Epidemiology of Celiac Disease and Non-Celiac Gluten-Related Disorders

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Abstract

The epidemiology of celiac disease and Non-Celiac Gluten related disorders is still an open field to be explored. Not many studies have been conducted in well-defined populations. We have reviewed the prevalence reported in studies using different methodology and addressed the findings obtained in old and new areas with the aim to increase awareness of the frequency of these disorders. The data available suggest the need to plan further proper epidemiological studies in order to understand the natural history of the disease and to assess the burden of these diseases on health systems.

Celiac disease has a global distribution. In childhood celiac disease, epidemiological studies have concentrated so far mainly on the determination of the incidence. There is a relative homogeneous prevalence in descendants of the Caucasian race. However, heterogeneity exists in various countries and continents. In some countries studies in blood donors have contributed to raise awareness of celiac disease and are the only information available.

The average prevalence in the United States of celiac disease is very similar to the one observed in Europe. The highest prevalence was found in the Saharawi population and the lowest in Japan. Recent reports have confirmed the occurrence of celiac disease in China and Central America, countries where previously it was considered that gluten-related disorders were nonexistent.

We reviewed the almost non-existent epidemiology of non-celiac gluten related disorders. The worldwide epidemiology of dermatitis herpetiformis suggests stronger heterogeneity than the observed in celiac disease. The incidence of allergy and autoimmune disease in the

U.S.A. and other industrialized nations is increasing. Gluten-related disorders are no exception.

We expect that an improved knowledge of the worldwide distribution of gluten-related disorders will help us to understand the role of different genetic factors and different environmental influences involved in the pathogenesis of these diseases. At a public level the epidemiological studies are necessary to assess the impact on health systems in the different countries.

Keywords

Epidemiology, celiac disease, non-celiac gluten-related disorders, dermatitis herpetiformis, gluten ataxia, prevalence, incidence.

1. Introduction

Celiac disease is a systemic process of autoimmune nature related to the existence of a permanent intolerance to gluten and manifests itself in genetically susceptible individuals. Although it is primarily a disease of the small intestine, it often affects several organs both in and outside the gastrointestinal tract. The clinical features are protean manifestations often without gastrointestinal symptoms, which make the diagnosis as well as the studies of the pathogenesis and its epidemiology more complicated. Studies of epidemiology are important to help to understand the causes of a disease and to quantify the burden of disease.

In childhood celiac disease, epidemiological studies have concentrated so far mainly on the determination of the incidence. Extensive research and literature exist throughout Europe. The determination on the prevalence of celiac disease in different countries involves children and adults.

In relation to the incidence: a demographically homogeneous Danish population study covering a 15-year period[1] found a crude rate of 0.10 by 1000 live births which was the lowest rate described in any epidemiological study per 1000 live births. In the Netherlands, a similar low incidence of 0.18 per 1000 live births[2] was found during the period from 1976 to 1990. In contrast, in other western countries, higher rates of 0.33 to 8 per 1000 live births were found. In Sweden, between 1970 and 1988 the cumulative incidence of celiac disease at 2 years of age per 1000 live born infants increased significantly from 0.31 in the first birth cohort to 2.93 in the last cohort[3]. According to the authors from Goteborg this incidence makes celiac disease one of the most common chronic diseases among Swedish children.

In Sicily, a maximum cumulative incidence rate by birth cohort was reached in 1986, to 1.65 per 1000 live births. When the incidence rate was adjusted for the years of follow-up, the actual standardized rate was 3 cases per 1000 live births[4] and recently in Spain, a prospective, multicenter, nationwide registry of new cases of celiac disease in children <15 years of age conducted from June 1, 2006 to May 31, 2007 an incidence rate of 7.9 cases of

celiac disease per 1000 live births was found. This rate is much higher than the present incidence rates of celiac disease observed in other European countries[5].

In this chapter we focus on the prevalence of celiac disease in adults. We reviewed the prevalence that has been observed in many studies, using different methods of formal epidemiology. Not many studies have been conducted in well-defined populations. We addressed the findings obtained in old and new areas with the aim to increase awareness of the frequency of celiac disease and to draw attention to the need to plan further proper epidemiological studies in order to understand the natural history of the disease.

Celiac disease has a global distribution. There is a relative homogeneous prevalence in descendants of the Caucasian race. Heterogeneity exists in various countries and continents. Several causes may explain the differences observed between countries, even in regions of the same country. A possible explanation is the variability in the knowledge and experience of general practitioners in the diagnosis of the disease due to the multiple forms of clinical presentation. This probably results in a delayed identification of the disease. Also at the specialist level, the awareness to suspect celiac disease varies. Also there are differences in availability of diagnostic tests and a proper interpretation[6]. It is also well-known that there is an increased incidence of subclinical or silent forms of celiac disease. The most frequent extraintestinal markers of subclinical celiac disease are iron-deficiency anemia, dermatitis herpetiformis, osteoporosis and recurrent aphthous stomatitis. The most frequent presentations in silent celiac disease are found in first-degree relatives, in diverse types of thyroid disease and in patients with insulin-dependent diabetes[7].

We expect that an improved knowledge of the worldwide distribution of celiac disease will help us to understand the role of different genetic factors and different environmental influences involved in the pathogenesis of celiac disease. At a public level the determination by epidemiology of celiac disease will help to assess the impact on health systems in the different countries.

2. Heterogeneity and Difficulties in Performing Epidemiological Studies

Most of the epidemiological studies have been carried out through the determination in blood of specific serological markers of celiac disease, like the detection of IgA anti-gliadin (AGA), IgA anti-tissue transglutaminase (tTG) and/or IgA anti-endomysium antibodies (EmA). The most important genetic markers of susceptibility, the HLA class-II antigens: HLA-DQ2 and/or HLA-DQ8 have not been taken into account in general but only in some studies. Full HLA-DQ typing of all patients has been investigated by Hadithi et al.[8]. Some authors have included the histological findings of the duodenal biopsy specimens, based on the presence of villous atrophy and more recent on the increase of epithelial lymphocytes without villous atrophy.

In the last decade, large genome-wide associations studies (GWAS), have identified more than 40 different non-HLA genes associated to celiac disease. However, these genes, identified by single nucleotide polymorphisms (SNPS) inside or near the genes, will only provide a small contribution to the heritability of celiac disease. No screening studies based on other genetic markers that possibly have an influence on the emergence and development of celiac disease, apart from the HLA genes in chromosome 6, have been published[9-11].

