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## Celiac disease in the developing countries: A new and challenging public health problem

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### Abstract

In the past, celiac disease was believed to be a chronic enteropathy, almost exclusively affecting people of European origin. The availability of new, simple, very sensitive and specific serological tests (anti-gliadin, anti-endomysium and anti-transglutaminase antibody assays) have shown that celiac disease is common not only in Europe and in people of European ancestry but also in the developing countries where the major staple diet is wheat (Southern Asia, the Middle East, North West and East Africa, South America), both in the general population and in the groups at risk. Gluten intolerance thus appears to be a widespread public health problem and an increased level of awareness and clinical suspicion are needed in the New World where physicians must learn to recognize the variable clinical presentations (classical, atypical and silent forms) of celiac disease. In the developing countries, both serological screening in the general population and serological testing in groups at risk are necessary for an early identification of celiac patients. The gluten-free diet poses a challenging public health problem in the developing countries, especially since commercial gluten-free products are not available.

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### HISTORY AND ORIGIN OF CELIAC DISEASE

Celiac disease (CD) is a permanent inflammatory disease of the small intestine triggered by the ingestion of gluten-containing cereals in genetically predisposed individuals. It was first described in the second century AD by Aretaeus of Cappadocia<sup>[1]</sup>, a contemporary of the Roman physician Galen, who used the Greek word “*koeliakos*”, which means “*suffering of the bowels*”. However, only in 1888 AD did Samuel Gee of St. Bartholomew’s Hospital<sup>[2]</sup> give the classical clinical description of CD. No real progress in treating the disease was made until the 1930s-1950s, when WK Dicke, a Dutch pediatrician, showed that the health of celiac children dramatically improved when wheat, rye and barley, which were unavailable during the 2<sup>nd</sup> World War, were removed from their staple diet, only to relapse at the end of the war when the consumption of wheat flour started afresh in the Netherlands<sup>[3]</sup>.

CD is the result of both environmental (gluten) and genetic factors (HLA and non-HLA genes), and the distribution of these two components can probably be used to identify the areas of the world at risk for gluten intolerance. In this respect, the world geographical distribution of CD seems to have followed the spread of wheat consumption and the migratory flows of mankind. Indeed, man was not originally a gluten eater, but led a nomadic life obtaining food by hunting, fishing and collecting fruit as well as vegetables, and for hundreds of thousands of years never had any contact with gluten-containing cereals. Only about 10000 years ago in a small region of South Western Asia, called the “*Fertile Crescent*” including Anatolia (Southern Turkey), Lebanon, Syria, Palestine and Iraq, were wild grains (wheat or *Triticum Dicoccoides* and barley or *Hordeum Spontaneum*) cultivated, due to the special environmental conditions created by the flooding of the Tigris and Euphrates<sup>[4]</sup>. In the *Fertile Crescent* some tribes changed from a nomadic lifestyle to one of stable settlement because land cultivation permitted food storage, and they later migrated westwards because new lands for cultivation were needed. They spread through the Mediterranean area (Northern Africa, Southern Europe) and the Danube valley (Central Europe) and their expansion continued from 9000 to 4000 BC by

which time the cultivation of wheat and barley had spread all over the Old Continent, also reaching Northern Europe (Ireland, Denmark and the Scandinavian countries). However, this expansion in farming was not limited to the diffusion of agricultural practices, but was also a “*demic*” expansion, because the peoples coming from South West Asia replaced the local inhabitants. Hence, the European and North-African populations share a genetic background with the peoples of South West Asian origin (Middle-East), including also DR3-DQ2 and DR4-DQ8, the CD-predisposing haplotypes<sup>[4]</sup>.

