BRIEF REPORT

POPULATION SEROPREVALENCE OF CELIAC DISEASE IN URBAN AREAS OF PERU

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ABSTRACT

The objective of the study was to determine the seroprevalence of celiac disease (CD) in urban areas of Peru using a population-based sample. A random sample of women and men 18 to 29 years old from 26 cities in Peru was screened. An anti-tissue transglutaminase IgA kit was used for the detection of CD. Results higher than 20 AU / ml were considered positive. The weighted prevalence of celiac disease was 1.2% (CI 95%: 0.0% - 2.4%), thus the estimated number of people living with CD in Peru was 341,783. CD prevalence in Peru is similar to the world average.

Keywords: Celiac Disease; Seroprevalence; Seroepidemiologic Studies; Transglutaminases (source: MeSH NLM).

INTRODUCTION

Intolerance to gluten (whether from wheat, barley or rye) leads to a wide spectrum of chronic enteropathies: a) gluten allergy; b) non-celiac sensitivity to gluten (NCSG); and c) celiac disease (CD). CD is an autoimmune disorder with a genetic predisposition linked to the alleles *HLA-DQ2* and *HLA-DQ8* [1,2]. Despite its recognized characterization, its diagnosis is always elusive.

When compared to CD, NCSG shows no association with any genetic or immunological alteration, nonetheless both conditions present a similar clinical picture. This seems to be due to the fact that a gluten-derived fragment, alpha-gliadin, would be the main target epitope associated with duodenal disorders present in both CD and NCSG [3].

Depending on its clinical presentation, CD can present evident symptoms (diarrhea, steatorrhea, fatigue, dyspepsia, and malnutrition), an extragastrointestinal clinical picture (iron deficiency anemia, fatigue, depression, peripheral neuropathies, and cerebellar ataxia), or an asymptomatic picture [4], often detected by routine serological screening or by its association with chronic complications such as malignant lymphomas [5].

Worldwide, the prevalence of CD is 1%, with a female:male ratio of 2.8:1. It is assumed that Latin America and Europe have similar prevalence of CD, which may vary between 0.46 and 0.64% [6].There are no population-based studies of prevalence in Peru, but there are clinical cases of CD that warn of the need for national serological mapping of the disease [7,8,9].

These tests detect antibodies that are reactive to gluten (IgA and/or IgG), such as anti-endomysial antibody (EMA), anti-gliadin antibody (AGA), and anti- transglutaminase antibody (tTGA). The latter is used for the early detection of CD at any age, which is then confirmed by

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an intestinal biopsy [10]. The purpose of the study was to determine the seroprevalence of CD in urban populations of Peru using a population-based sample.

THE STUDY

Subjects and study population

The study uses demographic and biological sampling information from the PREVEN study [11], which included women and men between 18 and 29 years old in 26 cities in Peru, selected through a multi-stage cluster sampling in households located in urban areas. Our study selected 1,208 samples by simple random sampling from 17,293 samples collected between 2005 and 2007 by the PREVEN study. Participants completed an epidemiological questionnaire and provided biological samples. The serum obtained was stored at –20 °C in the serum bank of the Research and Development Laboratories (LID) of Universidad Peruana Cayetano Heredia (UPCH).

Sample processing

Hemolyzed, lipemic samples were discarded; as well as cryovials with insufficient remaining volume (<10ul) of serum or samples without epidemiological information. The samples were processed by colorimetric enzyme-linked immunosorbent assay (ELISA). The IgA tissue antitransglutaminase kit (Diametra Diagnostic, Italy) was used according to the manufacturer's protocol, which has a sensitivity of 93% and specificity of 95% [12]. The samples and the reagent kit were defrosted at room temperature for about 30 minutes. One positive and one negative control were included. The samples were diluted 1:10 and placed in microwells coated with recombinant tissue transglutaminase. They were incubated for 30 minutes at room temperature.

The supernatant was discarded and the microwells were washed three times to remove the remaining unbound components. Anti-human IgA conjugate marked with horseradish peroxidase (HRP) was then added and incubated for 30 minutes at room temperature. After washing, the excess conjugate was removed, the substrate was added with trimethylbenzidine (TMB) and incubated for 15 minutes at room temperature protected from the light. The reaction was stopped with sulphuric acid.

The sample reading was made with a 450 nm filter and a 650 nm reference filter. As a confirmatory test, those samples with results >20 AU/ml were subjected to a second ELISA following the same procedures described. Those samples in which the second ELISA showed values >20 AU/ml were considered positive. Samples with ≤20 AU/ml values in the first or second ELISA were considered negative.

KEY MESSAGES

Motivation for the study: Celiac disease has different clinical presentations, being the undiagnosed cases the larger group yet to be recognized. A serological screening can be an early detection test for celiac disease; furthermore, it would avoid fatal complications.

Main findings: This is the first "extra-nosocomial" population-based study in Peru. A prevalence of celiac disease of 1.2% was found using the IgA tissue antitransglutaminase test.

Implications: Further population-based studies of celiac disease in Peru are recommended.

Statistical Analysis

For each sample included in the study, an expansion factor was calculated, corresponding to the inverse of the probability of participation. The probability of participation was the product of several probabilities: the probability of selection of the cluster within the city, the probability of selection of the dwelling within the cluster, the probability of selection of the participant within the dwelling, and the probability of selection of the individual for participation in the present study. Estimates were also adjusted for city level stratified sampling. Weighted prevalence is presented, with its respective confidence intervals. Pearson's chi-square test for weighted samples was used for the comparison of proportions. Stata 8.2 (College Station, Texas) was used for all calculations.

