



Alimentary Tract

Use of proton pump inhibitors and subsequent risk of celiac disease



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ABSTRACT

Background: The prevalence of celiac disease and the use of medications that inhibit acid secretion have both increased in recent decades.

Aim: To explore the association between antisecretory medication exposure and subsequent development of celiac disease.

Methods: In this population-based case control study, we identified patients with celiac disease diagnosed at all pathology departments in Sweden from July 2005 through February 2008. Patients were matched by age and gender with up to 5 controls. We identified prior prescriptions for proton pump inhibitors and histamine-2 receptor antagonists in all subjects. We used conditional logistic regression to measure the association between these prescriptions and the subsequent diagnosis of celiac disease.

Results: Prior proton pump inhibitor prescription was strongly associated with celiac disease (OR 4.79; 95% CI 4.17–5.51). Patients prescribed both proton pump inhibitors and histamine-2 receptor antagonists had a higher risk of celiac disease (OR 5.96; 95% CI 3.58–9.91) than those prescribed proton pump inhibitors alone (OR 4.91; 95% CI 4.26–5.66) or histamine-2 receptor antagonists alone (OR 4.16; 95% CI 2.89–5.99).

Conclusions: Exposure to antisecretory medications is associated with a subsequent diagnosis of celiac disease. The persistence of this association after excluding prescriptions in the year preceding the celiac disease diagnosis suggests a causal relationship.

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1. Introduction

Celiac disease (CD) is an autoimmune condition triggered by the ingestion of gluten in genetically-susceptible individuals [1]. The prevalence of CD has risen substantially in recent decades, and studies analyzing stored serum samples for serologic markers of CD have shown that this rise reflects a true increase in Western nations [2–4] and not merely an increase resulting from rising awareness of the condition among physicians and patients. An explanation for this rise is elusive, and environmental risk factors for the development of CD are largely unknown. Since approximately 40% of the population of the United States carries the human leucocyte antigen alleles DQ2 or DQ8 and are thus at risk of developing CD [5], identifying environmental risk factors will provide insight on the mechanism of CD pathogenesis. Most studies on environmental risk factors have focused exclusively on infant exposures and childhood

diagnoses [6,7] despite the fact that CD can develop at any age [8,9], and rates are increasing in all age groups [3], especially adults [10].

As the frequency of CD has been rising over the past few decades, so has the use of drugs that suppress gastric acid secretion such as proton pump inhibitors (PPIs) and histamine 2-receptor antagonists (H2RAs). In one cohort study of postmenopausal women in 2008, as many as 18.9% of all subjects were regularly taking a PPI [11]. PPIs and H2RAs can affect protein digestion, which normally begins in the stomach through the action of the pepsin proteinases in acidic gastric juice [12]. By raising the gastric pH to levels well above 4 at which pepsin activity ceases, antisecretory medications might enable food antigens, including gluten, to escape peptic digestion [12]. In addition, PPIs increase gastric mucosal permeability [13,14], which might facilitate the absorption of food antigens and their exposure to cells that elicit an immunological response. Despite this plausible mechanism for a cause-and-effect relationship, and despite their parallel rise in recent decades, to our knowledge there is no study measuring for a possible link between the use of antisecretory medications and the development of CD.

Using a population-based database linked to a national drug prescription registry, we aimed to determine whether patients with histologically proven CD were more likely than controls to have

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been previously exposed to antisecretory medications in general, and to PPIs specifically.

2. Methods

We performed a population-based case control study; patients with CD were identified at all ($n=28$) pathology departments in Sweden. The methods of identification have been described previously [15,16]. In brief, between October 2006 and February 2008, computerized biopsy reports from these pathology departments were queried for villous atrophy via SnoMed classification codes and, using the unique Patient Identification Number (PIN), these patients were linked to the Swedish Total Population Register [17]. A validation study involving detailed chart review of patients with villous atrophy demonstrated that this querying method identified patients with CD with a positive predictive value of 95% [16]. Each patient with CD was then matched via Statistics Sweden by age, gender, calendar period, and county with up to five control patients without CD.

