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ORIGINAL ARTICLE

Celiac disease seroprevalence in subjects with dyspeptic symptoms. A study on a Mexican population

C. Durán-Rosas[a], J. Lara-Carmona[a,*], K. Hernández-Flores[a], F.J. Cabrera-Jorge[a], F. Roesch-Dietlen[a], M. Amieva-Balmori[a], H. Vivanco-Cid[a], S. Santiesteban-González[b], P. Thomas-Dupont[a], J.M. Remes-Troche[a]

[a] *Laboratorio de Fisiología Digestiva y Motilidad Gastrointestinal, Instituto de Investigaciones Médico-Biológicas, Universidad Veracruzana, Veracruz, Mexico*
[b] *Centro Estatal de la Transfusión Sanguínea, Veracruz, Mexico*

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Abstract
Introduction and aims: Celiac disease (CD) is an autoimmune enteropathy that develops in genetically susceptible individuals. The typical gastrointestinal manifestation is diarrhea but symptoms of dyspepsia, such as epigastric pain, nausea, or satiety, can sometimes appear. Previous studies have reported that the prevalence of CD in patients with dyspepsia can be as high as 7%. The aim of the present study was to evaluate CD seroprevalence in subjects with dyspeptic symptoms and a control group in a Mexican population.
Material and methods: A case-control study was conducted on blood donors that answered the PAGI-SYM questionnaire for dyspepsia and in whom IgA antibodies to tissue transglutaminase 2 (IgA anti-tTG2) and IgG antibodies to deamidated gliadin peptide (IgG anti-DGP) were determined. CD seroprevalence in subjects with dyspeptic symptoms and in asymptomatic subjects was compared.
Results: A total of 427 subjects (76.3% men), with a mean patient age of 34 years (range of 18–65 years) were included. Of those participants, 87 (20.3%) had symptoms of dyspepsia (group A) and 340 (79.6%) were asymptomatic (group B). Antibodies were positive in one (1.15%) of the group A subjects (1/87, 95% CI 0.2–6 %), whereas they were positive in 4 (1.18%) of the group B subjects (4/340, 95% CI 0.4–2.9%, $p = 0.59$).

* Corresponding author at: Iturbide s/n entre Carmen Serdán y 20 de Noviembre, col. centro, Veracruz, Veracruz, Mexico. Tel.: 22993 180.
E-mail address: jose.remes.troche@gmail.com (J. Lara-Carmona).

Conclusions: CD seroprevalence in the study population with dyspeptic symptoms (1%) was not different from that of the control population. Thus, CD screening in Mexican patients with dyspepsia is not justified.

PALABRAS CLAVE
Enfermedad celiaca;
Dispepsia;
Antitransglutaminasa;
Antipéptido deaminado de gliadina

Seroprevalencia de enfermedad celíaca en sujetos con síntomas dispépticos. Un estudio en población mexicana

Resumen
Introducción y objetivos: La enfermedad celíaca (EC) es una enteropatía autoinmune que se desarrolla en individuos genéticamente susceptibles. Aunque la manifestación gastrointestinal típica es la diarrea, en algunas ocasiones puede aparecer síntomas dispépticos como dolor epigástrico, náuseas o saciedad. Estudios previos han reportado que la prevalencia de EC en sujetos con dispepsia puede ser tan alta como 7%. El objetivo de este estudio fue evaluar la seroprevalencia de EC en pacientes con síntomas dispépticos y un grupo control en una población mexicana.
Material y métodos: Estudio de casos y controles en donadores de sangre a los que se les aplicó el cuestionario PAGI-SYM para dispepsia y se realizó determinación de anticuerpos IgA contra la transglutaminasa tisular 2 (IgA-tTG2) e IgG contra el péptido deaminado de gliadina (IgG-DGP). Se comparó la seroprevalencia de EC en pacientes con síntomas dispépticos y sujetos asintomáticos.
Resultados: Se incluyeron 427 sujetos (76.3% hombres) con edad promedio de 34 años (rango de 18–65 años). De estos, 87 sujetos (20.3%) tuvieron síntomas de dispepsia (Grupo A) y 340 (79.6%) fueron asintomáticos (Grupo B). Se encontraron anticuerpos positivos en uno (1.15%) de los pacientes del grupo A (1/87, IC 95% 0.2–6%), mientras que en el grupo B se encontraron 4 sujetos positivos (1.18%) (4/340, IC 95% 0.4–2.9%, p = 0.59).
Conclusiones: La seroprevalencia de EC en la población estudiada con síntomas dispépticos (1%) no fue diferente de la población control. Por tal motivo, no se encuentra justificado la búsqueda de EC en pacientes con síntomas dispépticos en México.

