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ORIGINAL ARTICLE

Risk of colorectal adenomas in patients with celiac disease: a systematic review and meta-analysis☆

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KEYWORDS
Celiac disease;
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Abstract
Introduction and aims: Whether celiac disease increases the risk of presenting with colorectal adenoma or not, has not been extensively evaluated. This question becomes relevant when considering early screening methods in patients with the disease. The aim of our article was to determine the risk of colorectal adenomas in celiac disease patients.
Materials and methods: A computer-assisted search of the MEDLINE-Pubmed, EMBASE, LILACS, Cochrane Library, and Google Scholar databases was carried out, encompassing the time frame of 1966 to December 2016. The search strategy consisted of the following MESH terms: 'celiac disease' OR 'celiac sprue' AND 'colorectal' OR 'colorectal neoplasia' OR 'colorectal adenoma'. A fixed-effect model was used for the analyses. The first analysis dealt with the prevalence of all presentations of colorectal adenoma in patients with celiac disease and the second was on the prevalence of advanced adenomas. The outcomes were described as odds ratios (OR) with their 95% confidence intervals.
Results: The search identified 480 bibliographic citations, 17 of which were chosen for evaluation. Fourteen of those studies were rejected, leaving a final total of three for the analysis. Those studies included 367 cases of celiac disease and 682 controls. No significant heterogeneity was observed ($I^2 = 26\%$). There was no increased prevalence of colorectal adenomas in the celiac disease patients, when compared with the controls (OR: 0.94 [0.65-1.38]), and no significant difference was observed when assessing the prevalence of advanced adenomas (OR: 0.97 [0.48-1.97]).
Conclusion: Celiac disease was not associated with an increased risk of colorectal adenomas. However, due to the limited evidence available, more studies are necessary to determine whether there is an actual association.

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PALABRAS CLAVE
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Adenoma colorrectal;
Colonoscopia

Riesgo de adenomas colorrectales en pacientes con enfermedad celiaca: una revisión sistemática y metaanálisis

Resumen
Introducción y objetivos: No se ha evaluado de manera extensa si la enfermedad celiaca incrementa o no el riesgo de presentar adenoma colorrectal. Esta cuestión se hace relevante al considerar los métodos de cribado tempranos en pacientes con esta enfermedad. El objetivo de nuestro artículo fue determinar el riesgo de adenomas colorrectales en los pacientes con enfermedad celiaca.
Materiales y métodos: Se realizó una búsqueda electrónica en las bases de datos MEDLINE-Pubmed, EMBASE, LILACS, Cochrane Library y Google Scholar, integrando el periodo de tiempo de 1966 a diciembre de 2016. La estrategia de búsqueda consistió en los siguientes términos MESH: «enfermedad celiaca» O «esprue celiaco» Y «colorrectal» O «neoplasia colorrectal» O «adenoma colorrectal». Se empleó el uso de modelos de efectos fijos para los análisis. El primer análisis trató sobre la prevalencia de todas las presentaciones de adenoma colorrectal en pacientes con enfermedad celiaca y el segundo, sobre la prevalencia de adenomas avanzados. Los desenlaces se describieron como razones de momios (RM) con sus intervalos de confianza al 95%.
Resultados: La búsqueda identificó 480 citas bibliográficas, de las cuales 17 se escogieron para ser evaluadas. Catorce de aquellos estudios se rechazaron, dejando un total de 3 estudios para el análisis. Estos estudios incluían 367 casos de enfermedad celiaca y 682 controles. No se observó heterogeneidad significativa (I^2 = 26%). Al compararse con los controles, no se encontró un incremento en la prevalencia de adenomas colorrectales en los pacientes con enfermedad celiaca (RM: 0.94 [0.65-1.38]), y no se observaron diferencias significativas al valorar la prevalencia de adenomas avanzados (RM: 0.97 [0.48-1.97]).
Conclusión: La enfermedad celiaca no se asoció con el incremento de riesgo de adenomas colorrectales. Sin embargo, debido a la evidencia disponible limitada, se requiere de más estudios para determinar si existe una asociación real.

Introduction and aims

Celiac disease is a relatively common autoimmune disorder, triggered by intestinal exposure to gluten −a glycoprotein in wheat, barley, rye, and oats.[1] Classically, it has been described as a condition causing nutrient malabsorption, with diarrhea or failure-to-thrive as common clinical features in pediatric patients. However, atypical presentations may be more common in adult patients, with clinical elements such as iron-deficiency anemia or osteoporosis as possible initial features of the disease.[2]

One of the most relevant issues regarding celiac disease is the risk of developing both malignant and non-malignant tumors.[3] Its association with an increased risk for small bowel adenocarcinoma, as well as for lymphoproliferative disorders, such as enteropathy-associated T-cell lymphoma, has been well described.[4] Other neoplastic conditions may not have as strong an association, as demonstrated in the recent meta-analysis by Han et al.,[5] but interestingly, it failed to show a significant association with colorectal cancer. However, most of the studies evaluating a possible link between celiac disease and colorectal cancer are retrospective and do not always have a valid comparator. In addition, the definition of celiac disease, based on serologic findings only or on biopsy-based diagnoses, varies greatly.

