulb specimens were included in 89 (60%) of the 148 patients. Villous flattening was present in 87 of the 89 (98%) duodenal bulb specimens. PPI/H2RA use was present in 22 (15%) participants. Regular ASA/NSAID use was reported by 30 (20%) participants. Seven patients (5%) were users of both PPI/H2RAs and NSAID/ASA.

ASA/NSAID users

The mean age of ASA/NSAID users was significantly higher than that of non-users (47.4 vs 38.6 years, $p<0.01$). The distribution of villous flattening did not differ in users and non-users (Table 2).

PPI/H2RA users

The mean age of PPI/H2RA users was significantly higher than that of non-users (48.2 vs 39.0 years, $p<0.01$). Serologic status was significantly different between users and non-users; PPI/H2RA users comprised 12% of seropositive patients, compared to 55% of seronegative patients ($p<0.01$). On multivariable analysis, seronegative status remained associated with PPI/H2RA use after adjustment for age and severity of villous flattening (OR: 6.65, 95% CI: 1.24 – 35.79). The distribution of villous flattening did not differ in users and non-users ($p=1.0$).

DISCUSSION

In this cross-sectional analysis of newly diagnosed CD patients, we found that use of PPI/H2RAs and ASA/NSAIDs were both associated with older age. We also found that PPI/H2RA use was associated with seronegative status. Seronegative status remained associated with PPI/H2RA use on multivariable analysis.

PPI use has been shown to be associated with CD; in a population-based case-control study in Sweden, patients prescribed acid suppression medication (PPIs, H2RAs, or both) had increased risk of CD compared to those not prescribed these medications [8]. Inhibiting acid secretion could interfere with acidic deamidation of glutamine residues of gluten, resulting in potentially less immunogenic peptide fragments among users of these medications; the fact that the opposite is observed (i.e. an increased rate of CD) suggests that the mechanism of action by which PPIs could potentially increase the risk of CD is unknown. PPIs and H2RAs may affect protein digestion and increase gastric pH levels, causing some antigens, such as gluten, to not be digested [8]. Both PPIs and NSAIDs increase gastrointestinal mucosal permeability [8, 11, 12]. *H. pylori* has been suggested to be protective against CD [13]. Using PPIs as a component to treating *H. pylori* could result in both removing H. pylori's protective effects while also introducing the possible risks related to PPIs described above. Another possibility is that the stomach's processing of gluten may change gluten's immunogenicity.

Eleven patients (7%) in our population presented with seronegative CD. Seronegative CD is an uncommon, but authentic variation of CD [14]. One study found 72 patients over 10 years presenting with CD to a tertiary care center. These patients had more than one seronegative antibody, positive genetic tests for CD, biopsies consistent with CD, responded to the gluten-free diets and tested negative for other causes of villous flattening [14]. As seronegative CD may be pathophysiologically distinct from seropositive CD, [15] the effects of PPIs on increasing intestinal permeability might be playing a role. [16, 17] However, our findings should be considered with caution given the small amount of patients (n=11) who presented with seronegative CD. Replication in a separate cohort is warranted prior to translating these findings into actionable recommendations regarding CD risk and diagnostic practices for those with suspected seronegative celiac disease.

Our study has several limitations. This was a cross-sectional study, so temporality between medication use and villous flattening development cannot be established. The lack of a standardized biopsy protocol in this observational study may have led to heterogeneity in biopsy specimen orientation and interpretation. We had a low number of patients taking PPIs/H2RAs (N=22) and ASA/NSAIDs (N=30). There was no method for validating inter-observer agreement for identification of villous flattening; nevertheless, interobserver agreement between academic pathologists regarding the presence of villous flattening has been reported by our group as very good. [18] Use of medications was based on patient self-report, and was ascertained via retrospective record review, not corroborated by checking patient prescription records. We did not have information on length of time that patients were taking these medications. In addition to these limitations, our study has several strengths. It is a dual-center study spanning two large CD referral centers. Additionally, we had inclusion and evaluation of duodenal bulb specimens in a substantial proportion of these patients, allowing us to consider distribution of villous flattening as an outcome.