Introduction and aims

Celiac disease (CD) is an autoimmune enteropathy characterized by chronic inflammation and atrophy of the small bowel mucosa secondary to gluten intake that develops in genetically susceptible individuals. Overall prevalence is estimated at 1.4%, with some variability, according to continent. Prevalence is 1.3% in South America, 1.8% in Asia, and is estimated at 0.5—0.7% in Mexico.[1] An increase in incidence and prevalence has been observed over time, although whether that is due to an actual increase in the number of cases or to the development of more sensitive and specific diagnostic methods, as well as greater clinical suspicion, has not been established.[2,3] Its diagnosis requires the combination of specific serology and the identification of intestinal villous atrophy; in some cases, screening for the specific histocompatibility alleles, HLA-DQ2 and HLA-DQ8, is necessary. The clinical characteristics of the entity include chronic diarrhea, with signs of malabsorption, such as weight loss, vitamin deficiency or malnutrition, and dermatologic manifestations.[4] Atypical manifestations of iron-deficiency anemia, infertility, and osteopenia, have also been described. In addition, these patients can present with other gastrointestinal symptoms that do not tend to manifest in the classic manner, such as diffuse abdominal pain, vomiting, constipation, dyspepsia, and irritable bowel syndrome (IBS). In that context, dyspepsia has been considered a potential clinical characteristic in the presentation of CD.[5]

Dyspeptic symptoms (nausea, early satiety, postprandial fullness, epigastric pain) are highly prevalent in the general population and can manifest in patients with diseases, such as peptic ulcer or neoplasia, but they often present in the absence of organicity, as well.[6] Some studies indicate that 0.5–7.0% of patients with dyspepsia can present with CD, but at present, results continue to be controversial.[7,8] In Mexico, even though CD patient characteristics and the relation of CD to IBS[9–11] have been described, we have no evidence on the prevalence of CD in the Mexican population with dyspeptic symptoms. Therefore, the aim of our study

was to evaluate the prevalence of CD in a group of individuals with dyspeptic symptoms and compare it with a control group.

Material and methods

Study design and population

A cross-sectional case-control study was conducted (according to STROBE) on subjects that went to a state-operated blood transfusion center to voluntarily donate blood, within the time frame of February to May 2018, in the city of Veracruz. All study subjects filled out the institution's required health questionnaire and gave their informed consent.

Mexican adults, above 18 years of age, were included in the study. The exclusion criteria were a history of abdominal surgery, the presence of alarm symptoms, diagnosed diabetes mellitus, a history of inflammatory bowel disease, and serologic reactivity for hepatitis B surface antigen, IgG antibodies to hepatitis C virus, and human immunodeficiency virus.

Interventions and evaluations

Anthropometric measurements, age, and sex of the participants were recorded. A complete blood count, blood chemistry, and liver function tests were carried out as the protocol of the blood donation process. The subjects considered ''optimum donors'' underwent the following evaluations:

Gastrointestinal symptoms: the Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity Index (PAGI-SYM) questionnaire was applied, to evaluate the frequency and severity of dyspeptic symptoms. It is composed of 20 items, divided into 6 subcategories, utilizing a 6-point Likert scale from 0 to 5 (0 = absence of the symptom, 1 = very mild, 2 = mild, 3 = moderate, 4 = severe, and 5 = very severe). Greater attention was paid to the subscales of fullness/early satiety, bloating, and abdominal pain, given their higher sensitivity to changes in the clinical status of patients with dyspepsia. For the purpose of the present study, we considered dyspepsia to be present in all subjects that marked any symptom as having an intensity of at least 3 (moderate) on the Likert scale.

Antibody determination: 5 mL of peripheral venous blood was collected from each subject. The serum was separated from the blood samples through centrifugation and stored at $-80\,^{\circ}C$, until analyzed. The enzyme-linked immunosorbent assay (ELISA) determined the IgA antibodies to tissue transglutaminase 2 (IgA anti-tTG2), with a dilution factor of 1:101 for the samples, as recommended by the manufacturer, and the IgG antibodies to the deamidated gliadin peptide (IgG anti-DGP) (Testline Clinical Diagnostics). Titers $\geq$20 IU/mL were considered positive for each of the antibodies.

CD seroprevalence was diagnosed, if at least one of the antibodies was positive. CD seroprevalence was compared between the subjects with dyspeptic symptoms and the asymptomatic subjects.