Most colorectal cancers derive from benign asymptomatic neoplastic lesions, known as adenomas.[6] They can be detected and effectively treated through endoscopic or surgical polypectomy, before progressing to adenocarcinoma. There are many risk factors that increase the chances of developing colorectal adenomas and their progression to malignant tumors. In fact, knowing the true extent and influence of such risk factors is crucial in deciding on screening colonoscopy or any other preventive measure.[7]

Whether celiac disease increases the risk of developing colorectal adenoma has not been extensively evaluated. This question becomes relevant when considering early screening methods for celiac disease patients. Our aim was to determine the risk of colorectal adenoma in celiac patients according to the available evidence.

Materials and methods

Criteria for study inclusion

Our meta-analysis was conducted in accordance with the recommendations of the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) Group.[8] Controlled studies with either case-control or cohort study designs were considered for review. Uncontrolled observational studies and case series were excluded.

Search strategy

A computer-assisted search of the MEDLINE-Pubmed, EMBASE, LILACS, Cochrane Library, and Google Scholar databases was carried out, encompassing the time frame of 1966 to December 2016. The search strategy consisted of the following MeSH terms: ''celiac disease'' OR ''celiac sprue'' AND ''colorectal'' OR ''colorectal neoplasia'' OR ''colorectal adenoma''. There were no language restrictions. We also reviewed the references cited in the relevant papers identified. Additionally, abstracts from the Digestive Disease Week and the 2010-2016 United European Gastroenterology Week were manually reviewed.

Two authors independently performed the bibliographic search for potentially relevant studies. Compatible abstracts were reviewed to check compliance with the eligibility criteria. The findings of each author were then compared. If there was disagreement about a particular study, its inclusion was decided by a third author. If there was evidence of duplicated data, the authors of the original paper were contacted to determine that study's inclusion or exclusion.

Quality Assessment

The methodological quality of the studies included in the meta-analysis was independently evaluated by two authors using the Newcastle-Ottawa assessment scale for case-control and cohort studies.[9] If there was disagreement on a particular subject, a third author resolved the difference. The PRISMA checklist was employed to ensure adequate meta-analysis quality.

Statistical analysis

The meta-analysis was carried out using the Review Manager (REVMAN) Version 5.2 software (Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration 2013). Heterogeneity was evaluated using the I^2 statistic and the chi square test. If there was no significant heterogeneity, a fixed-effect model was used for the analysis. The first analysis was on the prevalence of any type of colorectal adenoma in patients with celiac disease, after which we analyzed the prevalence of advanced adenomas between the groups compared. In both cases, the outcome was described as odds ratios (ORs) with their 95% confidence intervals (95%CI). Sensitivity analyses were performed when there was significant heterogeneity or methodological quality differences. Potential publication bias was estimated through the Egger Test.

Figure 1 Flow Chart showing the selection process of the studies in the meta-analysis.

Results

The search identified 480 bibliographic citations. Of those references, 17 that potentially fulfilled the inclusion criteria were chosen for further analysis. Fourteen of those studies were rejected:[10–23] 2 included duplicated data, confirmed by their authors, and the other 12 compared the frequency of malignant colorectal neoplasia, but not the presence of colorectal adenomas. Finally, 3 studies were included for analysis, as shown in Figure 1. Those studies evaluated 367 celiac disease patients and 682 healthy subjects as controls. The 3 studies had case-control designs.

Dickey[24] studied patients diagnosed with celiac disease that were above 40 years of age, had a history of altered bowel habits or iron-deficiency anemia, and that underwent colonoscopy. The control subjects were patients over 40 years of age that had a history of altered bowel habits and/or iron-deficiency anemia but were not diagnosed with celiac disease. Lebwohl et al.[25] included patients over 40 years of age diagnosed with celiac disease that underwent colonoscopy for any reason within a 44-month period. The controls were healthy subjects that underwent colonoscopy. The exclusion criteria included a history of colorectal cancer. Finally, Pereyra et al.[26] selected celiac disease patients older than 18 years of age that underwent colonoscopy for any reason and compared them with a control group matched for age, sex, reason for referral, and family history of colorectal cancer. They also analyzed adherence to a gluten-free diet to evaluate its impact as a predictor of colorectal neoplasia. The median age of the subjects enrolled in each of the studies was above 50 years.