## THE “NEW EPIDEMIOLOGY” OF CELIAC DISEASE

Until a few years ago, gluten intolerance was thought to be a disorder almost exclusively affecting Europeans or people of European origin (North Americans and Caucasian Australians) and the phenotype blue eyes and blond hair was described as typical of celiac patients. In this respect, serological screening in the general, unselected populations of the Western world, North America and Australia clearly demonstrated that the prevalence of gluten intolerance in these areas of the world likely ranges from 0.5%-1%, that is from 1:200 to 1:100 (Table 1).

On the other hand, until recent years CD had been observed only in sporadic cases among native African immigrants in Europe<sup>[9-11]</sup>, in a few African-Americans serologically screened for CD in the United States<sup>[12,13]</sup>, and in one black patient of South Africa<sup>[14]</sup>. Similarly, until a few years ago, there were only limited case studies and occasional observations of CD in Latin America<sup>[15-18]</sup>, in North Africa<sup>[19-21]</sup> and in the Middle East<sup>[22-25]</sup>, where gluten intolerance was believed to be rare. In addition, CD has been historically<sup>[26]</sup> considered absent in the Far East (China, Japan, Korea, Malaysia, etc.).

In contrast, recent large screening studies performed by means of simple, sensitive and specific tests (anti-gliadin, anti-endomysium and anti-tissue-transglutaminase antibodies assays) on the general population and at-risk groups in those developing areas of the world where there is a large consumption of wheat, showed that the prevalence of gluten intolerance had been underestimated and that it is, instead, similar to that of the so-called Western countries.

In African populations, specifically in the Maghreb area (the Northern Region of Africa including Morocco, Algeria, Tunisia, Libya and Egypt) very high incidences of CD have recently been reported both in the general population<sup>[27-30]</sup> and in at risk-groups<sup>[31,32]</sup>. In this respect, the highest world frequency in the CD-Insulin Dependent Diabetes Mellitus (IDDM) association (19 biopsy-proven CD cases among 116 IDDM patients, 16.4%) has been observed<sup>[33]</sup> in Oran (Algeria), and a recent serological screening in 2500 Tunisian healthy blood donors<sup>[29]</sup> showed that the prevalence of anti-endomysium antibodies in the general population is 1:355, which is close to that of Europeans. These high frequencies are not surprising because wheat and barley are the major staple foods in the Maghreb countries<sup>[29]</sup>, and because there is a high

**Table 1** Prevalence of CD in Europeans and people of European ancestry based on unselected population serological screenings<sup>[5-8]</sup>

Europe	
Czechoslovakia	1:218
Estonia	1:88
Finland	1:99
Hungary	1:85
Ireland	1:122
Italy	1:106
Norway	1:262
Portugal	1:134
Spain	1:118
Sweden	1:190
Switzerland	1:132
Netherlands	1:198
United Kingdom	1:100
United States	1:133
Australia	1:251

frequency of the DR3-DQ2 CD predisposing haplotypes in these populations<sup>[34-36]</sup>.

Another population in North Africa with an elevated prevalence of CD (5.6%), which is the highest known in the world today<sup>[27,35]</sup>, is the Saharawi people, who are of Arab and Berber origin, who have a high degree of consanguinity, and who live as refugees in Algeria (Sahara Desert). This elevated prevalence may be explained both by genetic factors, as the Saharawi population has a very high frequency of the DR3-DQ2 haplotype<sup>[36]</sup>, and by environmental factors, because in the last few decades they have changed their dietary habits. For example, the rates and duration of breast-feeding have been reduced and large amounts of gluten are now being consumed in early life as part of the staple diet, due to the humanitarian aids supplied by Western countries<sup>[37]</sup>. However, other genetic and environmental factors probably play an important role in explaining such a high frequency of CD in the Saharawi people, because gluten-containing foods are also the staple diet in Sardinia and similar frequencies of DR3-DQ2 have been observed in the Sardinian population, but here there is a much lower prevalence of CD<sup>[38]</sup>.