Statistical analysis

Descriptive statistics were utilized for the continuous variables and the chi-square test or Fisher's test were used for the categorical variables. Prevalence was determined, considering 95% confidence intervals (CIs). Sample size was calculated using convenience sampling and statistical significance was set at a $p < 0.05$. The results were analyzed through descriptive statistics utilizing the IBM® SPSS Statistics® version 22 program.

Ethical considerations

All the subjects were invited to voluntarily participate in the study. They gave their informed consent, approving the maintenance of data confidentiality. The study protocol met the current bioethical research regulations and was authorized by the research ethics committee of the *Instituto de Investigaciones Médico Biológicas*. The project was approved and registered under the number, IIMB-UV-2018-002. Patient anonymity was maintained, according to the current norms, and so informed consent was not required for data publication.

Results

Demographic characteristics

A total of 427 subjects were included in the study, of whom 326 (76.3%) were men and 101 (23.6%) were women. Mean patient age was 34 years, with a range from 18 to 65 years. Eighty-seven (20.3%) of the study participants (63% men, 37% women) presented with symptoms of dyspepsia (group A) and 340 (79.6%) (80% men, 20% women) were asymptomatic (group B). There was a higher percentage of women (37% vs 20%, $p = 0.001$) in group A, compared with group B, and age between the two groups was similar (35.3 ± 3.2 vs 34.7 ± 2.2, $p = 0.63$).

Frequency of dyspeptic symptoms

The most frequently reported dyspeptic symptom was postprandial fullness, at 52% ($n = 45$) of the subjects, followed by early satiety, at 46% ($n = 40$), upper abdominal distension, at 35% ($n = 30$), epigastric pain at 28% ($n = 24$), nausea, at 25% ($n = 22$), anorexia at 20% ($n = 17$), and vomiting, at 6% ($n = 5$).

Prevalence of CD

In group A, CD seroprevalence was 1.15% (1/87, 95% CI 0.2–6%), whereas it was 1.18% (4/340, 95% CI 0.4–2.9 %, odds ratio 0.96, $p = 0.59$) in group B (Fig. 1). In the dyspepsia group, the only seropositive subject was a 36-year-old woman with satiety and nausea, and her IgA anti-tTg2 and IgG anti-DGP levels were 46 IU/mL and 68 IU/mL, respectively. On the other hand, there were 4 seropositive subjects in the control group (3 women [32, 28, and 29 years of age] and one man [30 years of age]). The two antibodies were positive in all those cases, with a median of 54 IU/mL (range

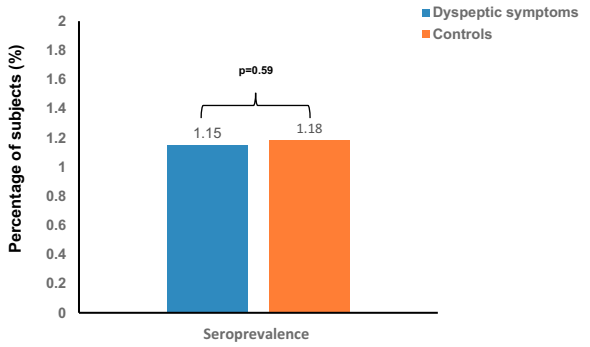

Figure 1 Prevalence of seropositivity between patients with dyspeptic symptoms and controls.

35–102) for IgA anti-tTg2 and a median of 42 IU/mL (range 32–77) for IgG anti-DGP.

Discussion

Over the past decades, CD has been thought to possibly simulate or coexist with functional gastrointestinal disorders, mainly IBS and dyspepsia, making its recognition more difficult. In that context, different studies have suggested screening for CD in patients with symptoms of IBS. For example, a systematic review reported that the prevalence of CD in patients with IBS symptoms varied from 2.6% to 5.7%, with a relative risk (RR) three-times higher than that of an asymptomatic population, and as a result, international guidelines have recommended serologic CD screening in those types of patients.[12,13]

As occurred with IBS, there are studies reporting a prevalence of CD as high as 7%, in patients with symptoms of dyspepsia.[7] However, results in patients with dyspeptic symptoms are controversial, due to the great heterogeneity of the studies and contradictory results.