In families with celiac disease, the presence of certain SNPS improves the prediction to suffer from celiac disease in first-degree relatives. In particular in the low HLA risk groups[12]. Romanos et al., have suggested using GWAS as a first step to achieve a better diagnosis and prognosis in high-risk families and in population-based screening[13]. In spite of the advances of the GWAS approach this technology still seems to be premature and expensive. Also the genes linked to the high risk SNPS, have not been identified as yet.

Despite the diversity and weaknesses of the epidemiological studies, e.g. the inability to detect Marsh I celiac patients by specific serological tests, it is acknowledged that the worldwide prevalence of celiac disease ranges from 0.5% to 1%. Differences among populations that have low gluten consumption

and/or a limited access to diagnostic tools exhibit lower prevalence. Therefore, in spite of technical failures, lack of orientation and/or the sampling of insufficient biopsies, the "gold standard" for the diagnosis of celiac disease continues to be the small intestinal biopsy[14]. During endoscopy, multiple biopsies in the duodenal bulb and at least 4 in the distal duodenum should be taken. In a multicenter study carried out in children, it was confirmed that in a 2.4% of 665 patients, the lesions were virtually limited to the duodenal bulb[15]. The majority of the studies published so far, do not comply with the protocol suggested by Bonamico et al.[15]. Taking small intestinal biopsies are not feasible for the screening protocol in population studies and without the improvements in the sensibility and specificity of the serological test to diagnose celiac disease, epidemiological studies would not have advance to the state were we are. Serological studies have allowed the possibility of mass screening programs which are useful in identifying patients who can benefit from gluten-free diet and follow-up, because in the general population celiac disease is frequent and clinically relevant, irrespective of histological severity[16]. Nevertheless, since the economic costs of screening and treatment versus the prevention of morbidity have not been calculated, the time for mass screening has not yet been reached[17].

2.1. Prevalence's at the Global Level

Until recently celiac disease was considered to be a disease of the Europeans. It is now endorsed that it affects all races and there is a gradual change in the global distribution; therefore, it is important to quantify the weight of the burden of the disease in each region. The outcome will have implications for the health systems in the different countries.

In Caucasians the average prevalence is estimated to be about 1-2% according to different studies using specific serological tests, evaluated by different methods and markers[18-20].

The presentation forms of celiac disease have changed remarkably. Until some years ago the classical forms predominated. They were clinically characterized by the presence of chronic diarrhea, steatorrhea, malabsorption, and weight-loss. In

the last few decades, the oligosymptomatic and the atypical forms with less or no digestive symptoms have significantly increased. At present we find a notable predominance of extra-intestinal manifestations, such as iron deficiency anemia and osteoporosis. The increase of celiac disease observed in some studies may be due to the success of the case-finding approach and to the accessibility of more sensitive and specific serological tests for diagnosis[21,22].

2.2. Prevalence Studies in Blood Donors

Epidemiologic studies carried out in volunteer blood donors, are not considered representative of what happens in the general population, in part because of the limitation of age selection. In addition anemia, a relatively frequent presentation form of celiac disease, excludes blood donation by healthy volunteers. However, in some countries studies in blood donors have contributed to raise awareness of celiac disease. For example in North India, using tTG antibodies and duodenal biopsy in tTG positive subjects found in 1,610 blood donors of whom 98.2% were males, a prevalence of celiac disease of 1 in 179 donors (0.56%)[23]; In Madrid, Spain in 2,215 apparently healthy blood donors screened with tTG antibodies, they found a prevalence of celiac disease of 1 in 370 or 1 in 222, if Marsh I lesions in duodenal biopsy were included[24].

In many countries the only available information on the prevalence of celiac disease has been obtained from blood donors[25,26].

Many epidemiological studies use the data obtained in blood donors as control of their studies; for example, in Tunisia, Ghozzi et al. have used EmA antibodies to study two hundred and eleven patients suffering from arthritis or arthralgia with no evident cause and two thousand and five hundred blood donors as control group. Five had EmA antibodies positive which represents 2.37% in the patient group and 0.28% in blood donors[27]. In Italy, Carroccio et al. compared the frequency of tTG and EmA in 80 consecutive non-Hodgkin's lymphoma (NHL) patients (median age, 61 years) with 500 blood donors. The frequency in NHL patients was 1.2% versus blood donors 0.4% (p=0.4). Of interest in this study is that in NHL patients the tTG assay often gave discordant results with the EmA assay. They found a high frequency of tTG

false positive tests[28]. Vancikova et al. in the Czech Republic determined the prevalence of celiac disease using a panel of specific antibodies sequentially in 1,312 healthy blood donors and 102 patients with primary osteoporosis, 58 patients with autoimmune diseases and 365 infertile women. They found AGA and/or tTG and EmA positive in 0.45% of healthy blood donors, 0.98% of osteoporotic patients, 2.7% of patients suffering from autoimmune disease and 1.13% of women with infertility[29]. In Eastern Saudi Arabia, Al Attas et al. found in a group of 145 patients with clinical suspicion of celiac disease that the serological (EmA positive) prevalence was 7.6%. Six of these patients had confirmed celiac disease by intestinal biopsy indicating a prevalence of celiac disease of 4%. In 80 patients with autoimmune diseases 2 were EmA-positive (2.5%) whereas none of the 20 patients with inflammatory bowel disease and none of the 100 healthy blood donors were found to be EmA-positive[30]. In Italy, sera from 220 patients with autoimmune thyroiditis, 50 euthyroid subjects with thyroid nodules and 250 blood donors were tested for tTG and EmA antibodies. The prevalence of celiac disease in patients with autoimmune thyroiditis (3.2%) was significantly higher than that found in blood donors (0.4%) ($p=0.022$, Fisher's exact test). The 50 euthyroid subjects had no antibodies and no signs of celiac disease[31]. Cuoco et al. found among 92 patients with autoimmune thyroid disease that 4 patients had positive AGA and EmA antibodies and celiac disease; among 90 patients with non-autoimmune thyroid disease only 1 patient had celiac disease. In 236 blood donors one subject (0.4%) was AGA and EMA positive and had celiac disease[32].

