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The New Epidemiology of Celiac Disease

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ABSTRACT

The prevalence of celiac disease (CD) varies greatly, but several reports have shown that CD is increasing in frequency in different geographic areas. The increase in prevalence can be partially attributed to the improvement in diagnostic techniques and disease awareness; however the equally well documented rise in incidence in the last 30–40 years cannot be so easily explained. The new epidemiology of CD is now characterized by an increase of new cases in the historical CD areas (northern Europe and the United States) and more interestingly in a spread of the disease in new regions (Asian countries). A significant change in diet habits, particularly in gluten consumption as well as in infant feeding patterns are probably the main factors that can account for these new trends in CD epidemiology.

Celiac disease (CD) occurs in a genetically susceptible host that is exposed to the necessary environmental factor—dietary gluten. Historically, CD was first described in areas where gluten containing grains were staple food. Over time, an increasing

incidence of CD has been observed in areas that were previously considered CD-free due to global changes in the diet, mostly related to higher consumption of wheat-based products (eg, pasta, pizza).

In Western countries several recent studies evaluated the overall prevalence of CD in the general population, usually by counting the number of clinically diagnosed CD patients plus those detected by serological screening of a population sample. In Europe and the United States, the mean frequency of CD in the general population is approximately 1% (1,2), with some regional differences, the reasons for which remain elusive. The prevalence of CD is as high as 2% to 3% in Finland and Sweden, whereas it is only 0.2% in Germany, although these areas share a similar distribution of causal factors (level of gluten intake and frequency of HLA-DQ2 and -DQ8) (1,3). Although the incidence of clinically diagnosed CD cases is increasing, still the larger part of the “celiac iceberg” remains undetected, with a ratio of 1:3 to 1:5 between diagnosed and undiagnosed cases (1,3). A 6.4-fold increase in incidence has been recently described in Scotland from 1990 to 2009 and particularly classical cases of CD are increasing, indicating a true rise in the incidence of pediatric CD (4).

In Western countries the overall prevalence of CD is on the rise as well. A recent US study showed that CD prevalence was only 0.2% in the year 1975, and increased 5-fold during the following 25 years (5). The reasons for these changes are unclear, but have to do with the environmental components of CD (changes in the quantity and quality of ingested gluten, infant feeding patterns, the spectrum of intestinal infections, gut microbiota colonization, etc). Variation in the pattern of infant nutrition could influence the prevalence of CD at the population level, as suggested by the analysis of an epidemic of early-onset CD observed in Sweden during the 1980–1990s. The Swedish data indicated that the disease risk was substantially lower in infants introducing small amount of gluten when still breast-fed (3). The protective role of breastfeeding has been supported by other observational, retrospective studies and summarized in a meta-analysis (6). As far as weaning, an increased risk of CD has been reported in infants introducing gluten-containing food either before the age of 4 months or after 6 months, supporting the view of the “window” period of facilitated tolerance (4–6 months) (7). These observations have recently been challenged by a large epidemiological survey performed in Norway (8). The major results of this study performed on a large population sample (324 CD cases and 81,843 cohort controls), were somewhat shocking: (a) breast-feeding did not exert any protection against development of CD. Instead, mean duration of breast-feeding had been significantly longer in CD children (10.4 months) than controls (9.9 months) and the disease risk was significantly higher in infants breast-fed for more than 12 months; (b) gluten introduction under continued breast-feeding was not protective; (c) in the adjusted analysis, only delayed (>6 months) but not early (<4 months) introduction of gluten was associated with an increased risk of CD8. The major limitation of the Norwegian study was that only children with clinically diagnosed CD were included in the analysis; therefore, any correlate (or lack of correlate) found in this study group does not necessarily apply to the overall celiac population (that is at least 3-fold larger). Another problem with this (and previous) case-control studies is the lack of an intervention arm. This situation will be clarified soon by 2 intervention, randomized, multicentre studies ongoing in Europe, both focused on large cohorts of at-family-risk infants prospectively studied since birth (9,10).

Apart from Europe and North America, the epidemiology of CD has been investigated in many other countries mostly populated by individuals of European origin (Fig. 1). The disease epidemiology reported from these areas largely overlaps with European and American data (11). CD is a common disorder in north Africa and

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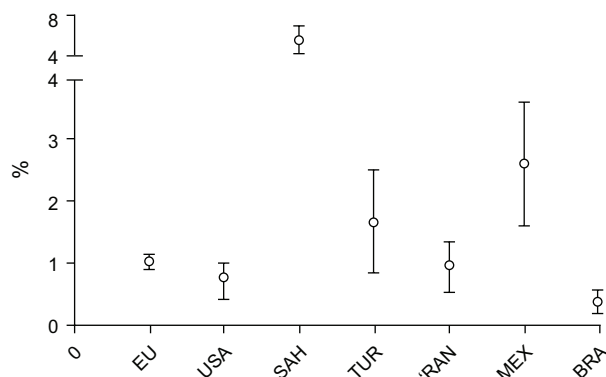


FIGURE 1. Mean prevalence of CD (95% CI) in different countries. BRA = Brasil; EU = Europe; MEX = Mexico; SAH = Sarahawis; TUR = Turkey; USA = United States.

