# A review on epidemiological features of celiac disease

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## Abstract

Many of the varying manifestations of celiac disease can occur without the enteric involvement, thus medical specialties should be familiar with the ways of diagnosing and treating the disease. The resolution to the problem of celiac disease is the gluten free diet which restores the damage of the mucosa and relieves from symptoms.

Celiac disease can appear with classical symptoms of malabsorption while it can arise with extraintestinal symptoms like fatigue, anorexia, arthralgy, osteoporosis, osteomalacia, short stature, gingival disorders, sidiropenic anemia, dermatitis herpetiformis and neurological disorders.

During the last decade, sensitive and specific methods have been developed for the identification of specific antibodies at the serum of patients with celiac disease which had a tremendous impact on clinical expression, epidemiology and diagnostic approach of the disease. Nonetheless biopsy of small intestine remains the gold standard for the diagnosis of celiac disease.

It is interesting to say that while once celiac disease was considered to be a rare disease, recent studies have shown that the prevalence reached 1/250 of the general population or 0.5% to 1.0% percent in Europe.

Taken this into consideration, it is clear that celiac disease is a disease whose prevalence is continuously revised with a raising tendency.

**Keywords:** celiac disease, epidemiologic features, Greece.

## Introduction

It took almost two thousand years for the discovery that a common protein, which was induced relatively late in the evolutionary course (about 10,000 years ago), can cause a disease that involves not only the gastrointestinal tract but also other systems. Many of the varying manifestations of celiac disease can occur without the enteric involvement thus physicians of other specialties should be familiar with the basic qualities and the ways of diagnosing the disease.

The first reference (1) was at the book of chronic diseases of Aretaeus the Cappadocian, one of the most distinguished physicians in ancient Greece of the 1st century A.D. The chapter entitled «on the coeliac diathesis» was the first description of celiac disease (from the greek word *'κοιλιακή'* meaning abdominal). The books of Aretaeus were first translated in Latin on 1500 A.D. and the new word 'coeliac' was used for the translation of the word 'κοιλιακή'. Celiac disease remained unclear until 1887 Samuel Gee gave a lecture titled 'On the celiac affection' (2) at the Hospital for Sick Children, Great Ormond Street, in London. At this lecture he recognized the contribution of Aretaeus and moved on to give an accurate description of celiac disease based on his clinical observations.

With clinical manifestations mostly restricted to the gastrointestinal tract or attributed to malabsorption, the assumption that the target organ and the key of pathogenesis was the enteric system was sensible. The cure of celiac disease was empiric till 1940-50 when the Dutch pediatrician William Dicke (3) recorded the harmful influence of wheat in children with celiac disease. Withdrawal of the dietary products that contained wheat resulted to complete remission of the gastrointestinal symptoms and reversion to healthy status. The induction of small intestine biopsy at 1950-60 verified the gastrointestinal tract as a target organ. The characteristic features of villi atrophy, crypt hyperplasia and raise of intraepithelial lymphocytes with improvement after the induction of gluten free diet, became the main points in diagnosing celiac disease. In 1961 Taylor (4) published an immunological study of celiac disease. In this study he commented: '... a limitation in accepting the immunological theory as etiology was the lack of satisfactory presentation of antibodies against the protein described'. He moved on to the presentation of the circulating antibodies against gliadin, the protein which is responsible for celiac disease. This provided more data that celiac disease was immunologically induced and the immunological response is not confined at the mucosa of the small intestine. The antigliadin antibodies became a useful tool in diagnosing celiac disease. The reliability of the reports before 1960 remains questionable as a precise diagnose of celiac disease could not be made before the induction of biopsy of the small intestine.

In 1966 Marks et al (5) presented an enteropathy in 9/12 patients with dermatitis herpetiformis, a pruritic, bullous cutaneous rash which appears at the ectatic areas of knees and elbows. The enteropathy in dermatitis herpetiformis had an important similarity with the one in celiac disease. Later it was shown that the enteropathy and the cutaneous rash were gluten-dependent but the involvement of the skin may occur even without the histological indications of enteric involvement. This was the first proof that the enteric system is not the only leader in this disease.

Since then the knowledge of celiac disease has grown and many sides were enlightened and are explored till today. Thus new clues have been added about immunological and genetic base of celiac disease, the way of diagnosis of celiac disease, the clinical presentation and its epidemiology, while many questions remain still unanswered. Below we will refer to epidemiological and laboratory data of celiac disease.

