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ORIGINAL RESEARCH ARTICLE

Isotretinoin Use and Celiac Disease: A Population-Based Cross-Sectional Study

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Abstract

Background and aim Isotretinoin, a vitamin A analogue, can promote a pro-inflammatory milieu in the small intestine in response to dietary antigens. We hypothesized that oral isotretinoin exposure would increase the risk of celiac disease (CD).

Methods We contacted all 28 pathology departments in Sweden, and through biopsy reports identified 26,739 individuals with CD. We then compared the prevalence of ever using oral isotretinoin to the prevalence in 134,277 matched controls through conditional logistic regression. Data on isotretinoin exposure were obtained from the national Swedish Prescribed Drug Registry. As the only indication for isotretinoin use in Sweden is acne, we also examined its relationship to CD. Data on acne were obtained from the Swedish Patient Registry.

Results Ninety-three individuals with CD (0.35 %) and 378 matched controls (0.28 %) had a prescription of isotretinoin. This corresponded to an odds ratio (OR) of 1.22 [95 % confidence interval (CI) 0.97–1.54]. Risk estimates were similar in men and women, and when we restricted our data to individuals diagnosed after the start of the Prescribed Drug Registry. Restricting our analyses to individuals diagnosed aged 12–45 years did not influence the risk estimates (OR 1.38, 95 % CI 0.97–1.97). Meanwhile, having a diagnosis of acne was positively associated with CD (OR 1.34, 95 % CI 1.20–1.51).

Conclusions This study found no association between isotretinoin use and CD, but a small excess risk of CD in patients with a diagnosis of acne.

Key Points

In certain circumstances, retinoic acid seems to promote inflammatory responses to dietary antigens. Retinoic acid has been linked to inflammatory bowel disease

Oral isotretinoin does not seem to be associated with celiac disease

However, the main indication for oral isotretinoin, acne, may be more common in patients with celiac disease

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1 Introduction

Celiac disease (CD) is characterized by small intestinal inflammation and occurs in about 1 % of the Western population [1, 2]. Individuals with CD are at increased risk of a number of disorders, including lymphoproliferative malignancy [3], neuropathy [4], type 1 diabetes [5] and thyroid disease [5].

Other than gluten exposure and DQ2/DQ8 [6], short duration of breastfeeding [7] may be an important risk factor. Breastfeeding is known to influence the microbiota [8] in the child, and patients with CD have an aberrant duodenal microbiota composition [9, 10]. But breastfeeding may also protect against intestinal inflammation [11], and we hypothesized that substances that induce intestinal inflammation may also increase the risk of CD.

Retinoic acid plays an important role for the regulation of the intestinal immune system [12]. Together with interleukin-15 (IL-15) [13], retinoic acid seems to promote inflammatory responses to dietary antigens [14]. Oral isotretinoin, a form of retinoic acid, has been implicated in one study to trigger inflammatory bowel disease [15], though this association has not been confirmed [16, 17].

In this study, we looked for an association between oral isotretinoin (13-cis-retinoic acid) and CD. To do so, we matched data from the Swedish Prescribed Drug Registry to histopathology data from 26,739 individuals with CD. A secondary aim was to examine the association between acne and CD.

2 Methods

2.1 Data Sources

During the years spanning 2006–2008, we obtained computerized biopsy reports from all 28 Swedish pathology departments [18]. These biopsies had been carried out between 1969 and 2008. Searches for biopsy reports were carried out by local information technology personnel who delivered data on personal identity number [19], morphology (for a list of relevant morphology codes according to the Swedish SnoMed system [20]), topography (duodenum or jejunum), and date of biopsy. Cases were determined on the basis of these biopsies. Controls were provided by the government agency, Statistics Sweden, using the matching parameters described below. After identifying cases and controls, we cross-checked these individuals with the Swedish Prescribed Drug Registry. The Prescribed Drug Registry began on July 1, 2005 [21], and accounts for some 84 % of the total drug utilization (>99 % of all dispensed drugs) in Sweden.

2.2 Study Design

We performed a population-based cross-sectional study of patients in Sweden with biopsy-diagnosed CD (i.e., cases) and non-CD controls. We measured for an association between isotretinoin prescription and case status. In this cross-sectional study, we included isotretinoin exposure that took place both before and after CD diagnosis (and the corresponding date of matching in controls). Exposure was measured regardless of temporal relationship with case/control ascertainment because of the fact that the Swedish Prescribed Drug Registry commenced in 2005, while the CD patients and controls were ascertained during the years spanning 1969–2008. A sensitivity analysis that incorporated temporality (see Sect. 2.7 below) resulted in fewer than 50 prescriptions for isotretinoin in the whole cohort.