Middle East countries as well; however the diagnostic rate is still very low in these countries, mostly due to low availability of diagnostic facilities and poor disease awareness. In the Saharawis, an Arab population living in the western Sahara, the prevalence of CD in the general population is exceptionally high (5.6%) for reasons that are currently unclear. There are only anecdotal reports of CD in Sub-Saharan African countries.

In a recent study co-authored by David Branski, a serologic CD screening was performed in a representative sample of a young adult general population in Israel (12). The prevalence of overt CD diagnosed before recruitment was 0.12% (0.1% in men and 0.14% in women). The overall prevalence based on positive serology was 1.1%. Six of 9 subjects with positive serology underwent endoscopy, showing histological changes compatible with CD. The ratio of overt to silent CD was 1:8. These findings suggested that CD is highly prevalent in the young adult population in Israel.

The knowledge of the epidemiology of CD in the Asia Pacific region is still limited and mostly confined to India, where CD is being more frequently recognized, both in children and adults. However, as efficiently described by an Indian task force, CD in India is “submerged in an ocean of malnutrition.” The frequency of CD in India seems to be higher in the northern part of the country, so called “celiac belt,” a finding that is at least partially explained by the wheat-rice shift from the north to the south. The prevalence of CD amongst apparently healthy blood donors ($n = 1610$) was 1:179 (0.56%) (13), a finding that overlaps with data from Western countries. In a large population sample ($n = 2879$) Makharia and coworkers found CD prevalence to be 1.04% (1 in 96) and the prevalence of positive serological test (anti-transglutaminase antibodies) to be 1.44% (1 in 69) (13). Based on these data, it is estimated that 5 to 8 million people are expected to have CD in India. Of such a large pool of patients, only a few thousand patients have been diagnosed so far. If there is a real difference in the prevalence of CD in northern and southern parts of India, India may prove to be a model to understand the interplay between genetics and environmental causes of CD.

With >1.3 billion people, China is the most populous nation and the second largest by land area in the world. Both CD-causing factors—gluten consumption (particularly in the northern part of the country) and HLA-predisposing genotypes DQ2 and DQ8 (even though with a lower prevalence than in Western countries)—are largely diffused in China. In the current literature a total of 18 cases of biopsy proven CD were described in Chinese patients (14). CD is

also on the map in China; however, epidemiological studies are needed to quantify the impact of this condition in this country. Finally, CD is likely to be rare in Japan, Indonesia, Korea, the Philippines and many smaller Pacific islands because of low wheat consumption and a low frequency of HLA-DQ2.

As concern policies of disease detection, the debate on mass screening versus case finding is still open. Currently, mass screening for CD is not performed in any country, with the noteworthy exception of the small S. Marino Republic in Europe (31,534 inhabitants in 2012) (15). The major limitations of mass serological screening are (1) difficulty in establishing the proper screening age, due to variability in the natural history of gluten sensitization, and (2) ethical issues in treating subjects with clinically silent CD, due to incomplete knowledge of the complications risk. Conversely, the efficacy of the celiac case finding (serological testing of at-risk individuals) is poor, with more than 50% cases remaining undiagnosed. It is however undisputable that groups with a higher disease frequency (eg, first-degree relatives of patients with CD, subjects with other autoimmune conditions, patients with symptoms suggesting CD as iron deficiency, osteopenia and irritable bowel syndrome) should be regularly tested for CD. In this context, it will be important to evaluate the efficiency of new screening strategies, based on the rapid determination, on a drop of whole blood, of serum CD autoantibodies (IgA anti-tTG) or HLA predisposing genes.

In summary, available data suggest that CD incidence is truly increasing and that the disease is currently much more common in some areas than previously appreciated. Further epidemiological studies aiming at clarifying the role of infant feeding in CD development and to measure the prevalence of CD as well as the relevant parameters (level of gluten intake, frequency and pattern of CD-predisposing genotypes) in new geographic areas will play an instrumental role for increasing the awareness of CD and, consequently, the detection rate of this chameleonic disorder. These studies will also be instrumental to explain the dynamic of gene-environment interaction driving the current CD epidemic worldwide.