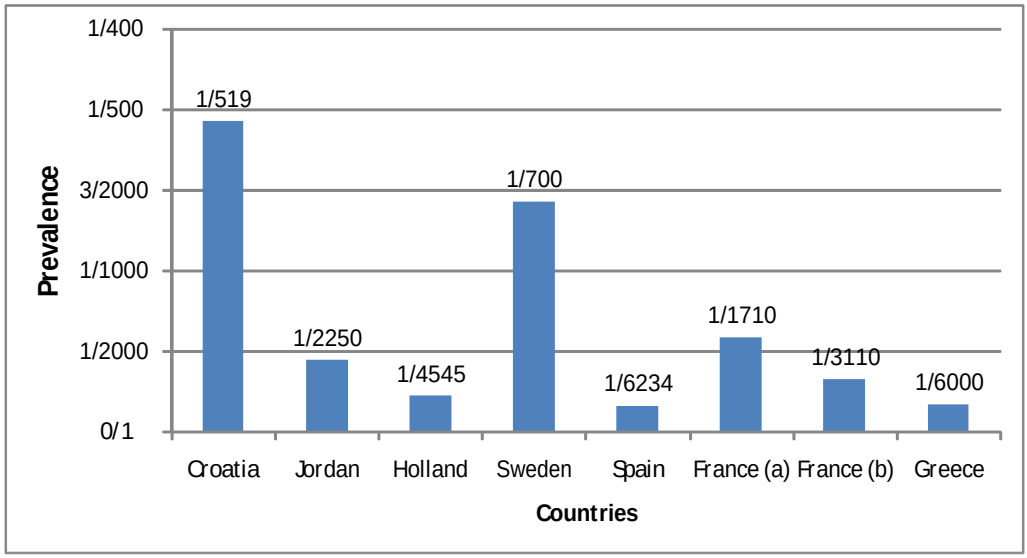
### Epidemiological picture of celiac disease

Celiac disease is an enteropathy of immunological origin in genetically predisposed people which is correlated with the consumption of gluten which is found in various cereals (wheat, rye, barley, oat)

and affects the small intestine causing villi atrophy and hyperplasia of the crypts.

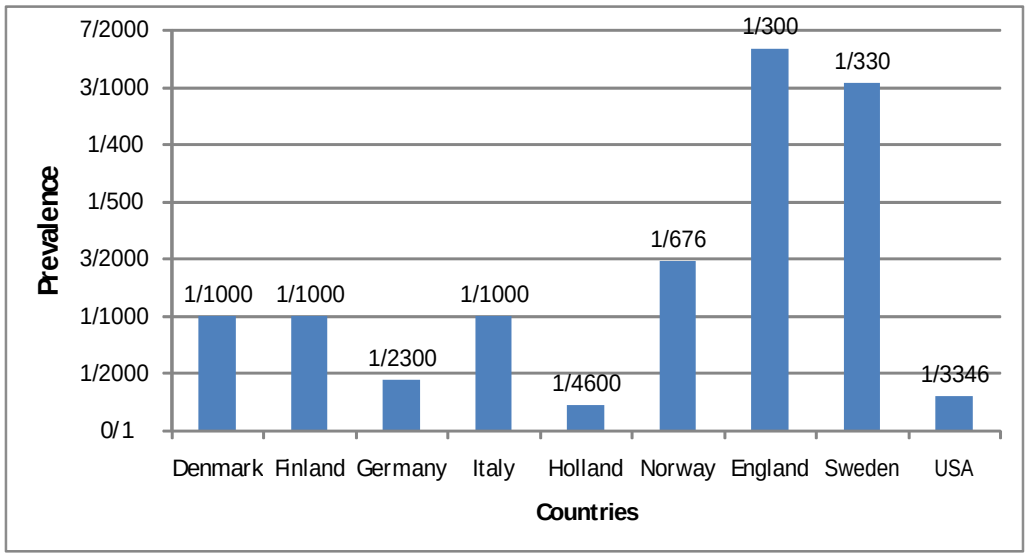
Celiac disease can appear with classical symptoms of malabsorption like steatorhea, weight loss, flatulence, growth delay or with non specific gastrïenteric complaints (abdominal pain, vomiting, diarrhea, constipation, dyspepsia) while it can arise with extraintestinal symptoms like fatigue, anorexia, arthralgy, osteoporosis, osteomalacia, short stature, gingival disorders, sidiropenic anemia, dermatitis herpetiformis, and neurological disorders (epileptic seizure, ataxia, migraine).