Ethical aspects

Participants provided verbal consent for their participation in the study. The original study's informed consent form contemplated the storage of samples for future studies without the inclusion of personal identifiers. As part of this study, only codes were used to identify the samples and link them to their epidemiological information. The present study was approved by the Institutional Research Ethics Committee of Universidad Peruana Cayetano Heredia (code SIDISI 60226).

RESULTS

Out of the 1,208 selected samples, 107 were discarded for being hemolyzed (73), lipemic (1), insufficient volume (18) and lack of epidemiological information (15). Finally, 1,101 samples were included in the analysis, of which 420 were male and 681 were female (Table 1).

A weighted prevalence of CD of 1.2% (95% CI 0.0-2.4) was obtained. The sample is representative of 3,399,734 people aged

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18-29 years, living in urban areas in Peru. Thus, it is estimated that in this population there are 40 797 people with CD (95% CI: 0-81 594).

Although the weighted prevalence in women (0.7%) was lower than in men (1.9%), this difference is not statistically significant (p=0.253). Similarly, the prevalence in the 21-23 age group is higher than for other age groups, no statistically significant difference is found (p=0.144).

Of the total number of individuals, 623 lived in the coastal region, 281 to the sierra and 197 to the jungle. The prevalence of CD in the sierra (1.8%) was not significantly higher than that found on the coast or in the jungle (1.1 and 0.9%, respectively).

Although few participants spoke Quechua or Aymara (119 and 19, respectively), no statistically significant differences were found in the prevalence of CD between these and the rest of the participants in the study (p=0.288 and p=0.811, respectively).

DISCUSSION

This is the first study in Latin America to evaluate the prevalence of CD by serological screening for tissue antitransglutaminase IgA in a population-based sample, and a prevalence of 1.2% was found. If the prevalence for other ages and geographical areas of the country in 2007 had been the same, then it is estimated that for that year the number of people living with celiac disease in Peru was 341,783.

Table 1. Demographic characteristics of the 1,101 participants selected for the study

Variable	Screened	Prevalence[a]
	n = 1,101	n (%)
Gender		
Male	420	6 (1.9)
Female	681	9 (0.7)
Age (years)		
18-20	353	8 (0.9)
21-23	261	3 (2.6)
24-26	233	1 [b]
27-29	254	3 (0.7)
Region		
Coast	623	7 (1.1)
Sierra	281	5 (1.8)
Jungle	197	3 (0.9)
Native tongue		
Quechua	119	3 [b]
Aymara	19	0 [b]

[a] Weighted prevalence; [b] could not be calculated as there was only one

In the United States, the prevalence of undiagnosed CD is increasing. A study determined the presence of IgA tissue antitransglutaminase in stored samples (for at least 20 years at –20 °C), to determine changes in prevalence over a 50-year period [13]. Samples taken between 1948 and 1954 showed a prevalence of 0.2% and those taken between 1995 and 2003 showed a prevalence of 0.8%, both in adults over 50 years. On the other hand, in samples of persons aged 18 to 49 taken between 2006 and 2008, a prevalence of 0.9% was found. Previously in the mentioned study the presence of IgA was revealed in the old samples using nephelometry.

Another study conducted in Argentina [14], using AGA (IgA and IgG) and EmA (IgA) as serological markers, determined a CD prevalence of 0.6%. Our study reveals a higher prevalence, probably because of the age group and the type of serological test used. On the other hand, a study in Brazil [15] in people of 18-65 years old without anemia found a prevalence of 0.33% using the anti-TBM IgA and anti-EmA IgA test. The low prevalence found may respond to the fact that anemia is an atypical presentation of CD.

Epidemiological studies exploring the population risk of presenting CD are scarce in Latin America [6]. In Peru, the few clinical reports that exist warn of the presence of CD in a "low frequency" and linked to the classic type of the disease [7-9,16].

Serological screening for CD is recommended instead of the use of invasive methods such as biopsies, being an early diagnostic choice to rule out CD. According to ESPGHAN (European Society for Pediatric Gastroenterology, Hepatology and Nutrition) [17], the diagnosis of CD can be confirmed with anti-transglutaminase levels above ten times the upper normal limits (≥20 U/ml, reference value for our study), this levels are compared to Marsh-3 type villous atrophy. This emphasizes the usefulness of the IgA tTGA serological test as the most reliable serological marker for CD, not only because of its high specificity and sensitivity, but also because of its usefulness, as samples can be stored for extended periods of time,being possible to reuse them in cryopreserved samples [18], as in our case. Indeed, having a reliable serological test would allow for a reduction in costs and time in the diagnosis of CD.

The absence of information on gastrointestinal symptoms and history of CD could constitute a limitation of the present study, however, the clinical correlation of serology is quite well known.

Our study found a higher prevalence of CD in people from the sierra. This could correspond to genetic differences, or to environmental factors, such as height and consequent hypoxia. Although other studies have found higher preva-

lence in women [6], our study found higher prevalence in the male population, a difference for which we found no cause.

In conclusion, the present study is the first to be carried out in Peru based on a population sample of young adults, showing a higher prevalence than reported in other studies of the American continent, but similar to the world average. More studies of seroprevalence in populations that are atypical for CD are suggested, taking into account the different forms of clinical presentation, since in most cases celiac disease has no apparent symptoms.

Authorship contribution: KB participated in the technical execution, data analysis and obtained the funding for the study. DCM participated in the conception and design of the study, interpretation of the results and writing of the first version of the manuscript. CC participated in the statistical analysis and interpretation, critical review and writing of the final version of the article. Both KH and PG are the principal investigators of the PREVEN study. All the authors finally approved the last version of the article.

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Conflicts of interest: All authors have none to declare.

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