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Global Prevalence of Celiac Disease: Systematic Review and Meta-analysis

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BACKGROUND & AIMS: **Celiac disease is a major public health problem worldwide. Although initially it was reported from countries with predominant Caucasian populations, it now has been reported from other parts of the world. The exact global prevalence of celiac disease is not known. We conducted a systematic review and meta-analysis to estimate the global prevalence of celiac disease.**

METHODS: **We searched Medline, PubMed, and EMBASE for the keywords celiac disease, celiac, celiac disease, tissue transglutaminase antibody, anti-endomysium antibody, endomysial antibody, and prevalence for studies published from January 1991 through March 2016. Each article was cross-referenced with the words Asia, Europe, Africa, South America, North America, and Australia. The diagnosis of celiac disease was based on European Society of Pediatric Gastroenterology, Hepatology, and Nutrition guidelines. Of 3843 articles, 96 articles were included in the final analysis.**

RESULTS: **The pooled global prevalence of celiac disease was 1.4% (95% confidence interval, 1.1%–1.7%) in 275,818 individuals, based on positive results from tests for anti–tissue transglutaminase and/or anti-endomysial antibodies (called *seroprevalence*). The pooled global prevalence of biopsy-confirmed celiac disease was 0.7% (95% confidence interval, 0.5%–0.9%) in 138,792 individuals. The prevalence values for celiac disease were 0.4% in South America, 0.5% in Africa and North America, 0.6% in Asia, and 0.8% in Europe and Oceania; the prevalence was higher in female vs male individuals (0.6% vs 0.4%; $P < .001$). The prevalence of celiac disease was significantly greater in children than adults (0.9% vs 0.5%; $P < .001$).**

CONCLUSIONS: **In a systematic review and meta-analysis, we found celiac disease to be reported worldwide. The prevalence of celiac disease based on serologic test results is 1.4% and based on biopsy results is 0.7%. The prevalence of celiac disease varies with sex, age, and location. There is a need for population-based prevalence studies in many countries.**

Keywords: Epidemiology; Gluten; Diet; Autoimmune Disorder.

Celiac disease (CD) is an autoimmune enteropathy triggered by dietary gluten in genetically susceptible individuals.[1] Until a few decades ago, CD was considered to be an uncommon disease affecting mainly children and limited to individuals of European ancestry.[1] In the 1970s, the diagnosis of CD required a sequence of 3 small intestinal biopsies, but the current guidelines suggest that its diagnosis should be based on the combination of a positive celiac-specific serologic test and small intestinal biopsy specimens showing villous abnormalities.[2,3] Simplification of the diagnostic criteria and widespread use of serologic tests have made it possible to estimate the true prevalence of CD in the general population.[1]

Over the past 2 decades, CD has emerged as a major public health problem. Initial prevalence studies in the general population came from European countries and it was estimated to affect approximately 1% of the European population.[4,5] CD subsequently was reported from other parts of world with predominant Caucasian

Abbreviations used in this paper: Ab, antibody; AEA, anti-endomysial antibody; AGA, antigliadin antibody; CE, celiac disease; CI, confidence interval; tTG, tissue transglutaminase.

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populations such as North America, Australia, and Brazil.[6–8] In the past few decades, population-based data on the prevalence of CD also have been reported from the Middle East, India, and so forth.[9–11]

The prevalence of CD-predisposing HLA haplotypes in the general population and per-capita wheat composition, the 2 primary determinants of CD prevalence, vary from one region to the other.[12,13] However, it is unclear if there is any variation in the prevalence of CD in different parts of the world. Although most reviews on CD suggest that the global prevalence of CD is approximately 1%, there has been no meta-analysis on this topic.[12] A systematic review of the global prevalence of CD by Biagi et al[14] had several limitations including an incomplete review of the literature, a lack of assessment of the quality of studies, and a lack of assessment of the risk of bias or heterogeneity. A few other systematic reviews on this topic had similar limitations and the authors of these systematic reviews did not attempt to pool the data.[15,16]

We therefore conducted a systematic review and meta-analysis of the published studies on the prevalence of CD to estimate the pooled prevalence, and variation in the prevalence, of CD around the world.

Methods

We conducted an extensive search on Medline, PubMed, and EMBASE with the following medical subject heading terms and keywords "celiac disease," "celiac," "coeliac disease," "tissue transglutaminase antibody," "anti-endomysium antibody," "endomysial antibody," and "prevalence." Each one was cross-referenced with "Asia," "Europe," "Africa," "South America," "North America," and "Australia." Because the European Society of Gastroenterology, Hepatology and Nutrition released the first modern guidelines for diagnosis of CD in 1990, we considered the year 1990 as a dividing year for well-defined diagnostic criteria for CD and all relevant articles published from January 1991 to March 2016 were included in this meta-analysis.[17] Studies published after January 1991, with inclusion of study population before January 1991, were excluded from this systematic review. The articles also were identified using a hand search of the references of the studies whose full texts were accessed. There were no language restrictions on the search. Abstracts that were not published as full texts were not included in the present study.

Two authors (P.S. and A.A.) performed the literature search, reviewed all the full texts, and individually decided whether the study should be included or not based on predecided inclusion and exclusion criteria. Disagreements between the 2 authors were resolved by discussion. In case of persistent disagreement, the senior author (G.K.M.) reviewed the study and made the final decision.

Seroprevalence of Celiac Disease

For the present study, seroprevalence of CD in the population was considered as subjects having a positive anti–tissue transglutaminase (tTG) antibody (Ab) and/or anti-endomysial antibodies (AEAs). Because antigliadin antibody (AGA) is no longer recommended in the diagnostic algorithm of CD, studies reporting AGA alone were not considered for the estimation of seroprevalence of CD in the present systematic review.[3]

Diagnosis of Celiac Disease

CD was diagnosed if any of the following criteria were present: a combination of at least 1 positive celiac-specific serologic test such as anti-tTG Ab, AEA, or AGA, and demonstration of histologic changes of modified Marsh grade 2 or more on the small intestinal biopsies; and in the absence of data on celiac-specific serology, a combination of the presence of histologic changes of modified Marsh grade 2 or more on small intestinal biopsies and demonstration of clinical and/or histologic improvement after initiation of a gluten-free diet.[3]

Inclusion Criteria

All of the studies reporting the prevalence of CD in the general population were screened. Studies were included if they reported anti-tTG Ab or AEA as the initial screening test. Studies in which individuals did not undergo a biopsy after positive serology were included to calculate the pooled seroprevalence of CD but not for the pooled prevalence of CD.

Exclusion Criteria

The exclusion criteria included the following: (1) studies in which only high-risk subjects such as those with type 1 diabetes mellitus underwent testing; (2) studies documenting the prevalence based on self-reporting, database, or hospital registries; (3) if multiple studies were performed on the same stored sera, only the latest study was included; and (4) studies using AGA as the first-line or the sole screening test were excluded because AGA is no longer recommended as a sole screening test for CD.[3] However, if AGA was used in combination with either anti-tTG Ab or AEA on all the individuals enrolled in a study, then these studies were included.

Risk of Bias Estimation

The risk of bias was calculated using the risk of bias tool for prevalence studies developed by Hoy et al.[18] Based on this tool, studies were assessed for external and internal validity using a 10-point checklist and