**Figure 1. Prevalence of celiac disease by number of births**




During the last decade, sensitive and specific methods have been developed for the identification of specific antibodies at the serum of patients with celiac disease which had a tremendous impact on clinical expression, epidemiology and diagnostic approach of the disease. Nonetheless, biopsy of small intestine remains the gold standard for the diagnosis of celiac disease. The resolution to the

**Figure 2. Prevalence of celiac disease by clinical picture**

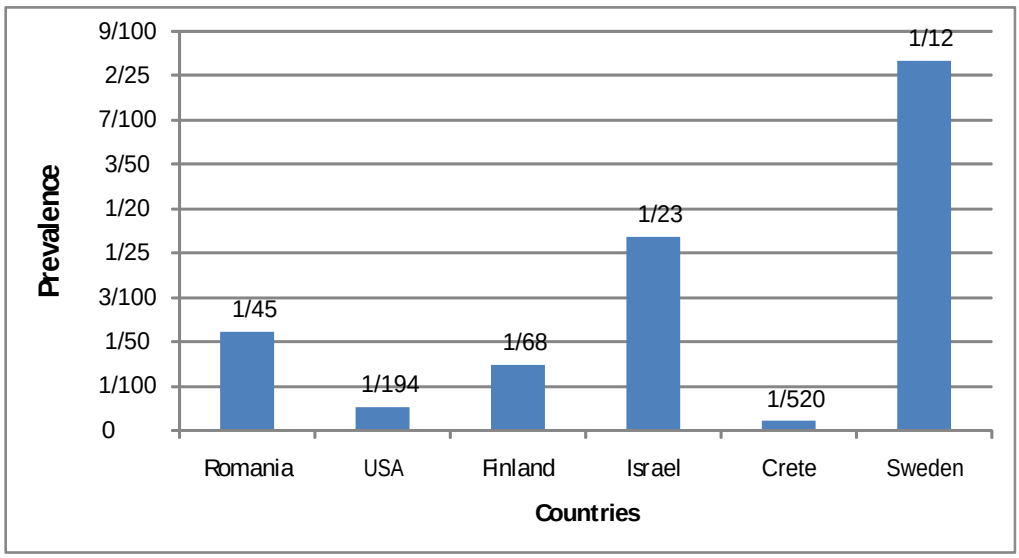


problem of celiac disease is the gluten free diet which restores the damage of the mucosa and relieves from symptoms.

Celiac disease is considered a disease of Europe and countries where Europeans have migrated, including North America and Australia. In Europe the prevalence is at least 1/1500 with figures being clearly bigger in some countries. So in Italy (6) the prevalence is near 1/250, in England (7) 1/200 while in Ireland (8) the incidence has recently been revised up to 1/122 of the population. In U.S.A (9) the incidence according to Celiac Disease Association is 1/133. We should report that in Greece (10) is considered being around 1/3000 to 1/6000 births, while the only study that was recently conducted in Greece, at the North-East area, regarding 2304 adults from general population, found that the prevalence of celiac disease was 1/558 (diagnosis was serological with subsequent histological conformation). Celiac disease has been reported also in Indians, Arabs, Sudanese, while it rarely appears in Chinese or Japanese people and the African race. Many studies have shown an incidence of 1% in different European populations like children of school age in Finland, adults and children in England. There have been reports of cases in children from Eastern Europe, North, South and Eastern Africa, Middle East and South Asia (11). The white race in South Africa has (not unexpectedly) had cases diagnosed with celiac disease, although there is a report of a patient of the black race.

The prospective for celiac disease being a big issue at the area of health in developing countries is lightened by the report of a high incidence of celiac disease at refugee children in North Africa. In this study (12), 5.6% of the children from Saudi Arabia had antibodies against endomysium, which has great specificity for celiac disease. This creates many thoughts, as in such populations the main food is cereals, in contrast to the developing countries.