These studies confirm that the prevalence in blood donors is not representative for the prevalence of celiac disease in a population and the prevalence is inferior to the one found in diseases known to be associated with celiac disease.

2.3. Prevalence in High-Risk Groups

There are various risk groups, which have a greater predisposition to suffer from the disease than the general population. The most common risk groups are first-degree relatives. They show an average prevalence between

10 to 20%[33]. The family members who carry the HLA-DQ2 and/or HLA-DQ8 antigen and the siblings exhibit the highest risk to suffer from celiac disease. Some authors have found a higher prevalence in brothers, than among the rest of family members[34-36]. Hansen et al found a high prevalence of celiac disease 10.4% (95% C.I. 4.6-16.2%) in young Danish type-1 diabetics[37]. A study in young people under the age of 20 in Sweden, suffering from type-1 diabetes mellitus, found a low prevalence of 0.7% in symptomatic children. However, at 5 year's follow-up after diagnosis, the prevalence increased to 10%[38].

Studies of prevalence of celiac disease have been carried out in high risk groups as shown in Table 1, in first-degree relatives, in individuals with Down´s syndrome and in type-1 insulin-dependent juvenile diabetes (See Table 1). A study in 35 patients with Turner syndrome found a prevalence of celiac disease of 8.1 (3 patients with villous atrophy, or 10.8 (if 4 antiendomysium antibody-positive are considering as suffering from celiac disease. This prevalence is quite high and Bonamico and coworkers have suggested that the association of these two disorders could not be coincidental[39].

Table 1. Risk Groups for the Development of Celiac Disease.

Risk groups for celiac disease (Ref 33 and 40-69)
• First- and Second-Degree Family Members[33]
• Chronic Iron Deficiency Anemia and Refractory Anemia[40,41]
• Osteoporosis, Osteopenia and Osteomalacia[42,43]
• Diabetes Mellitus type-1 (mainly in Children and Adolescents)[44-46]
• Endocrinopathies of Autoimmune Origin, especially Thyroid Diseases[47-49]
• Autoimmune Hepatitis and Primary Biliary Cirrhosis[50]
• Skin Diseases, Dermatitis Herpetiformis, psoriasis[51-53]
• Chromosomal Abnormalities such as Down syndrome[54], Turner syndrome[55], and Williams Syndrome[56,57]
• Neurological disorders, Gluten Ataxia, Epilepsies, Occipital Calcifications, Polyneuropathies[58-61]
• Recurrent Polyarthritis and Poly-Arthralgias[53,62]
• Recurrent Headaches of Migraine-type[63]
• IgA Nephropathy[64-67]
• Repeated Miscarriages, Menstrual Disorders, Infertility[68,69]

2.4. Prevalence in Europe

The prevalence in Europe is slightly higher in the countries of Northern Europe than in the Mediterranean basin. It appears that the differences in prevalence have diminished in recent years[70]. The Scandinavian countries, the United Kingdom and Ireland, have shown a prevalence ranging from 1 to 2.5%[71-74].

A study conducted in Holland among blood donors found a low prevalence of 0.3% in 1,999[75]. A larger study in the Netherlands including 50,760 individuals who had previously participated in two large population-based studies on health status in relation to lifestyle factors, were screened by identification of self-reported adherence to a gluten-free diet and subsequent confirmation of the diagnosis of celiac disease found a prevalence of coeliac disease 0.016% (95% confidence interval 0.008-0.031). In a random sample of 1,440 of all participating subjects were screened by serological tests and by the typing of human lymphocyte antigens. A prevalence of 0.35% (95% C.I. 0.15-0.81) was found. The prevalence of adult-recognized celiac disease in the Netherlands is one of the lowest in Europe, while the prevalence of unrecognized celiac disease is comparable with other Southern European countries, which suggests that celiac disease is underdiagnosed in the Netherlands[76].

A study performed in adolescents in Switzerland showed a prevalence of 0.75%[77].

The mean prevalence of celiac disease in European countries is within the medium range at global level. Although celiac disease was traditionally regarded as a disease with predominance in children, in the last decades the majority of cases are diagnosed in adults[78].

There are longitudinal studies conducted in Finland which confirm the increase in the prevalence of celiac disease, over the past few decades. In a large cohort of 8,000 participants selected from the general population, the average prevalence from 1978 to 1980 was 1%, rising to 2% in the period from 2000 to 2001[79].

A centralized international mass screening of 29,212 participants in Finland, Germany, and Italy by means of a tTG antibody test and when the tTG test was positive or showed border-line results then an EmA test was performed. This large study found a mean prevalence of celiac disease of 2.4% (2.0-2.8) in Finland, 0.3% (0.1-0.4) in Germany, 0.7% (0.4-1.0) in Italy. Sixty-eight percent of antibody-positive individuals showed small-bowel mucosal changes typical for celiac disease (Marsh II/III) lesions[80].

The epidemiological differences between neighboring countries may be due to differences in the socio-economic levels of the different populations, as well as to environmental health measures. The prevalence of tTG in celiac disease is lower in Russian Karelia than in Finland, in spite of the similar frequency of HLA risk haplotypes in both regions. It has been hypothesized that this may be associated with a protective environment characterized by inferior prosperity and standards of hygiene in Karelia[81]. Unfortunately the availability of the diagnostic tools and knowledge of the disease in primary care centers are very different from one country to the other.

2.5. Prevalence in United States

The average prevalence in the United States of celiac disease is very similar to the one observed in Europe. In the last years, a greater awareness of celiac disease and a more active search through information campaigns and the dissemination of knowledge by patient´s associations and internet active groups have contributed to a higher prevalence. Patients with symptomatic celiac disease in the USA showed prevalence of 1.7% in 2003[82].

Another study compared the results obtained with samples collected between the years 1948-54, to two cohorts of samples collected between 1995-2003 and 2006-2008. The authors found a notable increase of up to four times higher in the last periods[83].

In a retrospective comparative study during a 15-year period of follow-up conducted in healthy volunteers found a prevalence of 1 in 501 subjects in

1974 versus 1 in 219 subjects was found[84]. (Table 2 shows a summary of studies performed in U.S.A.).

These epidemiological changes in time of celiac disease in the U.S.A. are seen in many other countries. Not only in the well-known geographical areas where celiac disease is present, such as northern Europe, but also in regions where celiac disease was unknown, such as in Central America and Asian countries. This aspect is described later. To a large extent, the increase in the prevalence of celiac disease is due to the changes in dietary habits in the last few decades. There has been a considerable increase in the consumption of foods containing gluten.