2.3 Case Status: Celiac Disease

We defined CD as having villous atrophy (histopathology stage Marsh 3) [18] according to a biopsy report. As these were the first instances of villous atrophy for individuals, these were regarded as incident cases. In a patient chart validation of 114 randomly selected individuals with villous atrophy, 108 (95 %) had CD [20]. The biopsy reports were on average based on three tissue specimens [22], which should rule in approximately 95 % of all CD cases [23]. Some 88 % of patients with villous atrophy have positive celiac serology at the time of celiac diagnosis (defined as date of first biopsy with villous atrophy) [20].

2.4 Controls

The government agency Statistics Sweden matched each CD individual with up to five controls, using the following matching criteria, on the date of CD diagnosis of their corresponding case: age, sex, county of residence at time of biopsy, and calendar year. Controls were sampled from the Swedish Total Population Register with the exception that they should not have an earlier record of small intestinal biopsy prior to the date of CD diagnosis of their corresponding case.

2.5 Sample Size

After removal of duplicates and other data irregularities, our data file was identical to that of our study on mortality in CD [24]. We then excluded patients who died or emigrated prior to July 1, 2005, since the Prescribed Drug Registry started on this date, and therefore our final dataset consisted of 26,739 individuals with CD and 134,277 matched controls.

2.6 Exposure Variable

Exposure information was derived from the Swedish Prescribed Drug Registry. Isotretinoin (oral use) was identified through the relevant Anatomical Therapeutic Chemical (ATC) code (D10BA01). Patients who died or emigrated prior to July 1, 2005 (the inception of the Swedish Prescribed Drug Registry) were excluded from this analysis.

2.7 Statistical Analysis

We used conditional logistic regression to calculate odds ratios (ORs) for the association between CD and ever oral isotretinoin use. Each individual with CD was compared with his or her matched controls within the same stratum, with regard to isotretinoin exposure. This eliminated the effect of age, sex, county and calendar year on our risk estimate. We then summarized stratum-specific data and calculated an overall OR for CD.

In a priori secondary analyses, we tested for the association between CD and isotretinoin use stratified by sex and restricted to the age group spanning 12–45 years, as this group is most likely to be exposed to isotretinoin [15]. So as to detect a possible dose-response effect, we measured point estimates based on the number of prescriptions of isotretinoin (none, less than three prescriptions, or three or more prescriptions).

In an additional pre-planned analysis, we adjusted for education according to four a priori-defined categories [25]. We used data on education as proxy for socioeconomic status [four groups: ≤9 years of primary and secondary school, 2 years of high school (usually programs for manual or clerical work), 3 years of high school (theoretical programs) and college/university studies] [26]. These data were obtained from the Swedish Education Register maintained by Statistics Sweden. Some 4 % of individuals had no data on education and were fitted into a separate fifth category in the multivariate analysis.

In a sensitivity analysis, we subsequently restricted our calculations to those patients with CD and corresponding controls who were diagnosed subsequent to July 1, 2005, the date of inception of the Swedish Prescription Drug Register.

A post hoc power analysis found that we had an 80 % power (at 0.05 significance level) to detect a relative risk of 1.39 for CD among isotretinoin users.

Although it is not known whether acne is more common in patients with CD, given the possibility that an observed relationship between isotretinoin use and CD could be influenced by acne, in our model we also examined the OR for CD among patients with a diagnosis of acne. Data on acne were obtained from the Swedish Patient Registry and defined according to international classification of disease (ICD) codes (ICD-7: 714,1; ICD-8: 706; ICD-9: 706; ICD-10: L70). While we did measure the association between an acne diagnosis and CD, we did not adjust our isotretinoin data for acne since acne per se is the only medical indication for isotretinoin in Sweden.

We used SAS version 9.2 (Cary, NC, USA) for all analyses. We report ORs with corresponding 95 % confidence intervals (CIs). All p values reported are two-sided.

2.8 Ethics

The Ethics Review Board of Stockholm, Sweden, approved this study and deemed that no individual informed consent was required since data were strictly register-based. The study and analysis did not deviate from the approved protocol.

3 Results

Some 63 % of the study participants were female (Table 1). The median age at CD diagnosis was 27 years (interquartile range 5–50 years). As reported previously, the median year of diagnosis was 1998 and the vast majority of both cases (CD 96.7 %) and controls (94.3 %) were born in the Nordic countries [24]. The median age at first exposure to isotretinoin was 18 years, with the youngest subject being 5 years old and the eldest 69 years old.

A total of 93 individuals with CD (0.35 %) and 378 matched controls (0.28 %) had a prescription of oral isotretinoin. Individuals with isotretinoin were at a non-significantly increased risk of CD (OR 1.22, 95 % CI 0.97–1.54). Additional adjustment for socioeconomic status did not influence our risk estimates (Table 2).