**Figure 3. Prevalence of symptomatic 'atypical celiacs'**

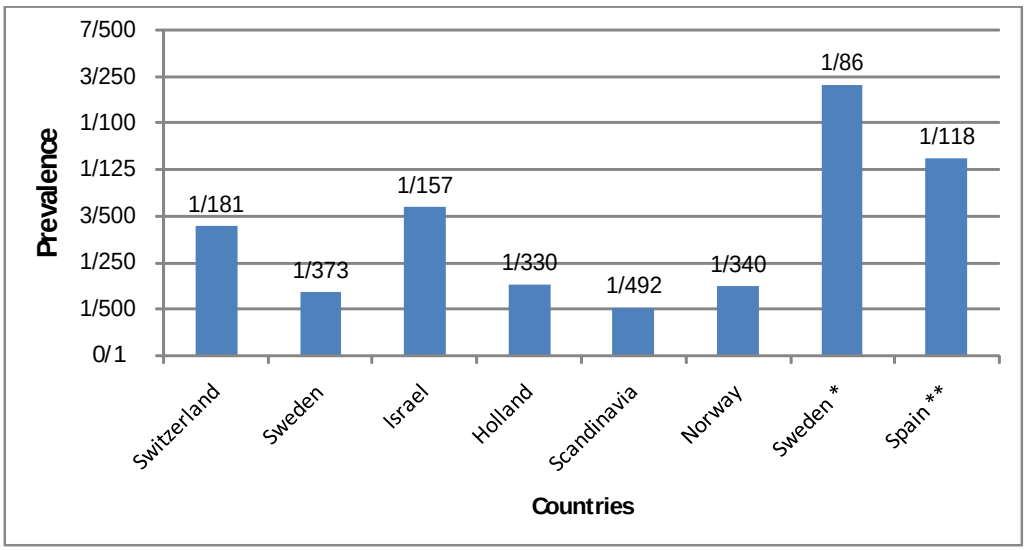



What is going on with celiac disease in America (13)? It has been reported in Brazil, Argentina, and Chile along with Indians of North America in Chile. While there are no reports from Central America, there are reports from Cuba and children of black race with origin from Western India which live in England. In South America celiac disease is considered a rare disease even though the number of diagnosed cases is increasing. Lately serological reports show a frequency that reaches the

European one. Recently some minorities have been diagnosed with celiac disease in U.S.A. finding the disease between African-Americans, people born in Cuba, in Puerto Rico, in Dominican Republic and in Asians from China and Philippines. There is a small incidence of celiac disease in minorities in U.S.A. due to lower frequency of HLA DQ2 or DQ8 and problems in accessing health services. There are no studies which specifically check for celiac disease in African-Americans, Spanish or native population in U.S.A. It is interesting that several studies in America have reported celiac disease at races other than the white race and especially in African-Americans. One recent study which was conducted in Canada described celiac disease between Asian Canadians with origin from South India, Japan and China. Also at another report from Canada celiac disease has been reported at locals to the Salish seacoast.

The use of serological methods has as a result the raise of prevalence of celiac disease in many populations from different countries around the world, including groups that traditionally were considered not having an association with celiac disease. Celiac disease is found in many cases in developing countries either in native population or in emigrants that live in them.

**Figure 4. Prevalence of silent celiac disease**



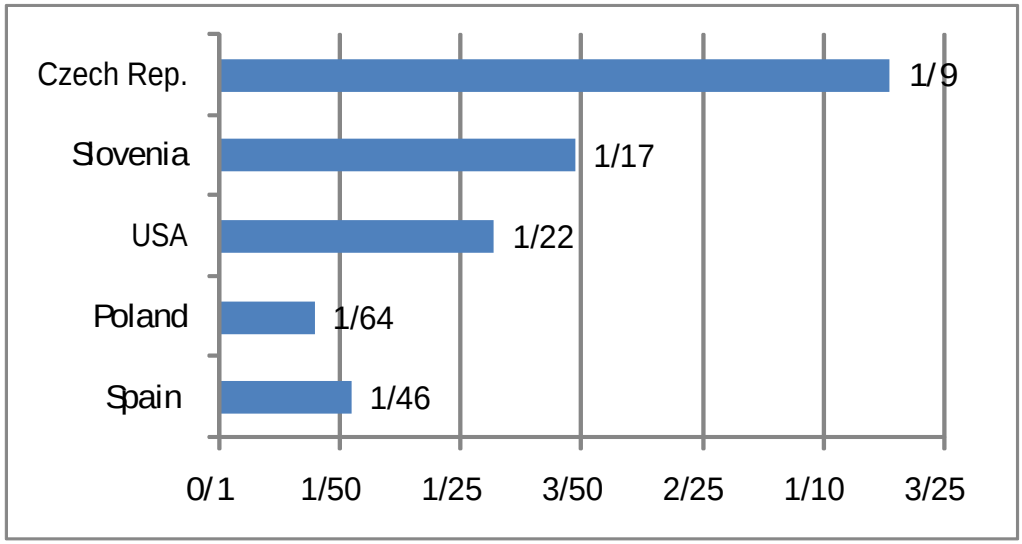

* Sweden (<3 y. old)
** Spain (<2.5 y. old)

Celiac disease is a disease with a clear preference regarding the gender with ratio being 'in favor' of the women at 2/1 (even though some studies report a tendency for a smaller difference) (14). Also we should add that celiac disease is an illness which can be found in any age and its appearance can occur at any point of life. The smaller age that we met celiac disease in bibliography was a five month old infant while on the other hand the older person regarded a patient eighty two years old. It seems that there is a genetic predisposition for expressing celiac disease which is activated by several environmental, psychological or some infectious factors. These factors which activate celiac disease are not fully understood. An interesting study came from Sweden (15) regarding 2151 children with celiac disease, showed that the possibility of appearance of celiac disease was much more higher if the time of birth was at summer comparing with the time of birth being the winter but only in children whose the age of diagnosis was below two years old (the ratio was in favor of summer at a point 1.4/1).