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Celiac Disease and Autoimmunity

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ABSTRACT

Celiac disease (CD) has a multifactorial etiology with complex genetics and frequently occurs in association with other autoimmune disorders. Even though triggered by a dietary antigen, it shows many autoimmune features, the most peculiar being the presence of high titers of anti-tissue transglutaminase 2 autoantibodies, produced in the small intestinal mucosa since the early stages of the disease. More than 60% of CD-associated susceptibility loci are shared with at least another autoimmune condition, suggesting common pathogenic mechanisms. In particular, recognition of peptides by HLA molecules, posttranslational modifications required for optimal peptide binding and immune mechanisms leading to tissue damage have been found in CD as well as in other autoimmune diseases. This review briefly summarizes the main autoimmune features of CD, underlining the similarities with other autoimmune disorders, in particular with type 1 diabetes mellitus. Furthermore, the role of gluten and microbiome in driving autoimmunity is discussed.

Key Words: anti-tissue transglutaminase, celiac disease, gluten, type 1 diabetes

Increasing evidence supports the categorization of celiac disease (CD) as an autoimmune disorder. The association of CD with other autoimmune diseases is striking: type 1 diabetes mellitus, autoimmune thyroiditis, Sjogren syndrome, connective tissue diseases occur more frequently in patients with CD than in the general

population. Similarly to many autoimmune disorders, CD shows a gender bias with a female to male ratio of about 2:1. Furthermore, multiple autoimmune phenomena are observed in CD, the most characteristic of which is the presence of high titers of autoantibodies against tissue transglutaminase 2 (TG2) in patient sera. TG2-specific immunoglobulin A (IgA) are primarily used for diagnosis, with sensitivity and specificity close to 100%. Even in patients who show negative serum TG2-specific antibodies, it seems that such antibodies are still produced locally, as suggested by the presence of deposits in the small intestine (1). In fact, it has been shown that in the small intestinal mucosa of untreated patients with CD around 10% of plasma cells are TG2-specific cells (2). Antibodies from different patients target the same conformational TG2 epitope formed by spatially close amino acids of adjacent domains (3). Monoclonal antibodies from single plasma cells have a restricted usage of variable heavy and variable light chains segments (2). CD associated anti-TG2 antibodies have limited inhibitory activity (2) and their role in CD pathogenesis is still unclear. TG2 is a multifunctional enzyme that has been involved in a variety of physiological functions, including matrix assembly and tissue repair, receptor signaling, proliferation, cell motility, and endocytosis. A role of TG2 in CD beyond its established function in deamidation and presentation of gluten peptides to the adaptive immune system is thus suspected, although not clearly delineated. In vitro studies have suggested that TG2 IgA autoantibodies might modulate enterocyte differentiation and proliferation (4); they also inhibit angiogenesis *ex vivo* and *in vivo* and impair vascular functionality (5). IgA against extracellular forms of TG2 present in the liver, muscle and lymph nodes, have been detected in patients with CD, indicating that this TG2 is accessible to the gut-derived autoantibodies also in those locations. Moreover, anti-TG3 or -TG6 rather than -TG2 autoantibodies are present in dermatitis herpetiformis and in neurological manifestation of gluten sensitivity, respectively, suggesting that the heterogeneity of disease manifestations may reside in the specificity of the autoimmune response. The mechanisms leading to their production in CD are not completely known. The upregulation and activation of TG2 observed in inflamed sites may generate additional antigenic epitopes, by cross-linking or deamidating external or endogenous proteins. Unmasking of normally hidden epitopes in an inflamed environment, with more efficient antigen processing and presentation, has also been hypothesized as an important mechanism resulting in autoimmunity. The most accepted hypothesis to explain the observed dependence on the presence of dietary gluten for the production of anti-TG2 autoantibodies is that gluten-reactive CD4 T cells provide the required help to TG2-specific B cells in a hapten carrier-like manner by involvement of TG2-gluten complexes (6). Of note, anti-TG2 are not the only autoantibodies present in patients with CD, indeed antibodies to actin and calreticulin have also been detected in the sera of patients with CD. Recent efforts to dissect the autoantibody response in CD integrating genomic and proteomic technologies and performing high-throughput large-scale screening have led to the identification of 13 new CD-associated autoantigens (7).

CELIAC DISEASE AND TYPE 1 DIABETES MELLITUS SHARE GENES AND MECHANISMS

Similar to other autoimmune diseases, CD is a polygenic disorder with genes coding for the HLA class II molecules (DQ2.5 and DQ8) playing a major role. Interestingly, HLA-DQ2-DQ8 heterozygous show high risk for type 1 diabetes mellitus (T1D) development and in fact HLA-DQ8 transdimer has been shown to bind efficiently both gliadin peptides and peptides derived from GAD65 and IA-2 (8). The mechanisms governing the recognition of

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