In Southern Asia there are still no data available on CD prevalence in the general and unselected populations. Therefore, because in past decades reports of gluten intolerance were sporadic, CD was believed to be very rare in this area of the world<sup>[39-41]</sup>. In contrast, several recent studies suggest that gluten intolerance is also common in South Asia. For example, CD has been diagnosed in 26% to 49% of Indian children presenting with chronic diarrhea at tertiary care hospitals<sup>[42,43]</sup>, and during the last few years a large number of CD patients have been observed in many case studies in the Indian Subcontinent, especially in Northern India<sup>[44-51]</sup>. In addition, during these years some studies<sup>[52-57]</sup> reported CD in South Asian patients who had immigrated to Europe or North America. In this respect, a recent Italian multi-center study<sup>[5]</sup> on immigrant children with CD showed that 3 were native to Pakistan and 1 to Sri-Lanka (formerly Ceylon, to the south of India), while in previous studies<sup>[54,55]</sup> respectively 10 and 13 CD children of Punjabi descent were reported in the UK. Interestingly,

**Table 2** Prevalence of unrecognized (silent/subclinical) celiac disease among the “healthy” general population in the Middle East (serological screenings)<sup>[61-66]</sup>

Populations	Prevalence (%)	References
Turkish school children	1:115 (0.87)	61
Iranian blood donors	1:166 (0.60)	62
Iranian children	1:165 (0.61)	63
Israeli blood donors	1:157 (0.63)	64
Turkish blood donors	1:87 (1.15)	65
Anatolian adults	1:100 (1)	66

**Table 3** Prevalence of silent/subclinical forms of celiac disease among groups at risk in the Middle-East (serological screenings)<sup>[63-80]</sup>

Disease groups and countries	Prevalence (%)	References
Chronic diarrhea		
Iran (children)	6.5	63
Kuwait (children)	18.5	67
Iraq (adults)	20	68
Iran (children)	20	69
Inflammatory bowel disease	7.8	70
Iran (adults)		
Autoimmune hepatitis		
Iran (adults)	3.6	71
Down's syndrome		
Turkey (children)	1	72
Irritable bowel syndrome		
Iran (adults)	11.4	73
Short stature		
Saudi Arabia (children)	9.5	74
Turkey (children)	55.3	75
Type 1 diabetes mellitus		
Saudi Arabia (children)	10	76
Israel (children)	8.3	77
Turkey (adults)	2.4	78
Iran (adults + children)	2.4	79
Saudi Arabia (children)	8.1	80

in the Punjab (Northern India), gluten intolerance is called “*summer diarrhea*” and in summer the “*chapattis*”, which are the typical staple food, are made of wheat while in the winter maize flour is used. However, the people living in South Asia have the CD-predisposing HLA genes because they are Aryan in origin<sup>[58,59]</sup> and their staple diet is rich in wheat-derived foodstuffs<sup>[50,60]</sup>. These data clearly support the hypothesis that celiac disease is widespread in South Asia, but likely under-diagnosed. Therefore, both greater attention and awareness among physicians as well as mass serological screenings in the general populations are needed to establish the real prevalence of CD in these countries.

During the last few years many studies have shown that CD is very common in Middle Eastern countries, with a prevalence similar to and even higher than in the Western countries, both in the general population and in the at-risk groups. This discovery can be attributed to the use of serological tests (anti-gliadin, anti-endomysium and anti-transglutaminase antibodies assays) as screening tools in the “*healthy*” general populations, which have permitted the diagnosis of many silent and subclinical CD cases that otherwise would not have been recognized (Table 2).

Similarly, gluten intolerance has a high prevalence in the Middle East among individuals at risk for CD who often suffer from silent/subclinical forms of celiac disease and have been recognized by means of serological screening tests (Table 3). These data on the new epidemiology of CD among Middle Eastern people do not appear surprising because these populations live in countries included in the “*Fertile Crescent*”, the region where CD originated<sup>[4]</sup> and where there is both a large consumption of wheat<sup>[81,82]</sup> and a high frequency of the HLA CD predisposing genes<sup>[83,84]</sup>.