Table 1 describes the main characteristics of the 3 studies, and their methodological characteristics are described in Table 2. No study was excluded due to methodological limitations. The Egger test showed a significant risk for publication bias ($p < 0.05$).

Figure 2 describes the findings on the prevalence of colorectal adenomas. A total of 1,049 patients were included in the present meta-analysis. No significant heterogeneity was observed ($I^2 = 26\%$). There was no increased prevalence of colorectal adenoma among celiac disease patients, when

Table 1 Characteristics of the studies in the meta-analysis.

Author	Location	Subjects	Controls	Celiac Disease Definition	Outcomes
Dickey	Northern Ireland	69 celiac disease patients with either altered bowel habits or iron-deficiency anemia	100 non-celiac disease patients with altered bowel habits or iron-deficiency anemia	Antibodies + endoscopy and biopsies	Colorectal neoplasia
Lebwohl et al.	The United States	180 celiac disease patients over 40 years of age	346 healthy subjects	Not clearly stated	Colorectal adenomas; Advanced colorectal adenomas
Pereyra et al.	Argentina	118 celiac disease patients over 18 years of age	236 age- and sex-matched healthy subjects	Antibodies + endoscopy and biopsies	Colorectal adenomas; Advanced colorectal adenomas

Table 2 Methodological characteristics of the studies in the meta-analysis.

Author	Adequate case definition	Representativeness of cases	Selection of controls	Definition of controls	Comparability of controls	Ascertainment of exposure	Same method of ascertainment
Dickey	Yes	Consecutive series	No	Yes	Yes	Laboratory + biopsies	Yes
Lebwohl et al.	Yes	Consecutive series	Not clearly stated	Yes	Yes	Not clearly stated	Yes
Pereyra et al.	Yes	Consecutive series	Yes	Yes	Yes	Laboratory + biopsies	Yes

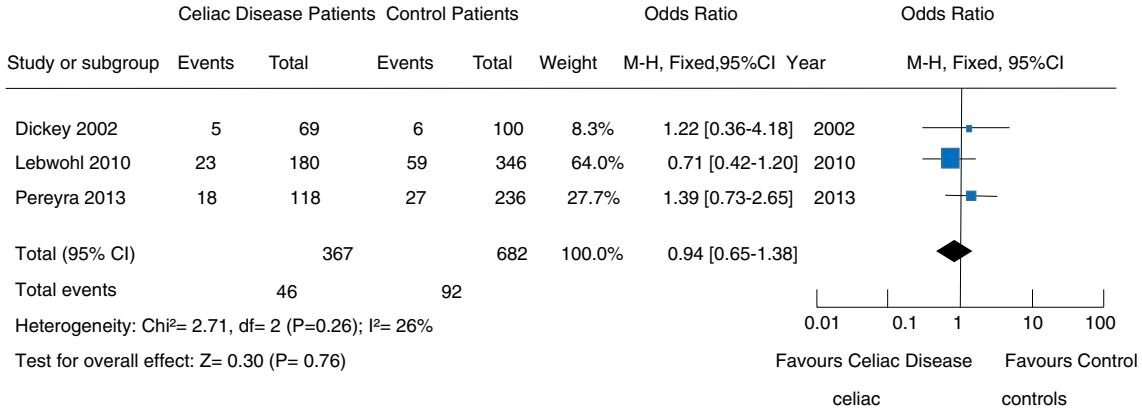

Figure 2 Forest Plot showing the pooled risk of colorectal adenomas between the celiac disease patients and controls.

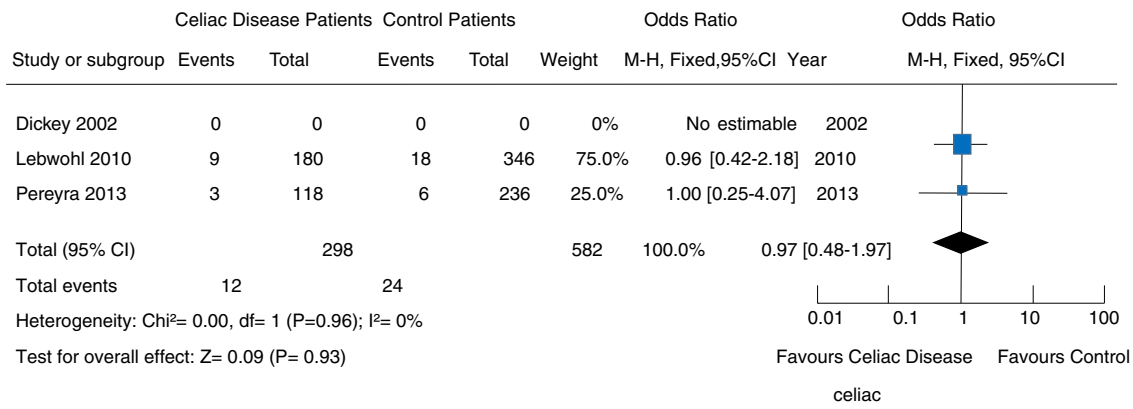

Figure 3 Forest Plot showing the pooled risk of advanced colorectal adenomas between the celiac disease patients and controls.