Importantly, in Mexico, dyspeptic symptoms are very prevalent and may be present in up to 12% of the open population.[14] Our study evaluated the prevalence of CD, based on the serology of a group of blood donors with dyspeptic symptoms, and compared them with asymptomatic subjects. CD seroprevalence in the study population with dyspeptic symptoms (1%) was not different from the control population. Therefore, unlike that occurring with IBS, we believe that CD screening in Mexican patients with symptoms of dyspepsia is not justified, due to its low prevalence. Our results are supported by a CD-specific serologic evaluation based on positive IgA anti-tTG tests. Those antibodies provide an excellent diagnostic yield, with 91% sensitivity, 96% specificity, 27% positive predictive value, and 99.6% negative predictive value.[1] In addition to determining those antibodies, we simultaneously quantified the IgG anti-DGP antibodies, given that they play an important role as CD predictors, in the context of selective IgA deficiency, preventing false negatives.[15,16]

Previous studies have shown a higher prevalence of CD in patients with dyspeptic symptoms.[17–19] Nevertheless, certain limitations of those studies should be mentioned, such as possible population selection bias, sample size, or the absence of statistical power. Those observations are reflected in a meta-analysis by Ford et al., in which a prevalence of positive serology for CD was found in 7.9% of the patients with dyspepsia, and when compared with the 3.9% reported in the controls, was not statistically signifcant.[8] Two published studies support the relation of dyspepsia to CD. On the one hand, Keshavarz et al. found 7% positive serology in dyspeptic patients, but their sample size was small and there was no control group comparison.[7] On the other hand, Sharma et al. reported a positive anti-tTG frequency of 5% in the patients with dyspepsia, albeit they used a lower positivity cutoff value of those antibodies, which could explain the higher percentage of cases found.[20] It should be pointed out that there was a higher percentage of female patients in the group with positive CD serology (up to 80% of cases), in both studies. That datum concurs with results reported in previous studies. In other words, the risk for CD is greater in women than in men (RR 1.42), as well as in girls compared with boys (RR 1.79).[21,22]

In contrast, there are studies similar to ours that do not show a higher prevalence of CD in patients with dyspepsia.[23,24] For example, Hujoel et al. analyzed a case series with more than 40,000 adults, for the detection of CD. The indications for serologic evaluation were diverse and included classic manifestations and non-classic manifestations, such as dyspepsia. In that large case series, the relative risk for CD in patients with dyspepsia was 0.42.[25] In addition, another study that evaluated the association of functional dyspepsia with CD in Latin America found CD in 1.23% of the group with dyspepsia and in 0.62% of the healthy controls, with no statistically significant difference.[26]

It is important to recognize that dyspepsia definitions and criteria have changed over time, which could influence the population that should be selected for ruling out CD in the context of dyspepsia. For example, in an Italian study that evaluated patients with symptoms of ''refractory'' functional dyspepsia, those authors reported that 1 out of 48 of said patients could be celiacs.[27] With clear criteria for defining refractory dyspepsia, CD screening could be justified in that group of patients. Another possible context could be the overlapping of dyspeptic symptoms with IBS, especially the diarrhea subtype.[11]

One of the limitations of the present study is that our population was made up of a larger number of men, which could be related to the fact that our study subjects were blood donation volunteers; women tend to have less iron reserve than men, making them less eligible for donating blood. Despite the fact that recruiting volunteers from a blood bank could result in selection bias, the presence of dyspepsia does not limit the ability to donate blood, and the high prevalence of dyspeptic symptoms in the general population must be recognized. The lack of duodenal biopsies to confirm CD is another limitation, but as mentioned above, we used a panel that has high sensitivity and specificity, and the antibody levels were high. Nevertheless, false positives are a possibility, when the diagnosis is not confirmed. Strikingly, seroprevalence was 1.18% in the control population, which could be considered higher than that expected, but it is within the confidence intervals reported in other similar studies on Mexican populations (0.27–1.29).[10] The fact that the evaluation was

carried out on patients with uninvestigated dyspepsia is an important point, given that the symptoms could be related to underlying organic disorders (peptic ulcer disease, NSAIDs, *Helicobacter pylori* infection) that were not evaluated. However, by being considered healthy volunteers for blood donation, the study subjects had no alarm symptoms, and their biochemical analyses (especially complete blood count) were normal.

Conclusion

In our study, CD seroprevalence in Mexican subjects with dyspepsia was similar to that of the asymptomatic population. Our findings are comparable to those reported in other countries. Based on our results, we believe that CD screening is not justified in Mexican patients with dyspeptic symptoms.

Financial disclosure

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Conflict of interest

Dr. José María Remes-Troche is a member of the advisory board of Takeda, Alfasigma, Biocodex, and Asofarma. He has received honoraria as a speaker on behalf of Takeda, Chinoin, Ferrer, and Alfasigma.

The rest of the authors have no conflict of interest.

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