Table 2. Prevalence in United States.

Characteristics	Year (Ref)	Studied population	Prevalence in (%)
Global	2003[82]	13,145 at-risk and non-at-risk	4.54-0.75
Nationwide	2012[83]	7,798 adolescents and adults	0.71
Cohort study	2010[84]	4,351 adults	0.19-0.45

2.6. Prevalence in Africa

In the countries of North Africa, Morocco, Algeria, Tunisia, Libya and Egypt, a high prevalence of celiac disease has been reported. The highest prevalence was found in the Saharawi population of Arab-Berber origin. The prevalence varies between 0.3 to 5.6%. There is a strong association with the haplotype HLA-DR3-DQ2 in the general population and a high consumption of cereal-based foods with gluten with less intake of vegetables and fruits[85].

There is little information on the prevalence of celiac disease in the countries of Sub-Saharan Africa. Some individual studies such as one conducted in Djibouti in the Horn of Africa region clearly confirms that

celiac disease does exist in these regions. The clinical presentation is similar to the observed in the rest of the world. Its diagnosis is more difficult due to the limited knowledge, low index of suspicion of the disease, as well as for the limited facilities to carry out a diagnosis[86]. In Africa and in general in the tropical countries the major causes of iron deficiency anemia are an increased Hookworm infestation, *Schistosoma mansoni* particularly in Egyptian patients and *Trichuris trichiura*. In the continent of Africa, the etiology of anemia in children besides iron deficiency includes malaria, bacterial or viral infections, folate deficiency and sickle-cell disease[87] (Table 3 illustrates as far as we know the only information available on celiac disease in Africa.

Table 3. Prevalence in Africa.

Country	Year (Ref)	Studied population	Prevalence in (%)
Sahara	2010[85]	975 Children and Adults	5.6
Inter-tropical (Horn of Africa)	2008[86]	Children and Adolescents During 3 years period 8 celiac disease patients diagnosed	Unspecified

2.7. Prevalence's in Middle East

Celiac disease is a frequent cause of chronic diarrhea, mainly in children and in patients with type-1 diabetes mellitus in diverse countries of the Middle East, such as Iran, Iraq and Kuwait[88].

The prevalence of celiac disease in adult blood donors in Iran[89] and Israel[26] is 0.6% for both countries; in Syria and Turkey the prevalence is 1.6%[90]. In Anatolia a similar result of 1% was found[91]. An Iranian study in children with chronic diarrhea, found a prevalence of 6.5%[92] and the prevalence in healthy children from Turkey was 1 in 115 (0.86%) based on serology. However the

prevalence of biopsy proven celiac disease was 1 in 158 (0.63%)[93]. Table 4 shows studies on prevalence in the middle east.

Table 4. Prevalence in Middle East.

Country	Year (Ref)	Studied population	Prevalence in (%)
Iran (South)	2013[88]	83 T1DM children	4.80
Iran (Tehran)	2003[89]	2,000 blood donors	0.60
Iran	2005[92]	825 children with chronic diarrhea	6.50
Iran(north and south)	2006[94]	2799 individuals	0.96
Israel	2002[26]	1571 blood donors	0.63
Turkey	2004[95]	2000 blood donors	1.30
Turkey (Anatolia)	2005[91]	906 adults	0.99
Turkey	2005[93]	1263 healthy children	0.86

T1DM = Type-1 Diabetes Mellitus

2.8. Prevalence in Asia

Celiac disease is still uncommon in Asia. Only several cases have been reported. The World Gastroenterology Organization and the Asian Pacific Association of Gastroenterology commissioned a working party to address the key issues in the emergence of celiac disease in Asia[96]. The working party suggested performing studies on the prevalence of celiac disease increase the awareness among physicians and patients as well as increase the recognition of atypical manifestations of the disease. Several problems were identified and represent challenges to be overcome. The working party found variability in performance of serological tests, a lack of population-specific cut-off values for

tests positive or negative, a need to educate dietitians for proper counseling and supervision of patients and improve the gluten-free infrastructure in food supply. To establish celiac patient's advocacy organizations was also emphasized.

2.9. Prevalence in India and Pakistan

In India celiac disease was recently described by an Indian Task Force as being "submerged in an ocean of malnutrition"[97]. Its frequency in India, seems to be higher in the Northern part of the country, creating the so-called "celiac belt". This finding is at least partially explained by the wheat-rice shift from the North to the South[98,99]. The "All India Institute of Medical Sciences" in New Delhi, has prospectively studied adolescent and adult patients presenting with nutritional anemia by tTG antibodies. Positive patients underwent an upper gastrointestinal endoscopy and duodenal biopsy. Ninety-six patients with a median duration of anemia of 11 months (range 1 to 144 months) were screened. 10 patients with nutritional anemia (iron deficiency 9, vitamin B12 deficiency 1) were diagnosed to have celiac disease[41].

There is limited data on the epidemiology in India. Possibly because of the presence of generalized malnutrition and epidemics of chronic diarrhea as well as the difficulty to make a diagnosis of celiac disease[100,101].

In the Delhi area with a large population sample of 2,879 participants, the prevalence of celiac disease was 1.04% (1 in 96)[102]. In a questionnaire-based survey of 4,347 schoolchildren (3–17 years) from Ludhiana, a city in Northern part of Punjab, India the prevalence was 1 in 310[103].

Based on these studies, it is estimated that 5 to 8 million individuals can be expected to have celiac disease in India, yet so far only a few thousand cases appear to have been diagnosed. There is a clear need for further epidemiological studies, in order to determine the regional differences in prevalence.

No epidemiological studies have been reported in Pakistan some studies however have reported patients with celiac disease and explained the difficulties such as in India, in making the diagnosis[104,105].

2.10. Prevalence of Celiac Disease in China

In China the major causative factor—gluten consumption (particularly in the Northern part of the country)—and risk HLA genotypes (HLADQ2 and -DQ8) are present, although with a lower prevalence than in Western countries[106-108]. It appears that there is a clear predominance in its distribution in the North. The knowledge on celiac disease in China has started in recent years, though no formal epidemiological studies have been performed yet[108,109]. In a recent series of 118 children with chronic diarrhea, admitted in pediatric hospitals in four major Chinese cities (Shanghai, Wuhan, Jinan, and Chengdu) the diagnosis of celiac disease was made in 14 patients (11.9%)[110]. The reports are of great importance since they confirmed the occurrence of celiac disease in China, a country where previously was considered to be nonexistent.