ORs were similar in men and women (Table 2), and when we restricted our data to individuals diagnosed after the start of the Prescribed Drug Registry (July 1, 2005).

Table 1 Characteristics of celiac disease patients and controls

Characteristics	Cases[a] (n = 26,739)	Controls[a] (n = 134,277)
Age at diagnosis/study entry (years)		
Mean/median/SD	29.3/27/24.4	29.8/27/24.6
<20	11,712 (44)	57,947 (43)
20–39	5,187 (19)	25,750 (19)
40–59	6,008 (22)	30,501 (23)
60–79	3,517 (13)	18,487 (14)
≥80	315 (1)	1,592 (1)
Gender		
Male	9,863 (37)	49,922 (37)
Female	16,876 (63)	84,355 (63)

SD standard deviation

[a] Values are number (%) unless otherwise stated

Table 2 Isotretinoin use and celiac disease

	Cases[a]	Controls[a]	Odds ratio (95 % CI)	*p* value
Any isotretinoin (regardless of temporality)	93 (0.35)	378 (0.28)	1.22 (0.97–1.54)	0.08
Restrict to patients diagnosed after July 1, 2005	10 (0.34)	39 (0.27)	1.32 (0.66–2.64)	0.44
Restricted to ages 12–45 years	39 (0.42)	141 (0.31)	1.38 (0.97–1.97)	0.08
Any isotretinoin, stratified by gender				
Men	41 (0.42)	162 (0.32)	1.27 (0.90–1.79)	0.18
Women	52 (0.31)	216 (0.26)	1.19 (0.88–1.62)	0.26
Adjusted for SES	–	–	1.22 (0.97–1.54)	0.08
Amount of exposure				
None	26,646 (99.7)	133,899 (99.7)	1.0	
<3 prescriptions prior to CD diagnosis	91 (0.34)	375 (0.28)	1.21 (0.96–1.52)	0.38
≥3 prescriptions prior to CD diagnosis	2 (0.01)	3 (0.00002)	3.33 (0.56–19.95)	0.22

CD celiac disease, *CI* confidence interval, *SES* socioeconomic status

[a] Values are number (%)

In a subanalysis, we examined the association between amount of isotretinoin and risk of CD. Few individuals had received three or more prescriptions during this time period (two individuals with CD and three controls). This corresponded to an OR (compared with no exposure) of 3.33 (95 % CI 0.56–19.95) (Table 2).

A diagnosis of acne was present in 363 patients with CD (1.4 %) and 1,354 controls (1.0 %) (OR 1.34, 95 % CI 1.20–1.51, $p < 0.0001$).

4 Discussion

In this nationwide case–control study, we linked data from biopsy records regarding CD from all Swedish pathology departments with data from the Swedish Prescribed Drug Registry. We found no association between oral isotretinoin exposure and CD, but a statistically significant positive association with acne, and we cannot rule out that this latter association has influenced the OR for CD among isotretinoin users in our study.

We are not aware of any studies on isotretinoin and CD, but one earlier study has suggested that this substance could trigger ulcerative colitis [15]. However, this positive association with inflammatory bowel disease has been contradicted by one case–control study [16] and by a recent meta-analysis based on 2,159 inflammatory bowel disease cases and more than 40,000 controls (Etminan et al. [17]: relative risk 0.99, with a 95 % CI of 0.52–1.90).

While the vitamin A metabolite, retinoic acid, can induce intestinal regulatory immune responses in concert with transforming growth factor β [12, 27], recent work has shown that, under conditions of intestinal stress such as in CD with high levels of IL-15, retinoic acid prevents rather than promotes oral tolerance [14]. Specifically, retinoic acid activates dendritic cells to induce the release of pro-inflammatory cytokines IL-12p70 and IL-23, which lead to decreased regulatory T cell differentiation. Intriguingly, children with vitamin A deficiency show less efficient response to oral vaccine therapy [28, 29], and studies in mice have shown that in the absence of vitamin A mice cannot mount efficient mucosal vaccine responses and protective immunity against pathogens [30]. Altogether, these findings suggest that retinoic acid may have adjuvant effects and promote inflammation. In line with this hypothesis, a link between isotretinoin and inflammatory bowel disease was proposed [31]. Importantly, it is the context in which retinoic acid operates that determines whether retinoic acid will promote inflammation or tolerance in the gut. Hence, retinoic acid would promote CD only in individuals who already have upregulation of IL-15 in the gut such as those individuals who experience an episode of gastroenteritis (rotavirus or *Campylobacter*) while taking isotretinoin. In others, retinoic acid may promote immune-regulatory effects in the absence of IL-15 upregulation. Unfortunately, we lack data on IL-15 in this study.