CD is also a common disorder in Latin America, both in the more developed (e.g. Brazil and Argentina) and in the less developed (e.g. Cuba, Chile, Uruguay) countries. This phenomenon is noteworthy because a large proportion of Latin American people share common European ancestry and because wheat is commonly present in their staple diet. A high prevalence (1:167; 0.60%) of undiagnosed CD cases has been recently observed following serological screening among the general population in Argentina<sup>[85]</sup>, in Uruguayan children (1:51; 1.96%)<sup>[86]</sup> and in 2 studies<sup>[87,88]</sup> on *healthy* Brazilian blood donors, 1:276 (0.36%) and 1:292 (0.34%) respectively. These rates are higher than those of the first serological screening performed on a general population<sup>[89]</sup> in Latin America (i.e. Brazil), where the observed prevalence of undiagnosed subclinical CD patients was 1:681 (0.15%). However, this lower prevalence might be due to the fact that most of the studied subjects were men (while CD is more frequent in women), that anemic subjects were excluded from the screening in the study design (iron-deficiency anemia is a very common atypical form of CD), and that a single serological test (IgG anti-gliadin antibodies assay) was used as a first-level screening test.

In Latin America there is also a high prevalence of gluten intolerance among the groups at risk. In Cuba, undiagnosed CD prevalence among children with type-1 diabetes mellitus, with Down's syndrome<sup>[90]</sup> and among undernourished children<sup>[91]</sup> was respectively 2.5%, 2.3% and 2%. Similarly, in Brazilian children and adolescents with type-1 diabetes mellitus<sup>[92]</sup> or with Down's syndrome<sup>[93]</sup>, the prevalence of undiagnosed and subclinical forms of CD was 4.8% and 5.6%, while the rate of silent cases of gluten intolerance among first degree relatives of celiac patients was 13.66%<sup>[94]</sup>. Overall, these data on the general population and on groups at risk clearly indicate that the epidemiology of gluten intolerance in Latin America is comparable to that of European and North American Caucasian populations.

## CELIAC DISEASE AWARENESS AND DIETARY HABITS

On the basis of the above-mentioned studies performed in developing countries, it might seem that CD is increasing worldwide and is a new “*endemic disease*”. However, this is not accurate because CD was probably widespread in the developing countries where wheat was consumed, but was undiagnosed because physicians had no knowledge of its different clinical presentations (especially delayed/atypical and subclinical forms). Indeed, only some CD patients present the classical symptoms, while many of

them are oligo-symptomatic, usually displaying very mild complaints or with silent forms of celiac disease (the so-called *celiac iceberg*). Thus, the reported low frequencies of gluten intolerance in the developing countries were likely the result of low levels of awareness and clinical suspicion among physicians, which led to cases going unrecognized or to a delayed diagnosis. For example, a recent study<sup>[73]</sup> in Israel revealed that 12% of adult patients diagnosed with irritable bowel disease and serologically screened for CD had gluten intolerance, while in India<sup>[50,95]</sup>, the Middle East<sup>[96]</sup>, North Africa<sup>[97]</sup> and Latin America<sup>[85,98]</sup> the majority of the Indian, Arab, African and Latin-American CD patients presented atypical complaints, such as short stature, failure to thrive and refractory anemia, which are the result of delayed diagnosis.

However, some environmental factors, such as the traditional practices of prolonged breast feeding and late weaning in the developing countries, might be responsible for the milder symptoms and higher age at CD diagnosis. Indeed, these dietary habits have a protective effect on gluten intolerance leading to a later CD onset with atypical and milder symptoms, which are more difficult to diagnose<sup>[99]</sup>. Moreover, the failure to recognize the early and mild Marsh features in intestinal biopsy (Marsh stages 1, 2 and 3a) might frequently result in a missed CD diagnosis in the developing countries, where many very common conditions other than gluten intolerance (i.e. malnutrition, parasitic and bacterial infections of the intestine) can give rise to histological changes similar to mild celiac features<sup>[100]</sup>.