Table 5. Prevalence in Asia.

Country	Year (Ref)	Studied population	Prevalence in (%)
India Punjabis (City of Leicester UK)	1993[111]	20 celiac adults	2.7-3.8
India(north)	2011[102]	10,488 adults	1.04
India(Punjab)	2006[103]	4,347 children	0.32
China	2011[110]	199 children with Chronic diarrhea	11.9
Japan	2014[112]	172 IBD adults Positive tTG and DGP No HLA high risk	0

IBD = Inflammatory Bowel Disease; DGP = Deamidated Gliadin Peptides

2.11. Prevalence of celiac disease in Japan and the South East Asian Islands

In Japan, in a recent study, the prevalence of celiac serological markers was 18% in a series of 172 patients with inflammatory bowel disease, compared with the 1.6% in 190 healthy individuals recruited in the general population. However, no duodenal biopsies were performed and no information on genetic markers of susceptibility were available[112].

There are no data on the prevalence of celiac disease in the South East Asian countries, including Malaysia, Korea, Taiwan, the Philippines and the smaller islands of the Pacific. It is assumed that there is a low incidence, due to the low consumption of products containing wheat flour, along with a low frequency of HLA-DQ2 and HLA-DQ8 in the general population. There is a limited availability to study celiac disease by specific serological markers in these countries.

The average prevalence of the risk haplotype HLA-DQ2 is low in Japan and in Southeast Asia. It is present only in 5-10% in the general population and the mean prevalence of the HLA-DQ8 in Asia is less than 5%[113]. The ingestion of wheat-based products is low, but has increased in the past few years.

2.12. Prevalence of Celiac Disease in New Zealand

New Zealand forms part of an island continent whose inhabitants have a large proportion of predecessors of white race, with Anglo-Saxon predominance and genetic haplotypes of susceptibility for celiac disease as well as a high cereal consumption of wheat.

In a comprehensive study conducted in Western Australia, a prevalence of 0.4% of celiac disease was found in this population[113].

A study to determine the prevalence of celiac disease and of gluten avoidance in New Zealand children, found that 1% of these had celiac disease, but 5% reported gluten avoidance. The predictors of gluten avoidance in children without properly diagnosed celiac disease suggest important regional

differences in community belief or medical practice regarding implementation of a gluten-free diet[114].

2.13. Prevalence of Celiac Disease in Australia

In a retrospective analysis performed in an Australian community of stored serum samples taken in 1994-1995 from 3,011 subjects, assays for IgA-tTG and IgG-tTG antibodies were performed. Positive or equivocal samples were retested with a different commercial tTG assay. The prevalence of tTG antibodies in this population is 1.56%; the prevalence of celiac disease is 0.56%. According to these authors, the value of a single positive result of a tTG assay in screening for celiac disease in the community is poor and an assessment with different assays may decrease the need for gastroscopy and distal duodenal biopsy[115].

In an Australian rural community a prevalence of 12 of 3,011 found (1 in 251) was based on positive EmA antibodies and duodenal biopsy compatible with celiac disease[116].

Table 6. Prevalence in Australia and New Zealand.

Country	Year (Ref)	Studied population	Prevalence in (%)
New Zealand	2000[113]	1,064 adults	1.2
Australia	2001[116]	3,011 adults	0.4
New Zealand	2002[114]	916 children	1.0
Australia	2009[115]	3,011 adults	0.6

2.14. Prevalence of Celiac Disease in Mexico

Information regarding celiac disease in Mexico is limited; however, on the basis of the prevalence of tTGA in a large group of healthy blood donors a high prevalence of tTGA positivity 27 of 1,009 (2.6%) was found. This

suggests that in the adult Mexican Mestizo population the presence of celiac disease is high[117]. A recent update[118] using the weighted prevalence for double-positive serology IgA tTG and IgA EmA the prevalence was 0.59% (95% CI, 0.27 – 1.29). A high prevalence of 5.9% biopsy-proven celiac disease was found in Mexican Mestizo patients with type-1 diabetes mellitus[119]. Interestingly, in a study of prevalence in United States in 7,798 persons aged 6 years and older who participated in the National Health and Nutrition Examination Survey 2009-2010, they found a prevalence of 0.71% (95% confidence interval (CI), 0.58-0.86%) i.e. 1 in 141. This study also reported celiac disease to be rare among minority groups, including Hispanics. The prevalence was 0.03%, or 1 of 2,519 and in Mexican Americans (0%)[83]. This discrepancy illustrates the possible effect of environmental factors in determining the prevalence of celiac disease in people with the same genetic background.

2.15. Prevalence of Celiac Disease in El Salvador and Costa Rica

There are no epidemiological studies published in Central America. The first study using the modified Marsh classification and the full HLA-DQ typing in El Salvador, has been recently published. Of the 32 cases, 23 were celiac disease risk genotype carriers[120]. Similar results have been reported from Costa Rica, in 35 patients[121].

2.16. Prevalence of Celiac Disease in Brazil

A study carried out in Brazil, which included a total of 214 symptomatic children, aged between 12 and 36 months, were studied by serological screening and subsequent confirmation by jejunal biopsy in the positive cases. Five cases (2.3%) were found[122]. The prevalence of celiac disease in a group of first-degree relatives of Brazilian celiac patients, between March 2001 and November 2004, in two centers in Brasilia was studied. They found among the 188 first-degree relatives a prevalence of 4.8%[123].

In another study in adults carried out in Brazil, conducted in an urban area on 2,086 blood donors reported a prevalence of 1.4%. This prevalence is lower than the previous study but it is similar to the prevalence found in European countries or in North America[124].

2.17. Prevalence of Celiac Disease in Argentina

Similar studies in hospitals have been carried out in several cities in Argentina including a multicenter study of the prevalence in a pediatric population in 5 urban districts of Argentina. A total of 2,219 patients, ages between 3 and 16 years were analyzed. A prevalence of celiac disease 1.26% was found. 33% of the cases were symptomatic[125].