The Swedish National Prescribed Drug Registry records all dispensed prescriptions in the country [18]. Data in the registry includes the recipient's PIN, the medication, and date of prescription. Initially established to monitor drug safety [18], the registry has been used extensively for pharmaco-epidemiological research to measure practice patterns [19], adverse effects [20], and efficacy of drugs including PPIs [21]. PPIs were first introduced in Sweden in 1988, and H2RAs were introduced in 1982. We queried the registry for all patients who were identified as a CD patient or control who were prescribed any PPI (omeprazole, esomeprazole, pantoprazole, lansoprazole, and rabeprazole) or any H2RA (cimetidine, ranitidine, famotidine, nizatidine, niperotidine, roxatidine, and lafutidine) since the inception of the registry.

We measured the prevalence of any prior prescription of any PPI prior to the date of diagnosis of CD or inclusion as a control. Patients diagnosed with CD or included as a control prior to July 1, 2005 (the inception of the Swedish National Prescribed Drug Registry) were excluded from this analysis. We used conditional logistic regression to measure for an association between any PPI prescription and the subsequent diagnosis of CD. We tested whether the effect of PPI exposure on the risk of CD was modified by age and gender by testing the statistical significance of the interaction term of these latter variables with PPI exposure. We then measured for an association between the prescription of H2RAs alone (i.e. with no prescription of PPI), PPIs alone (i.e. with no prescription of H2RAs), or both H2RA and PPI (in series or in parallel) and a subsequent diagnosis of CD. Duration of exposure was measured as the number of PPI prescriptions, and stratified analysis by the number of PPI prescriptions (<3 vs. ≥ 3) was performed. The association between PPI prescription and CD was also stratified by age group, gender, and particular PPI; for the latter analysis, patients who were prescribed more than one type of PPI were included in more than one stratum. Since receipt of a PPI prescription and a CD diagnosis may both correlate with higher socioeconomic status, we repeated the main analysis, adjusting for the individual's degree of educational attainment; in the case of children, this was measured as the highest educational attainment of the individual's parents.

Because the presentation of CD often includes gastrointestinal symptoms [22], patients with such symptoms may be prescribed a PPI immediately prior to the diagnosis of CD, as a therapeutic trial. To address this potential protopathic bias, we repeated this analysis, excluding all first PPI prescriptions that were made in the one-year preceding the diagnosis of CD or the date of inclusion as a control.

Associations were calculated as odds ratios (OR) and corresponding 95% confidence intervals (CI). Statistical calculations were

Table 1

Characteristics of celiac disease patients and controls. Unless otherwise specified, data are expressed as $N(\%)$.

| Characteristics | Cases ($n=2934$) | Controls ($n=14,584$) |
|--|-----------------------|----------------------------|
| Age in years at diagnosis (cases)/ study entry (controls) | | |
| Mean/median/SD | 32.8/28.5/24.7 | 32.7/28.0/24.7 |
| <20 | 1218 (42) | 6075 (42) |
| 20–39 | 565 (19) | 2808 (19) |
| 40–59 | 584 (20) | 2909 (20) |
| 60–79 | 484 (16) | 2395 (16) |
| ≥ 80 | 83 (3) | 397 (3) |
| Male gender | 1138 (39) | 5654 (39) |

performed using SAS version 9.2 (Cary, N.C.). This study was approved by the ethics committee of the Karolinska Institute, Stockholm, Sweden.

3. Results

There were 2934 patients with CD and 14,584 matched controls included in the analysis. Characteristics of CD patients and controls are listed in Table 1. The mean age was 33, with 42% of individuals younger than 20 years. 61% of the cohort was female.