In conclusion, we found that both NSAIDs and acid suppression medication use were associated with patient age in those with newly diagnosed CD. Acid suppression medication users were more likely to have seronegative CD. Future studies, which should include data on length of time of medication use, are warranted to detect associations between medication use and CD, particularly with regard to the risk of seronegative disease.

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Table 1

Characteristics of newly diagnosed celiac disease patients (n=148)

	Number (%)
Age (mean/median, SD)	40.4/41.2, 14.6
Location of diagnosis	
CUMC	73 (49)
BIDMC	75 (51)
Gender	
Male	46 (31)
Female	102 (69)
Mode of presentation	
Classical	62 (42)
Non-classical	86 (58)
Serologic status at time of endoscopy (TTG/DGP/EMA) *	
Seropositive	136 (93)
Seronegative	11 (7)
Acid suppression medication status	
PPI and H2RA use	3 (2)
PPI or H2RA use	19 (13)
Any PPI use	18 (12)
Any H2RA use	7 (5)
No acid suppression medication use	126 (85)
Aspirin/NSAID use	
Both Aspirin and NSAID use	3 (2)
Aspirin or NSAID use	27 (18)
Any Aspirin use	16 (11)
Any NSAID use	17 (11)
No Aspirin or NSAID use	118 (80)
H. pylori gastritis	4/88 (5)

Legend: CUMC: Columbia University Medical Center; BIDMC: Beth Israel Deaconess Medical Center; H2RA: Histamine-2-receptor antagonists; PPI: Proton Pump Inhibitor; NSAID: Nonsteroidal anti-inflammatory drugs

* Serologic status was unknown for 1 patient

Table 2

Comparison of ASA/NSAID users and non-ASA/NSAID users among patients with newly diagnosed celiac disease

	ASA/NSAID Users (%)	ASA/NSAID Non-Users (%)	P value
Total	30 (20)	118 (80)	
Age (mean/median, SD)	47.4/47.5 (16.6)	38.6/39.5 (13.5)	**0.003**
Gender			0.89
Male	9 (20)	37 (80)	
Female	21 (21)	81 (79)	
Mode of presentation			0.15
Classical	16 (26)	46 (74)	
Non-classical	14 (16)	72 (84)	
Serologic status at time of endoscopy (TTG/DGP/EMA)			0.70
Seropositive	27 (20)	109 (80)	
Seronegative	3 (27)	8 (73)	
Distribution of villous flattening *			0.30
More severe in the bulb	3 (13)	21 (87)	
Less severe in the bulb	2 (33)	4 (67)	
Equal severity for bulb and D2	8 (24)	26 (76)	

* Patients without both bulb and D2 specimens were not included.

** Categorized by the most severe Marsh score on any given patient. Patients with unspecified histologic severity were not included.

Table 3

Comparison of PPI/H2RA users and PPI/H2RA non-users among patients with newly diagnosed celiac disease

	PPI/H2RA Users (%)	PPI/H2RA Non-Users (%)	P value
Total	22 (15)	126 (85)	
Age (mean/median, SD)	48.2/48.5 (16.3)	39.0/39.5 (13.9)	**0.004**
Gender			0.56
Male	8 (17)	38 (83)	
Female	14 (14)	88 (86)	
Mode of presentation			0.71
Classical	10 (16)	52 (84)	
Non-classical	12 (14)	74 (86)	
Serologic status at time of endoscopy (TTG/DGP/EMA)			**0.002**
Seropositive	16 (12)	120 (88)	
Seronegative	6 (55)	5 (45)	
Distribution of villous flattening *			1.0
More severe in the bulb	4 (17)	20 (83)	
Less severe in the bulb	1 (17)	5 (83)	
Equal severity for bulb and D2	5 (15)	29 (85)	

* Patients without both bulb and D2 specimens were not included.

** Categorized by the most severe Marsh score on any given patient. Patients with unspecified histologic severity were not included.