In the adult population in Argentina, Gómez et al., found a prevalence of 1.16%, in a study of 2,000 individuals, chosen in the general population[126].

Table 7. Prevalence in Mexico, Central and South America.

Country	Year (Ref)	Studied population	Prevalence in (%)
Mexico	2006[117]	1,009 adults tTG screening	2.6
El Salvador	2014[120]	32 adults	Undefined
Costa Rica	2014[121]	35 adults	Undefined
Brazil(Brasilia)	2010[122]	214 children	2.3
Brazil(Brasilia)	2008[123]	188 First-degree relatives	4.8
Brazil(Curitiba)	2,086[124]	Adults blood donors	0.23
Argentina	2012[125]	2,219 children	1.26
Argentina(La Plata)	2001[126]	2,000 adults	0.59

2.18. Conclusions

The true prevalence of celiac disease is still impossible to ascertain. A multidisciplinary approach to make the diagnosis is necessary. The collaboration between clinicians, immunologists, geneticists, and pathologists is essential to integrate clinical, serological, genetic, histological criteria as well as the response to the gluten-free diet. Many patients have atypical symptoms or none at all. Many patients have minimal lesions without villous atrophy such as those patients with Marsh 1 lesion. These patients require a differential diagnosis that is beyond the current epidemiological studies.

The most challenging observation to understand the epidemiology of the disease is the observation demonstrating that there is a clear difference in prevalence between children and adults.

In a large study of 4,230 subjects in Terrassa, Barcelona, Spain found population-based celiac disease prevalence of 1:250. The prevalence of celiac disease in childhood was five times higher than in adults. The authors correctly have pointed out that whether this difference is due to environmental factors in childhood or due to latent celiac disease in adulthood. This remains to be demonstrated in prospective longitudinal studies[127]. The outcome will have consequences to understand the epidemiology and natural history of the disease.

Major changes that are bound to alter the epidemiology of celiac disease and gluten related disorders are taking place such as the rice cultivation in several regions in China where wheat cultivation now predominates. Maize from the Mexican highlands has been the dominant food in Mexico and Central America, the potato developed in the Peruvian Andes and the Quinoa in Bolivia, is now complemented with gluten containing diets.

Several environmental changes point to an increase of celiac disease in these regions. The eradication of intestinal parasites which contributes to a change in the intestinal immune response, from TH2 to TH1, changes in the intestinal microbiota probably in individuals living in urban areas, changes in dietary habits due to the influence of "fast foods" and changes in traditional

diets as described above as well as the widespread use of antibiotics will in some way or other alter the epidemiology of celiac disease[106].

The review presented in this chapter indicates the worldwide importance of celiac disease and the gluten related pathologies and should help to clarify the need to implement measures in National Health systems, to cope with this expanding disease. As Greco et al have estimated:-"*In the near future, the burden of celiac disease will increase tremendously. Few Mediterranean countries are able to face this expanding epidemic*"[128].

3. Epidemiology of Non-celiac Gluten-Related Disorders

3.1. Epidemiology of Dermatitis Herpetiformis

A study in the UK at the Clinical Practice Research Datalink of the University of Nottingham, has quantified the incidence and prevalence of celiac disease and dermatitis herpetiformis between 1990 and 2011. A total of 9,087 incident cases of celiac disease and 809 incident cases of dermatitis herpetiformis were identified. Although dermatitis herpetiformis has been called celiac disease of the skin[129] to underline the common genetic background and the relation to gluten, the expression of either or both of these diseases is different. In Nottingham the incidence rate of celiac disease increased from 5.2 per 100,000 (95% CI, 3.8-6.8) to 19.1 per 100,000 person-years (95% CI, 17.8-20.5; IRR, 3.6; 95% CI, 2.7-4.8) while the incidence of dermatitis herpetiformis has decreased over the same time period from 1.8 per 100,000 to 0.8 per 100,000 person-years (average annual IRR, 0.96; 95% CI, 0.94-0.97)[72]. Although the prevalence of nutritional deficiencies, autoimmune diseases, and lymphoma occurred at a similar rate in patients with dermatitis herpetiformis as in patients with celiac disease without dermatitis herpetiformis, a recent study has confirmed that the prevalence of villous atrophy is significantly higher in the patients who presented with celiac disease than in those who presented with dermatitis herpetiformis only (61.8vs.12.5%;p = 0.005)[51].

At least two studies in the USA and in Finland show an expected prevalence of dermatitis herpetiformis in families significantly higher than previously calculated. This is possibly due to shared genetic factors and environment factors[130,131]. In Tampere and Helsinki, an analysis of 105 families with dermatitis herpetiformis showed that 13.6% of parents, 18.7% of siblings and 14.0% of children were affected. The authors suggested that this segregation pattern fits well to a dominant mode of Mendelian inheritance. However they added that gender may also be important because the first-degree relatives affected with dermatitis herpetiformis were more often females[131]. In Brazil two pairs of monozygotic twins have been studied after a gluten-free diet for 16 to 21 years. They were concordant for celiac disease. However, dermatitis herpetiformis was present in three patients belonging to the two pairs of twins, demonstrating partial concordance of dermatitis herpetiformis in monozygotic twins[132].

These observations fit with a multifactorial and polygenic disease pathogenesis similar to other autoimmune diseases.

At the Tampere University Hospital, the causes of death during 1971-2010 were studied in 476 consecutive patients with dermatitis herpetiformis diagnosed from 1970 onwards. 97.7% of the patients adhered to a gluten-free diet. All-cause and cerebrovascular disease mortality was significantly reduced. The standardized mortality rate due to lymphoproliferative malignancies was significantly increased (6.86) only in the first 5 years of follow-up[133].

The worldwide epidemiology of dermatitis herpetiformis shows a great heterogeneity. In Asia dermatitis herpetiformis is very rare. Twenty two cases have been described from China[134] and 35 cases in Japan[135]. Very few cases have been reported from Iran[136], Singapore[137], and Maylasia[138].

In southern Sweden, there were 96 cases in a defined population of 425,000 inhabitants. The incidence of dermatitis herpetiformis was 1.05-1.13/100,000 inhabitants/year and the prevalence was approximately 20 to 25 per 100,000 inhabitants.