Overall, 1096 (6.3%) of the 17,518 subjects had at least one prior PPI prescription (Table 2). CD patients were more likely to have a prior PPI prescription compared to controls (16% vs. 4%, OR 4.79; 95% CI 4.17–5.51). The association between PPI prescription and CD was similar among men (OR 5.10; 95% CI 4.10–6.36) and women (OR 4.59; 95% CI 3.84–5.50). The association between PPI exposure and CD was modified by age; it was strongest among individuals younger than 20 (OR 14.66; 95% CI 8.04–26.75) and became progressively weaker as age increased, but remained statistically significant even in the oldest age stratum (OR for patients ≥ 80 : 1.84; 95% CI 1.03–3.29). After adjusting for educational attainment, the overall association between PPI exposure and CD remained essentially unchanged (OR 4.94; 95% CI 4.30–5.69).

When considering prescriptions for any prior antisecretory medication, this was more common in CD patients than controls (OR 4.87; 95% CI 4.26–5.56). When considering the type of antisecretory medication, we noted the weakest risk of CD for patients prescribed an H2RA alone (OR 4.16; 95% CI 2.89–5.99), and the strongest risk for those with both H2RA and PPI prescriptions (OR 5.96; 95% CI 3.58–9.91). Increasing number of PPI prescriptions did not increase the risk of CD (see Table 2).

On sensitivity analysis done to address protopathic bias, the relationship between PPI exposure and subsequent risk of CD remained significant after excluding any initial exposures in the year prior to diagnosis of CD or inclusion as a control (OR 2.28; 95% CI 1.67–3.10).

4. Discussion

We have found a strong association between the prescription of PPIs and the subsequent diagnosis of CD (OR 4.79; 95% CI 4.17–5.51). This association was present in both genders and across all age strata, though it was particularly strong among younger patients. Moreover, we found that patients prescribed both PPIs and H2RAs had a risk of CD (OR 5.96) that was greater than the risk for those prescribed PPIs alone (OR 4.91), which was greater still than the risk for those prescribed H2RAs alone (OR 4.16). This suggests that the risk of CD increases with the degree of acid suppression, although it is not clear that patients who were prescribed both PPIs and H2RAs achieved greater acid suppression than those prescribed PPIs alone. So as to address the possibility that incipient

Table 2
Prior antisecretory medication exposure and celiac disease.

| | Cases (n = 2934) | Controls (n = 14,584) | OR (95% CI) | p-Value |
|---|------------------|-----------------------|-------------------------------|-----------------------------|
| Any prior PPI | 464 (16) | 632 (4) | 4.79 (4.17–5.51) ^a | <0.0001 |
| Any prior acid suppression (PPI or H2RA) | 513 (18) | 711 (5) | 4.87 (4.26–5.56) ^b | <0.0001 |
| Type of acid suppression | | | | <0.0001 |
| None | 2421 (82) | 13,873 (95) | 1.0 ^b | |
| H2RA only | 49 (1.7) | 79 (0.5) | 4.16 (2.89–5.99) | |
| PPI only | 436 (15) | 598 (4) | 4.91 (4.26–5.66) | |
| H2RA and PPI | 28 (1) | 34 (0.2) | 5.96 (3.58–9.91) | |
| Sensitivity analysis | | | | |
| First prescription for PPI at least one-year before diagnosis of CD or inclusion as a control | 64 (2) | 146 (1) | 2.28 (1.67–3.10) | <0.0001 |
| Any prior PPI, stratified by gender | | | | |
| Men | 191 (17) | 248 (4) | 5.10 (4.10–6.36) | <0.0001 |
| Women | 273 (15) | 384 (4) | 4.59 (3.84–5.50) | <0.0001 |
| | | | | [p for interaction 0.4662] |
| Any prior PPI, stratified by age | | | | |
| <20 | 44 (3.6) | 16 (0.3) | 14.66 (8.04–26.75) | <0.0001 |
| 20–39 | 104 (19) | 87 (3) | 6.97 (5.14–9.44) | <0.0001 |
| 40–59 | 144 (25) | 191 (7) | 4.75 (3.72–6.07) | <0.0001 |
| 60–79 | 154 (32) | 277 (12) | 3.69 (2.91–4.68) | <0.0001 |
| ≥80 | 21 (25) | 62 (16) | 1.84 (1.03–3.29) | 0.0390 |
| | | | | [p for interaction <0.0001] |
| Any prior PPI, adjusted for education | – | – | 4.94 (4.30–5.69) | <0.0001 |
| Duration of exposure | | | | <0.0001 |
| None | 2470 (84) | 13,952 (96) | 1.0 | |
| <3 prescriptions | 356 (12) | 392 (3) | 5.74 (4.90–6.72) | |
| ≥3 prescriptions prior to CD diagnosis | 108 (4) | 240 (2) | 3.02 (2.37–3.86) | |
| PPI type | | | | |
| Omeprazole | 357 (12) | 445 (3) | 4.94 (4.23–5.77) | <0.0001 |
| Lansoprazole | 60 (2) | 125 (0.9) | 2.42 (1.77–3.32) | <0.0001 |
| Esomeprazole | 78 (2.7) | 103 (0.7) | 3.87 (2.87–5.23) | <0.0001 |
| Pantoprazole | 26 (1) | 39 (0.3) | 3.12 (1.89–5.15) | <0.0001 |
| Rabeprazole | 0 (0) | 4 (0.03) | NC | 0.3685 |

