Author's response to reviews

Title: The Association Between Celiac Disease and Eosinophilic Esophagitis in Children and Adults

Authors:

Michael J Stewart (michael.stewart@dal.ca)
Eldon Shaffer (shaffer@ucalgary.ca)
Stephan J Urbanski (stefan.urbanski@cls.ab.ca)
Paul L Beck (plbeck@ucalgary.ca)
Martin A Storr (gidoc@gmx.com)

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Author's response to reviews: see over
Subject: The Association Between Celiac Disease and Eosinophilic Esophagitis in Children and Adults; Revised manuscript for consideration

Dear Dr. Foote,

Thank-you for the opportunity to address the concerns and comments regarding our manuscript that have been raised by the two reviewers. We found the reviews quite useful and have revised our manuscript to address the issues that were raised.

This revised manuscript uses *red* font to indicate revisions from the previous version. Specific responses to each reviewer’s comments can be found below.

Best Regards,

Michael Stewart
REVIEWER 1

Major comments:

1) The most obvious issue is that pediatric gastroenterologists routinely biopsy the entire upper GI tract, while adult GI doctors rarely do this. The authors could examine this and find out the percent of pediatric patients with both biopsies of the esophagus and duodenum and compare this with the adult data.

   Author’s response: Thank you for the suggestion. Pediatric gastroenterologists do seem to be more liberal with routine biopsies of the entire upper gastrointestinal tract. It would be interesting to look at and quantify this variation in routine practice. Unfortunately, when we extracted the data from the database we did not capture the number and location of all biopsies obtained. We have added a sentence to the discussion addressing this possible detection bias.

2) The data is only as good as the diagnosing physicians. We have no idea from the data how good the physicians are at diagnosing both EoE and CD. The prevalence of both conditions (EoE and CD) in the study population needs to be compared to other North American population derived data / study results. For EoE the authors can compare the EoE prevalence to Olmsted County data and for CD the authors can compare to US derived NHANES data from the recent publication from the Mayo Clinic that demonstrated that CD occurs in ~0.7% of the population with only 17% aware that they have CD.

   Author’s response: Thank-you, this point is well taken: it is difficult to interpret data without being able to verify the quality of the data presented. To that end, we have sought to demonstrate that the rate of CD and EoE diagnosis in our cohort compares to other North American populations. Our only concern with your suggestion of comparing the prevalence of these conditions in our population to the other published prevalence data is that our paper reports incidence data over only a 5-year period and therefore we cannot make any reliable prevalence estimates.

   He have been able to compare our CD incidence to rates recently published by Ludvigsson and colleagues who reviewed incident cases of CD in Olmsted County from 2000-2010 (Ludvigsson, J. F. et al, 2013). Over the 10-year study period the average age- and sex-adjusted incidence of CD in Olmsted County was 17.4 per 100,000 person-years. This compares quite favorably to the age and sex-adjusted incidence rates we present in this paper which ranged from 10.4 to 15.7 cases per 100,000 population.

   Similar data from Olmsted County reported that from 2001 to 2005 the average incidence of EoE was 9.45 cases per 100,000 person years (Prasad et al. 2009). This is certainly in-line with the age- and sex-adjusted incidence rates we report which demonstrate a steady increase from 2.1 cases per 100,000 population in 2004 to 10.7 cases per 100,000 population in 2008. This rapid rise in EoE incidence over the past decade has been reported elsewhere including a recent paper from Switzerland that looked at EoE incidence over the past 20 years and found incidence rates of 4.4 to 7.4 cases per 100,000 population over the same time-period as our study (Hruz, P et al., 2011).

   Based on the available incidence data from other populations we are very confident in the ability of the physicians that serve our population to diagnose both EoE and CD. Furthermore, the major strength of our data is the size of the population evaluated; the Swiss study evaluated a population of 90,000 and found 46 cases of EoE diagnosed over 20 years and the Olmsted County study evaluated a population of 120,000 and identified 76 EoE
cases over 29 years. Is this paper we report on 422 cases of EoE diagnosed over 5-years in a population of 1,200,000. Similarly, we report on 763 cases of CD over 5-years while the Olmsted County paper reports only 249 cases over 10-years in a population of approximately 1/10 the size as ours. The comparatively large size of our population, as well as the ability to compare incidence rates of CD and EoE within the same population rather then comparing to incidence rates from another jurisdiction bolster the quality of the data we present in this paper.
Major comments:

1) This is an epidemiological study investigating the association between eosinophilic esophagitis (EoE) and celiac disease (CD) in a large Canadian population sample. The incidence of EoE ranged from 2.1 to 10.7 cases per 100,000 population. The incidence of CD ranged from 10.4 to 15.7 cases per 100,000 population. The concomitant diagnosis of both EoE and CD was made in three patients, all of whom were pediatric males. The SIR for EoE in the CD cohort was 48.4 with a SIR for CD within the paediatric EoE cohort of 75.05.