In Utah in the U.S.A. with a main population of European descendants have higher incidence prevalence than in Asia. The prevalence of dermatitis herpetiformis in Utah in 1987 was 11.2 per 100,000. The mean incidence for the years 1978 through 1987 was 0.98 per 100,000 per year. The mean age at onset of symptoms for male patients was 40.1 years, and the one for female patients was 36.2 years. The male-female ratio was 1.44:1[139].

In Buenos Aires, Argentina 18 patients with dermatitis herpetiformis were found to have increased intestinal permeability even in patients with no evidence of histologic damage in biopsy specimens. They found that patients with linear IgA dermatosis appear to be a distinct population without gluten sensitivity[140]. Since the majority of patients with celiac disease and dermatitis herpetiformis have European ancestors it would be interesting to perform proper epidemiological studies in Argentina to study the environmental triggers.

The highest incidence and prevalence of dermatitis herpetiformis has been reported in Finland but there is some evidence that contrary to celiac disease, dermatitis herpetiformis is diminishing. The prevalence of dermatitis herpetiformis was 75.3 per 100,000 which is eight times lower than the prevalence of celiac disease in the Tampere area. The annual incidence of dermatitis herpetiformis for the entire 40 year period was 3.5 per 100,000, and in the three 10-year periods 5.2, 2.9 and 2.7 per 100,000, respectively[141].

The worldwide epidemiology of dermatitis herpetiformis suggests stronger heterogeneity than the observed in celiac disease.

3.2. Epidemiology of Gluten Ataxia

As pointed out by Hadjivassiliou gluten ataxia is one of the most common immune-mediated cerebellar ataxias and one of the few ataxias that are potentially treatable[142].

From a total of two hundred and twenty-four patients with various causes of ataxia in North Trent England, 132 were diagnosed as sporadic idiopathic ataxia patients. In The Institute of Neurology in London England 44 patients

were diagnosed with sporadic ataxia. From these groups of patients, 41% and 32% respectively had AGA antibodies and were confirmed to have gluten ataxia[143]. Familial and isolated cases of gluten ataxia have been described in Spain[144] and in Japan[145].

Further studies in neurological centers in other countries are necessary, because the experimental evidence seems to be incomplete. There is sufficient evidence to support immune-mediated basal ganglia dysfunction as an emerging clinical concept. The central nervous system dysfunction may be caused by a deviant immune response triggered by exogenous antigens such as gluten or streptococcal infection[146].

3.3. Epidemiology of Non-celiac Gluten Sensitivity

The incidence of allergy and autoimmune disease in the U.S.A. and other industrialized nations is increasing. Gluten-related disorders are no exception[147]. Many researchers particularly in the U.S.A. claim that non-celiac gluten sensitivity is the most common syndrome of gluten intolerance[148]. We have previously summarized the current thinking on non-celiac gluten sensitivity as follows[149]. This issue may have been the one with the greatest impact during the last decades, especially on the internet, in patients' associations and in the food industry. There is a lack of systematic studies which could improve the understanding and definition of this syndrome for the patients and assess the impact on public health services. We fully agree with the view expressed by Corazza and his group, who emphasize the lack of a clear definition of non-celiac gluten sensitivity. This hindrance is fundamentally related to the cause of this proteiform disease whose symptoms are presumably caused by different mechanisms[150].

It is therefore not surprising that Spence of Glasgow, Scotland wrote an article: - "*Do you think non-celiac gluten sensitivity exists*?" He describes the results of a recent poll undertaken by the general practitioners' journal in England, the British Medical Journal. 66% of the 941 who were asked and have had access to a higher education, responded that they believe it does exist, despite a lack of scientific evidence. "*Besides, about 20% of the*

American population purchase gluten-free products and, by 2017, it is estimated that this market will be worth about 6.6 million dollars"[151].

Recently Aziz et al. have determined the population prevalence of self-reported gluten sensitivity and referral characteristics to secondary care in Sheffield, UK. This study on a population-based questionnaire screened for gluten sensitivity, related symptoms and exclusion of celiac disease found that the self-reported prevalence for non-celiac gluten sensitivity was 13% (female 79%, mean age 39.5 years). These individuals had an increased prevalence of complying with the Rome III criteria for irritable bowel syndrome, in comparison with those without gluten sensitivity. The majority of patients with non-celiac gluten sensitivity have clinical and immunological differences to celiac disease[152].

3.4. Epidemiology of Gluten Allergy

According to clinical presentations and allergy testing, there are three types of food allergy: IgE mediated, mixed (IgE/Non-IgE), and non-IgE mediated (cellular, delayed type hypersensitivity). Among the most common of these allergies in children is wheat allergy. The prevalence of this kind of allergy in infancy is increasing and may affect up to 15-20% of infants. According to Ho et al. the alarming rate of increase calls for a public health approach in the prevention and treatment of food allergy in children[153]. The epidemiology of food allergy in general is outside the scope of this chapter. Wheat is one of the most common allergy caused by food. A recent study has reported that the prevalence in Japanese adults was found to be 0.21% by using a combination of questionnaire-based examination, skin-prick test and serum omega-5 gliadin-specific IgE test[154].

The prevalence of food allergy was investigated among patients reporting to The Institute of Child Health and Mediland Diagnostics in Kolkata, India. Among the 5,161 patients tested, wheat (22%) was the predominant allergen[155]. A large recent review has found that the overall prevalence of food allergy in Asia is fairly comparable to the West, although this kind of types of allergies differ in order of relevance in the consumption of type of food. Wheat allergy, though uncommon in most Asian countries, is the most

common cause of anaphylaxis in Japan and Korea and is increasing in Thailand[156].

See also the chapter with detail description of recent advances of gluten allergy.

3.5. Burden of Disease

As stated in the introduction and recently underscored:-"understanding epidemiology is crucial for hypothesizing about causes and quantifying the burden of disease"[72]. It is well known that patients with celiac disease have a greater burden of disease than the general population because of osteoporosis, autoimmune diseases, and malignancies (See also chapter by Lucendo et al.).

The statement made 10 years ago by Green et al. is valid today:-"There is a need for screening studies of patients with conditions associated with celiac disease to determine whether the large numbers of people with undiagnosed celiac disease currently are seeking health care"[157]. Currently, there is a need to quantify the increase in wheat allergy, as part of the increase in allergic conditions. Also it is necessary to quantify the relevance of other gluten related disorders for the awakening of the officers of national health systems to assess the total burden of these diseases and to be prepared for the application of adequate funds.