compared with control patients (OR 0.94 [0.65-1.38]). The pooled adenoma prevalence among celiac disease subjects was 12.53%, whereas it was 13.48% in control subjects. Advanced adenoma prevalence was assessed only in the studies by Pereyra et al.[26] and Lebwohl et al.:[25] this type of lesion was defined in both analyses as any adenoma with a predominant villous component and/or high-grade dysplasia and/or size > 10 mm. There was no significant difference in the prevalence of advanced adenomas (OR 0.97 [0.48-1.97]), as shown in Figure 3. It should be noted that only the study by Pereyra et al.[26] contemplated the possible link between dietary adherence and colorectal adenoma risk, finding that there was a higher prevalence of advanced adenoma in celiac disease patients with poor adherence to a gluten-free diet.

Discussion and conclusions

According to the results of our meta-analysis, celiac disease is not associated with an increased risk of colorectal adenomas. This coincides with the findings of other studies assessing the possible link between celiac disease and colorectal cancer.

As mentioned above, celiac disease has a well-established risk for the development of certain neoplastic conditions, even those that are not necessarily located in the small bowel. Such is the case of esophageal squamous-cell carcinoma[27] or oral cavity carcinoma.[28] Nevertheless, the risk for colorectal neoplasia has failed to show significant results in analyses of the available observational studies.

Some interesting observations can be made from the results of our meta-analysis. First, there was a considerably low adenoma detection rate among celiac disease patients and healthy controls (12.53 and 13.48%, respectively), given that the median age of the population under study was above 50 years. According to previously published studies, the prevalence of colorectal adenomas in the standard-risk population is higher.[29] This raises the following two questions: Were the control groups in the studies included in the present analysis adequately selected? Was the pooled prevalence of colorectal adenoma found in the celiac disease group accurate?

Selecting an adequate control group is one of the most challenging aspects of case-control studies. The low prevalence of colorectal adenomas in the control groups of the three studies analyzed makes it clear that there may have been a potential bias. Consequently, if the adenoma detection rate in the celiac disease patient group were compared with the adenoma detection rate in previously published studies, then a significantly lower prevalence of colorectal adenomas would be found among celiac disease patients. Whether this is secondary to a true lower risk of colorectal adenomas among celiac disease patients–perhaps due to their dietary modifications–or to a biased prevalence of adenomas in the celiac disease group, is not known.

Another interesting observation is that only Pereyra et al.[26] considered gluten-free diet adherence as a potential factor that could have an influential role in modifying the risk for developing colorectal adenomas among celiac disease subjects. The vast majority of patients included in the present meta-analysis were already diagnosed and treated –a feature that could play a major role in reducing the risk of colorectal neoplasia. In fact, Pereyra et al. found that low adherence to a gluten-free diet was independently associated with the presence of adenomas (OR 6.78 [1.39-33.2]). With the evidence that is currently available, it is impossible to determine whether a gluten-free diet has a protective role in this matter.

The questions raised in the previous paragraphs can potentially be answered by considering studies that evaluate the risk of colorectal adenomas in adult patients with untreated celiac disease, or that underwent colonoscopy immediately after the initiation of celiac disease treatment. To the best of our knowledge, no study has yet to follow that type of design. Another interesting approach would be to undertake a longitudinal, population-based study on the subject, as has previously been done on other issues concerning celiac disease patients. It is also important to highlight the retrospective nature of the studies included in our meta-analysis, and the logical limitations inherent in said design. Perhaps the most relevant limitation was the fact that other risk factors for colorectal adenoma, such as smoking, obesity, and diabetes, to name a few, were not contemplated.[30] Such information is vital for having a thorough understanding of the

baseline risk and potential confounders that may either underestimate or overestimate the prevalence of colorectal adenomas.

The main strength of our meta-analysis was that it summarized the pooled analysis of the three studies which, individually, had a rather limited sample size. Additionally, it described the abovementioned limitations of the existing literature on this specific topic, highlighting the need for a different approach to answering the questions posed. In conclusion, the currently available evidence fails to show an increased risk of colorectal adenomas among celiac disease patients, emphasizing the need for more data to accurately determine the true nature of this potential association.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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