Albeit not statistically significant, isotretinoin users were at a 22 % increased risk of CD. We cannot rule out that the underlying reason for isotretinoin treatment, i.e., the presence of acne, may have contributed to the association with CD, especially since the risk for CD among patients with acne was increased 34 %. Acne has been linked to increased mortality [32], and severe acne is likely to result in frequent contact with dermatologists. It is possible that, on some occasions, this may either have led to the discovery of dermatitis herpetiformis [33] or of CD-related symptoms. Both these conditions may have resulted

in a small intestinal biopsy showing villous atrophy and inclusion in our cohort. Finally, Bowe et al. [34] have suggested that acne can be associated with altered microbiota. It has recently been acknowledged that dysbiosis may play a role in the pathogenesis of CD [9, 10], and this might serve as a link between acne and CD. However, we cannot rule out that the association of CD and acne is due to surveillance bias as patients with acne are more likely to attend a doctor than controls and hence are more likely to get any formal diagnosis.

We used biopsy record data to ascertain CD. This has several advantages. Firstly, it allowed us to identify average patients with CD, as earlier research has shown that Swedish patients with CD identified through inpatient data [35] may have significantly more comorbidity than patients identified through pathology departments [36]. Secondly, villous atrophy has a higher positive predictive value for CD (95 %) [20] than having a CD diagnosis in the Swedish Inpatient Registry (86 %) [37]. Our earlier patient chart validation has also shown that symptoms in patients with villous atrophy (diarrhea 36 % and anemia 35 % [20]) are similar to those in CD [38, 39]. While we did not use the Inpatient Registry to identify CD, inpatient and outpatient data (combined they are called the "Patient Registry") were used to identify individuals with acne. We are unaware of any study validating the sensitivity and specificity of acne in the Patient Registry, but for most other disorders, the positive predictive value lies in the range 85–95 % [40].

In Sweden, villous atrophy has few other causes than CD, and when two examiners manually screened more than 1,500 biopsy reports with villous atrophy or inflammation, the second most common cause of villous atrophy, inflammatory bowel disease, only occurred in 0.3 % of the biopsy records with villous atrophy. Finally, our use of biopsy records to detect diagnosed CD should have a high sensitivity since >96 % of all Swedish gastroenterologists and pediatricians require a biopsy before CD diagnosis [20].

This study has several additional limitations. The Prescribed Drug Registry only began in July 2005, and we therefore chose to examine the association between isotretinoin and CD independent of temporality. For isotretinoin to play a role in the pathogenesis of CD, it would need to be instituted before diagnosis, and as the majority of patients were diagnosed before July 2005, causality cannot be inferred. Despite the large number of individuals with CD, and more than 140,000 controls, this study may have suffered from insufficient power due to the low number of exposures to isotretinoin. This is especially so in our analysis of amount of exposure (OR for CD was 3.33), where only two individuals with CD versus three controls had received three or more prescriptions with isotretinoin prior to CD diagnosis.

Finally, we did not have data on other small intestinal inflammatory disorders such as autoimmune enteropathy, and we cannot rule out that autoimmune enteropathy is linked to isotretinoin.

Although not the primary aim of this paper, we also examined the relationship between acne and CD. We urge caution when interpreting those results. The diagnosis of acne is most probably underestimated in the Patient Registry, as acne diagnosed by a general practitioner will not be registered.

5 Conclusions

This study found no association between isotretinoin use and CD, but a small excess risk of CD in patients with a diagnosis of acne.

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Competing interests Dr. Lebwohl: The author declares that he has no conflict of interest. Dr. Sundström: The author declares that he has no conflict of interest. Dr. Jabri: The author declares that she has no conflict of interest. Dr. Kupfer: The author declares that she has no conflict of interest. Dr. Green: The author declares that he has no conflict of interest. Dr. Ludvigsson: The author declares that he has no conflict of interest.

Details of ethics approval This project (2006/633-31/4) was approved by the Research Ethics Committee of the Karolinska Institute, Sweden, on June 14, 2006.

Authors' contributions International Committee of Medical Journal Editors (ICMJE) criteria for authorship read and met: BL, AS, BJ, SSK, PG, and JFL. Agree with the manuscript's results and conclusions: BL, AS, BJ, SSK, PG, and JFL. Designed the experiments/the study: BL and JFL. Collected data: JFL. Analyzed the data: BL. Wrote the first draft of the paper: BL and JFL. Contributed to study design, interpretation of data and writing: AS and PG. Interpretation of data; approved the final version of the manuscript: BL, AS, BJ, SSK, PG, and JFL. Responsible for data integrity: JFL. Obtained funding: JFL.

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