This is a simple epidemiological work that is clearly presented. The sample size is large, however the relevant disease association (EoE + CD) was present only in three cases, a finding that weakens the conclusions. Furthermore I don’t think this study really demonstrates that CD is significantly associated with EoE, since the prevalence of CD in patients with EoE was 3/421, i.e. the same (around 1%) expected in the general population. These contradictory findings are likely to be explained by a possible detection bias, in that a patient undergoing EGDS because of suspected EoE is more likely to end up with a diagnosis of CD than a subject who is not performing the EGDS.

Author’s response: Thank-you for your comments. We agree, this is a simple epidemiological study of a large Canadian population that we conducted to evaluate an association between eosinophilic esophagitis (EoE) and celiac disease (CD) that been suggested in the pediatric literature. While the absolute number of patients diagnosed with both conditions was small, and this may ultimately be an uncommon phenomenon, we feel that our large population and ability to compare incidence rates within the same population is one of the strengths of this study that leads to more reliable estimates of disease concomitance than those previously published.

Comparing the prevalence of either condition within our cohort to the other published prevalence data is fraught with difficulty. We identified our cohort based on incidence data over a five-year period and therefore we cannot make any reliable disease prevalence estimates. Ideally disease prevalence would be the best way to demonstrate a connection between these conditions; however, given the limited time period of this study we have presented SIRs to assess the association between EoE and CD. These SIRs provide a very conservative estimate of the degree of association since they relay on a patient being diagnosed with both conditions within the five-year study period. Our results likely underestimate the degree of association between these conditions but ultimately this study does demonstrate higher than expected disease concomitance using a well-accepted statistical tool and highlights the need for further study of this issue.

We have sought to clarify this issue in the second paragraph of the discussion.

It is conceivable that a patient undergoing an upper endoscopy for one condition may be more likely to be indecently diagnosed with another condition. This could serve to generate detection bias when it comes to the diagnosis of both conditions. We have also addressed this issue in the discussion.

Minor comments:

1) Page 2 line 12: The SIR of EoE in the CD cohort...("in the" is missing)

Author’s response: Thanks, this was added.
2) Pages 3-4: the introduction is too long, particularly concerning the description of EoE. There is no need to describe clinical and pathophysiological details here, since the study did not address these issues. Likewise the number of references on EoE should be cutted accordingly;

   **Author’s response:** This is a very good point – the introduction was far too long and as the reviewer stated, included details not necessary for the discussion of this study. We have removed the paragraphs that addressed eosinophilia in the upper GI tract, the histological diagnosis of EoE, and clinical features of EoE.

3) Page 4 line 7: change “effect” with “affect”

   **Author’s response:** Thanks, change made.

4) Page 6 line 3: the diagnostic criteria for celiac disease (CD) should be stated more clearly, e.g. patients with a Marsh 3a-c biopsy, Marsh 3a-c biopsy or Marsh 1 plus typical serological CD pattern (e.g. anti-tTG higher than 10x normal values, etc)

   **Author’s response:** This is a good point. In general the diagnosis of CD is made based on duodenal biopsies demonstrating Marsh stage 2, 3a-c, and 4 lesions while Marsh stage 1 biopsies are only considered to represent CD in the setting of an elevated serological marker. Unfortunately, at the time of the study our pathology service had no standardized method for reporting duodenal biopsies. Many comment on specific Marsh stage but this was not universal – some reports simply describes the specimen and concluded that it was ‘diagnostic’ of CD. When the pathology report was “indeterminate”, “suggestive of CF”, or “Marsh stage 1” we did seek out serologic testing. If we were able to find an elevated serological marker (anti-tTG) we considered this to be a positive case of CD. If the serological marker was normal or not available we considered this to be a negative case of celiac disease. We recognize that this is one of the limitations of a retrospective study.

5) Page 8 line 13: delete “in”

   **Author’s response:** Thanks, change made.