NC, not calculated; PPI, proton pump inhibitor; H2RA, histamine-2 receptor antagonist.

^a Reference population consists of those not prescribed a PPI.

^b Reference population consists of those not prescribed any PPI or H2RA.

symptoms of undiagnosed CD were the cause rather than the effect of the prescription for PPIs (protopathic bias), we performed an analysis that excluded all initial PPI prescriptions made in the year preceding the diagnosis of CD, and we found that the association remained significant (OR 2.28; 95% CI 1.67–3.10).

To date, studies on proposed or identified risk factors for CD have been largely limited to children [6,7,23–26]. Infant feeding practices [6], rotavirus infection [23], summer birth season [25,26] and birth by elective caesarian section [24] all have been suggested to increase the risk of CD. Less is known about risk factors for developing CD among adults. We hypothesized that PPI use is a risk factor for CD based on epidemiological and experimental observations. PPI use has become very common in recent decades, and PPIs are now one of the most commonly prescribed medication classes in the United States [27]. The rise in PPI use coincides temporally with the increased prevalence of CD in western countries [2–4].

PPIs are the most effective medications available for inhibiting gastric acid production. In patients chronically taking conventional-dose PPI therapy, gastric pH rises to levels >4.0 for approximately 50% of the day [28]. With the higher doses that often are prescribed in clinical practice, gastric pH levels can remain >4.0 for more than 80% of the day [29]. At these pH levels, there can be little peptic digestion of a number of food antigens that normally would be partially degraded in the stomach. PPIs also increase gastric mucosal permeability, which might enable those undegraded food antigens to be absorbed and exposed to cells that elicit an immunological response [11,12].

There is evidence that PPI effects on the peptic digestion and absorption of food antigens can have immunological consequences. For example, Untersmayr et al. have shown that mice fed parvalbumin manifest no evidence of food allergy unless they are also

treated with omeprazole, in which case they develop parvalbumin-specific IgE antibodies [30]. Clinical studies also have suggested that the use of antisecretory medications might result in food allergy in humans. In 152 adult outpatients who had no history of allergy and who were treated with an H2RA or a PPI for 3 months for example, 10% showed a rise in IgE antibody levels, and new, food-specific IgE antibodies developed in 15% [32]. Compared to a control group of 50 patients not taking antisecretory medications, this represented a relative risk for the development of food-specific IgE antibodies of 10.5 (95% CI 1.44–76.48). In a study that evaluated the development of hypersensitivity to hazelnut allergens in 153 outpatients taking antisecretory medications for 3 months, 5 (3.3%) were found to develop hazelnut-specific IgE antibodies; 4 of those developed specific skin reactivity and 2 manifested clinical food allergy to hazelnuts [31].

