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Risk of colorectal neoplasia in patients with celiac disease: A multicenter study

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Abstract

Background and aims: The association of celiac disease with colorectal neoplasia is controversial. The aim of this study was to determine the risk of colorectal neoplasia among patients with celiac disease.
Methods: We carried out a multicenter, retrospective case–control study, within four community hospitals. Celiac disease patients with a complete colonoscopy were regarded as cases and those without celiac disease as controls. For each case, two controls matched for age, sex, indication for colonoscopy and colorectal cancer family history, were randomly selected. The main outcome evaluated was risk of colorectal polyps, adenomas, advanced neoplastic lesions and cancer.
Results: We identified 118 patients with celiac disease and 236 controls. The risk of polyps, adenomas and advanced neoplastic lesions was similar in both groups (OR 1.25, CI 0.71–2.18, p = 0.40; OR 1.39, CI 0.73–2.63, p = 0.31; and OR 1.00, CI 0.26–3.72, p = 1.00, respectively). On multivariate analysis, age >75 years old, and first-grade CRC family history were associated with adenomas (OR 2.68 CI 1.03–6.98, OR 6.68 CI 1.03–47.98 respectively) and advanced neoplastic lesions (OR 15.03, CI 2.88–78.3; OR 6.46 CI 1.23–33.79, respectively). With respect to celiac disease characteristic, a low adherence to a gluten free diet was independently associated with the presence of adenomas (OR 6.78 CI 1.39–33.20 p = 0.01).

Abbreviations: CD, celiac disease; GFD, gluten free diet; CRC, colorectal cancer; OR, odds ratio; CI, confidence interval; ANL, advanced neoplastic lesions.

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Conclusions: Celiac disease was not associated with an increased risk of colorectal neoplasia. Nonadherence to a strict gluten free diet was associated with the presence of adenomas. Further studies addressing celiac disease characteristics are needed to confirm this observation.

1. Introduction

Celiac disease (CD) is an autoimmune disorder characterized by inflammation and villous atrophy of the small intestine, resulting in malabsorption of vitamins and nutrients.[1] It is a genetically determined condition in which persons with specific human leukocyte antigen types (DQ2 or DQ8) trigger an immunologic reaction to gluten.[2]

Patients with CD, particularly those not adhering to a strict gluten-free diet (GFD), are predisposed to develop many complications. Increased overall cancer mortality has been reported in adult patients with CD and even in their relatives, which supports the clinical importance of this disorder.[3,4] Holmes et al.[5] reported an increased risk of cancers of the mouth, pharynx and esophagus, and also of lymphoma in those celiac disease patients taking a reduced gluten, or a normal diet. This result supports the protective role of GFD against malignancy in celiac disease.

The mechanism for the development of malignancies in patients with CD is not clearly known. However, increased intestinal permeability of environmental carcinogens, chronic inflammation, chronic antigenic stimulation, release of pro-inflammatory cytokines and nutritional deficiencies due to the disease or the GFD have been suggested.[2–6] Lymphomas, mostly T-cell type, and other malignant tumors, particularly adenocarcinoma of the small bowel and squamous cell carcinomas of the esophagus and pharynx have been related with CD, but the association with colorectal cancer (CRC) is not well established.[7–13] The risk of developing CRC is influenced by both environmental and genetic factors. Possibly, untreated CD is protective; dietary fat or fat soluble agents including hydrocarbons or other carcinogens may be implicated in the pathogenesis of colon cancer if poorly absorbed and rapidly excreted.[7] Alternatively, immunological changes (increased intraepithelial lymphocytosis) may prohibit development of epithelial malignancies.[8] Additional studies are needed to further clarify the association with CRC in CD patients.

Askling et al.[14] have reported an increased overall colorectal cancer risk in CD patients mainly due to an increased risk in the ascending and transverse colon. However, Freeman et al.[15] reported a low prevalence of colonic neoplasia in a retrospective observational study, and recently, Lebwohl et al.[16] found no association between CD and CRC in a case–control study.

The controversy in published studies and the low prevalence of malignancies in CD patients led us to design this multicentric case–control study.

We aimed to determine the risk of colorectal neoplasia among patients with CD by quantifying the prevalence of colorectal polyps, adenomas and advanced neoplastic lesions in these patients compared with patients without CD, and to identify celiac disease characteristics associated with these lesions.

2. Materials and methods

A retrospective and multicenter case–control study was conducted using the Gastroenterology and Endoscopy electronic data base of four community hospitals of Buenos Aires, Argentina (Hospital Alemán, Hospital Italiano, Hospital Austral and Hospital CEMIC). We included all patients $\geq$18 years old with biopsy-confirmed CD according to previously established criteria[17,18] and who had undergone a colonoscopy. Celiac disease was defined on the basis of typical pathological features in small intestinal biopsies along with positive serologic test, consistence history and evidence for a response to a gluten-free diet. Only patients who had a complete colonoscopy (with cecal intubation), with satisfactory colonic cleansing were included for analysis. Satisfactory colonic cleansing was defined as an "excellent" or "very good quality" preparation according to a previously reported scale.[19] The following exclusion criteria were applied to all subjects: personal history of inflammatory bowel disease, CRC, familial adenomatous polyposis, hereditary non-polyposis colon cancer, colonoscopy without cecal intubation or unsatisfactory bowel cleansing. Patients with CD were regarded as cases and those without CD were regarded as controls. For each case, two controls were randomly selected and matched for age, sex, indication for colonoscopy and first- and second-grade family history of CRC.

We collected the following data from the medical records: age, sex, medical history, purpose of colonoscopy, time since diagnosis of CD, adherence to a GFD, endoscopic diagnosis (colorectal polyps plus size and location of these lesions) and histological diagnosis (type of adenomas, dysplasia and cancer). A telephone survey was carried out to assess patients on their CRC risk factors and history of disease (diabetes mellitus, cigarette smoking, first- and second-grade colorectal polyps and colorectal cancer family history). In cases we also evaluated time since diagnosis and the adherence to a GFD. For the last purpose we used the Biagi's validated questionnaire,[20] which is based on four simple questions. The questionnaire provides a final score in five levels (0–IV), which, from a clinical point of view, can be grouped into three levels. Patients with scores of 0 or I are those who do not follow a strict GFD. Patients with scores of II, on the other hand, follow a GFD but with important errors that require correction. Patients with scores of III and IV follow a strict GFD.

The main outcome measured was the risk of colorectal polyps, adenomas, advance neoplastic lesions (ANL) (size $>$ 1 cm, $>$75% villous component and/or high-grade dysplasia) and cancer. Colorectal adenomas were classified as low- or high-grade dysplasia according to Vienna classification.[21] Patients with multiple lesions were classified according to the most advanced lesion. Enteropathy associated T cell lymphoma (EATL) and other malignancy related with CD were also addressed. Results were expressed in total number of lesions and percentage. The differences in both groups