Even if there is not a certain distribution for celiac disease regarding the age, the gender and the time

of diagnosis, we would like to report relative data from a study that was conducted in England (16). At this study during the period 1990-2000 in the Royal Hallamshire Hospital, 264 people with celiac disease were recorded, 86 of them being male and 178 female (the ratio was about 1/2). The median age of diagnosis was 44.9 years old without important differences between genders.

**Figure 5. Prevalence of celiac disease in relatives of patients with celiac disease**




What's the case with celiac disease, is it a relatively rare disease which appears in some countries or is ultimately an almost global fact which is continuously detected more and more? About celiac disease, the model of iceberg has been described (17), thus there is a part that is visible (top) which is related with celiac disease which is known and the diagnosis has been made mostly based on symptomatology and screening programs regarding high risk groups and a bigger part (the submerged part of the iceberg) which is related with unknown cases of celiac disease. This big part of celiac disease can be defined if by separating in three categories. First there are non-diagnosed cases of celiac disease where there are lesions of the mucosa and several symptoms are present but they have not been detected. Then we have the silent form of celiac disease were there are distinctive morphological lesions at small bowel biopsy without any clinical suspicion or sympto-matology. At last there are latent cases of celiac disease where there is a genetic predisposition but there are no clinical or histological signs of the disease. It is possible that the initiation of consuming gluten containing products along with the effect of an environmental factor or an infection has as a result the appearance of celiac disease at some point of age. At some studies regarding the detection of celiac disease in Western countries it is found that for every diagnosed case of celiac disease collerates five to ten non-diagnosed cases of celiac disease, which means that the true incidence of the disease is overall larger than the one we know. One characteristic study (18) was made in Italy regarding 17,201 children where the frequency of celiac disease was 1/184 and the ratio of known to nondiagnosed cases was 1/7. In a study (19) that was conducted in Australia on 3011 people from the general population, 1/251 had celiac disease with the ratio of known to unknown cases being 1/3,5.

Further down we will report the incidence of celiac disease in children and adults who were presented and recorded in bibliography based on the cases that are known and have been diagnosed due to their symptoms. This, reminding the model of

iceberg, is just the top, while the biggest part remains under the surface [Figure 1 (10,20-23) and Figure 2 (8,24-30)].

There are as we said nondiagnosed cases where there is some clinical symptomatology but because of the symptoms being atypical or the suspicion for celiac disease was low the true diagnosis was not made. There are several studies where patients were checked retrospectively for atypical symptoms (like dyspepsia, abdominal pain, diarrhea, iron insufficiency) and in cases where there were lesions compatible with celiac disease, a histological examination followed. Thus at the following table (31-36), a figure of patients with celiac disease who had atypical symptoms and they were not yet diagnosed (one of them was conducted in Greece) is presented.

Furthermore in studies involving healthy groups, immunological screening for celiac disease was conducted and then a histological examination in those who were positive, so as to verify the diagnosis of the disease. So at the previous table (31,37-43) we can take a look at the number of people who are positive for celiac disease pointing to the silent part of the disease.

As we have mentioned celiac disease is a hereditary disease as it has a higher incidence among relatives of patients with celiac disease in comparison with the general population, while the appearance of celiac disease among first degree relatives reaches 10% (44). It is important to mention that a small percentage of these relatives have already been diagnosed with celiac disease while the rest of them belong to the cases where celiac disease is silent or people have few or atypical symptoms. Also, if in a family there are two brothers with celiac disease, the incidence of the disease at the first and second degree relatives is raised as it is mentioned in a recent study (45) in America. Thus we conclude that the relatives of the patients with celiac disease belong at a high risk group for the disease and possibly an immunological screening program which would lead to the diagnosis of new cases with celiac disease is necessary. At the following table (32,46-49) the incidence of celiac disease in relatives of patients with the disease is presented as it has been recorded in studies from different countries.

Celiac disease has a wide spectrum of manifestations, intestinal or extraintestinal, but it can be also combined with several autoimmune diseases or other conditions. So patients with celiac disease may also have for example dermatitis herpetiformis (50) at a percentage 2-3%.

**Conflicts of interest:** None declared.

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