CD is an autoimmune disease, not a food allergy. Gluten is known to trigger this autoimmunity in genetically-susceptible individuals, but CD is acquired through pathogenetic mechanisms that remain poorly understood. It is conceivable that PPI effects on gluten digestion and absorption might contribute to the development of the gluten-triggered autoimmunity that characterizes CD. Data are lacking regarding the effects of hypochlorhydria on the digestion and immunogenicity of dietary gluten. Gluten clearly is susceptible to partial peptic digestion [33,34], and gluten can be hydrolyzed down to a 33-mer peptide fragment that is resistant to any further digestion by gastric, pancreatic and intestinal brush-border membrane proteinases [35]. It has been suggested that this undigestible peptide might be an initiator of the inflammatory response to gluten in CD patients. How PPIs affect the production and absorption of this 33-mer peptide or other potentially immune-stimulating peptides is not clear. If reduction in gastric

acidity increases the risk of CD, this may account for the low rates of previous smoking among newly diagnosed CD patients [36], as smoking is associated with increased gastric acidity [37].

In addition to effects on protein digestion and absorption, there are other conceivable mechanisms whereby PPIs might contribute to the development of CD. For example, PPIs have immunomodulatory effects [38], and PPIs might increase the risk of enteric infections [39,40], which may be a risk factor for CD [7,23]. PPI use has been linked to microscopic colitis [41], a condition that is associated with CD and shares pathological features [42]. In addition, there is evidence that suppression of gastric acid by PPIs leads to gastric bacterial overgrowth and changes in the bacterial flora of the upper gastrointestinal tract but, to date, it is not clear that these bacterial alterations result in clinical disease [43,44]. In theory, alterations in the upper small-intestinal microbiome by PPIs [45] in ways that modulate the local inflammatory response in the mucosa could promote the development of CD in susceptible individuals. Which, if any, of these effects underlies the association between PPIs and CD is not known, and further studies on the mechanisms whereby antisecretory medications might contribute to the pathogenesis of CD clearly are needed.

The most significant limitation of this study is the potential for confounding by protopathic bias, by which early symptoms of CD may prompt prescription of a PPI prior to the eventual diagnosis of CD. The most effective means of addressing this potential bias is to exclude the most recent exposures. In our sensitivity analysis we therefore excluded any initial PPI prescription in the one-year period preceding the diagnosis of CD. When applying this exclusion, we found that the association between PPI use and subsequent diagnosis of CD remained strong (OR 2.28), though lower than the initial point estimate (OR 4.79). This strong and statistically significant estimate on the sensitivity analysis suggests that the association may be causal, but it remains possible that residual protopathic bias may be present. As such, these findings should be interpreted with caution. Given the relatively recent inception of the Swedish National Prescribed Drug Registry (2005), further sensitivity analyses with progressively longer exclusion periods prior to the outcome were not possible beyond the one-year mark. The “dose-response effect” observed, in which patients with the highest degree of pharmacologic acid suppression (i.e. patients on PPIs rather than H2RAs alone) had the highest risk of CD, is likewise suggestive of a causal association. Strengths of this study include its population based setting, the ascertainment of drug exposure by a national registry (not subject to recall bias), and the large sample size, allowing us to test for effect modification in stratified subpopulations.

In conclusion, in this population-based case-control study, we found that exposure to acid-suppressing medication was strongly associated with a subsequent diagnosis of CD. We also found that this association was most robust in younger individuals, and in subjects who were exposed to both H2RAs and PPIs. These findings should prompt future studies to elucidate the mechanism by which PPIs or acid suppression in general affects the pathogenesis of CD.

Conflict of interest statement

None declared.

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