Consequently, CD must be considered a worldwide public health problem, involving all the ethnic groups in all the areas of the world where there is a great consumption of wheat. Wheat availability is quickly increasing in the developing countries, depending both on the increased diffusion of “western” cultural patterns of nutrition, which provide gluten-containing cereals (e.g. bread, pasta) and on humanitarian interventions, which include sending wheat flour from the developed to the developing countries. It is probable that if this worldwide globalization of the food market continues, in the near future a higher prevalence of CD will be observed in the developing countries. In addition, the treatment of celiac patients in these areas of the world is very difficult for several reasons<sup>[37,60,81]</sup>, such as the impossibility to use commercial gluten-free products, which are too expensive for these populations, as well as the lack of patients’ associations and of information in the mass media and the population at large. It might be better and easier to promote, as a staple diet, cereals that are naturally gluten-free and are present in the developing countries (e.g. rice and millet). However, overcoming the difficulties of treating CD in the context of a developing country should be a primary goal for the international health organizations and further efforts are needed to face CD treatment problems in the New World.

In addition, immigration from the developing to the developed countries highlights the international aspect of CD. In this respect, a multicenter epidemiological investigation was recently performed in Italy (5), which reported celiac patients among immigrant children coming from developing countries and the spread of

CD in the world as in a common “*global village*”. Indeed, this study reports CD cases among immigrant children native of Eastern Europe, Northern, West and East Africa, the Middle East and Southern Asia, according to their acquisition of western dietary practices (i.e. short period or lack of breast feeding and early weaning with a great amount of gluten intake). Interestingly, CD was not observed in immigrant children from the Far East in this study, and this result was been related to the absence of CD in this area of the world<sup>[26]</sup>. Nevertheless, even if gluten intolerance is very rare or absent in the Far East, recently<sup>[54]</sup> three CD cases were observed in Canada among descendents of Japanese and Chinese immigrants. This finding suggests that genetic susceptibility to CD also exists among people of the Far East, where it might be underestimated, and raises important questions; that is, is the lack of CD in this area of the world due to the dietary habits of these populations (more rice than wheat in the staple diet)? Is gluten intolerance really rare or absent in the Far East because the CD predisposing (HLA and non-HLA) genes are uncommon in these people? Do their physicians not look for, diagnose and recognize CD because they have a low level of awareness and suspicion of gluten intolerance? These concerns are very important issues that require further studies, in particular serological screening in general, unselected populations and investigation for the HLA and non-HLA CD predisposing genes in the developing countries of the Far East (e.g. China, Korea, Malaysia, the Philippines).

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## CONCLUSIONS

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New recent epidemiological data show that CD is a common disease in the world, affecting not only Europeans and people of European ancestry, but also populations of the developing countries (Middle East, South Asia, Africa, South America), where its prevalence is similar to that of Western countries.

The origin and incidence of CD are related not only to genetic factors, and consequently to the migrations of mankind, but also to wheat consumption. Therefore, because use of wheat and other gluten-containing cereals is spreading all over the world, CD appears to be a widespread public health problem, involving also the populations of developing countries. Consequently, an increased level of awareness and attention towards gluten intolerance is also needed in the New World where physicians must learn to recognize the variable clinical (classical, atypical, silent forms) and histological (Marsh stages) presentations of the disease. Moreover, in the developing countries both serological screening in the general population and serological testing among at-risk groups are also necessary for an early identification of CD cases. However, treatment of celiac patients is difficult in the developing countries, where a gluten-free diet represents a real challenge both for patients and for physicians, mainly because gluten-free products are not commercially available. Therefore, further efforts are needed to define the most suitable therapeutic strategies to face celiac disease in the developing countries.

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