Greco and coworkers have called attention to the burden of celiac disease in the Mediterranean countries. They have calculated that in the next 10 years, the Mediterranean area will have about half a billion inhabitants, of which 120 million will be children. The projected number of celiac disease diagnoses in 2020 is 5 million cases (1 million celiac children), with a relative increase of 11% compared to 2010. Based on the 2010 rate, there will be about 550,000 symptomatic adults and about 240,000 sick children: 85% of the symptomatic patients will suffer from gastrointestinal complaints, 40% are likely to have anemia, 30% will likely have osteopenia, 20% of children will have short stature, and 10% will have abnormal liver enzymes[128]. The economic impact as discussed earlier with reference to non-celiac gluten sensitivity is already having major consequences, particularly in the U.S.A. In cases of non-celiac gluten sensitivity

the priority is in finding adequate criteria and tests to confirm the diagnosis and clearly separate the different entities which are included in this diagnosis.

References

1. Weile B, Krasilnikoff PA. *Low incidence rates by birth of symptomatic coeliac disease in a Danish population of children.* Acta Paediatr. 1992; 81: 394-8.
   http://dx.doi.org/10.1111/j.1651-2227.1992.tb12256.x
   PMid:1498504
2. George EK, Mearin ML, van der Velde EA, et al. *Low incidence of childhood celiac disease in The Netherlands.* Pediatr Res. 1995; 37: 213-8.
   http://dx.doi.org/10.1203/00006450-199502000-00015
   PMid:7731760
3. Ascher H, Krantz I, Kristiansson B. *Increasing incidence of coeliac disease in Sweden.* Arch Dis Child. 1991; 66: 608-11.
   http://dx.doi.org/10.1136/adc.66.5.608
   PMid:2039251 PMCid:PMC1792945
4. Magazzu G, Bottaro G, Cataldo F, et al. *Increasing incidence of childhood celiac disease in Sicily: results of a multicenter study.* Acta Paediatr. 1994; 83: 1065-9.
   http://dx.doi.org/10.1111/j.1651-2227.1994.tb12987.x
   PMid:7841706
5. Cilleruelo ML, Roman-Riechmann E, Sanchez-Valverde F, et al. *Spanish national registry of celiac disease: incidence and clinical presentation.* J Pediatr Gastroenterol Nutr. 2014; 59: 522-6.
   http://dx.doi.org/10.1097/MPG.0000000000000446
   PMid:24886992
6. Bai D, Brar P, Holleran S, et al. *Effect of gender on the manifestations of celiac disease: evidence for greater malabsorption in men.* Scand J Gastroenterol. 2005; 40: 183-7.
   http://dx.doi.org/10.1080/00365520510011498
   PMid:15764149
7. Tursi A, Giorgetti G, Brandimarte G, et al. *Prevalence and clinical presentation of subclinical/silent celiac disease in adults: an analysis on a 12-year observation.* Hepato-gastroenterology. 2001; 48: 462-4.
   PMid:11379333
8. Hadithi M, von Blomberg B, Crusius J, et al. *Accuracy of serologic tests and HLA-DQ typing for diagnosing celiac disease.* Ann Intern Med. 2007; 147: 294-302.
   http://dx.doi.org/10.7326/0003-4819-147-5-200709040-00003
   PMid:17785484

9. Karell K, Louka AS, Moodie SJ, et al. *HLA types in celiac disease patients not carrying the DQA1*05-DQB1*02 (DQ2) heterodimer: results from the European Genetics Cluster on Celiac Disease.* Hum Immunol. 2003; 64: 469-77.
http://dx.doi.org/10.1016/S0198-8859(03)00027-2

10. Megiorni F, Mora B, Bonamico M, et al. *HLA-DQ and risk gradient for celiac disease.* Hum Immunol. 2009; 70: 55-9.
http://dx.doi.org/10.1016/j.humimm.2008.10.018
PMid:19027045

11. Sollid LM. *Coeliac disease: dissecting a complex inflammatory disorder.* Nat Rev Immunol. 2002; 2: 647-55.
http://dx.doi.org/10.1038/nri885
PMid:12209133

12. Izzo V, Pinelli M, Tinto N, et al. *Improving the estimation of celiac disease sibling risk by non-HLA genes.* PLoS One. 2011; 6: e26920.
http://dx.doi.org/10.1371/journal.pone.0026920
PMid:22087237 PMCid:PMC3210127

13. Romanos J, van Diemen CC, Nolte IM, et al. *Analysis of HLA and non-HLA alleles can identify individuals at high risk for celiac disease.* Gastroenterology. 2009; 137: 834-40, 840 e1-3.

14. Villanacci V, Ceppa P, Tavani E, et al. *Coeliac disease: the histology report.* Dig Liver Dis. 2011; 43 Suppl 4: S385-95.
http://dx.doi.org/10.1016/S1590-8658(11)60594-X

15. Bonamico M, Thanasi E, Mariani P, et al. *Duodenal bulb biopsies in celiac disease: a multicenter study.* J Pediatr Gastroenterol Nutr. 2008; 47: 618-22.
http://dx.doi.org/10.1097/MPG.0b013e3181677d6e
PMid:18979585

16. Marine M, Fernandez-Banares F, Alsina M, et al. *Impact of mass screening for gluten-sensitive enteropathy in working population.* World J Gastroenterol. 2009; 15: 1331-8.
http://dx.doi.org/10.3748/wjg.15.1331
PMid:19294762 PMCid:PMC2658830

17. Mearin ML, Ivarsson A, Dickey W. *Coeliac disease: is it time for mass screening?* Best Pract Res Clin Gastroenterol. 2005; 19: 441-52.
http://dx.doi.org/10.1016/j.bpg.2005.02.004
PMid:15925848

18. Rostom A, Murray JA, Kagnoff MF. *American Gastroenterological Association (AGA) Institute technical review on the diagnosis and management of celiac disease.* Gastroenterology. 2006; 131: 1981-2002.
http://dx.doi.org/10.1053/j.gastro.2006.10.004
PMid:17087937

19. Green PH, Cellier C. *Celiac disease.* N Engl J Med. 2007; 357: 1731-43.
http://dx.doi.org/10.1056/NEJMra071600
PMid:17960014

20. Catassi C, Yachha SK. *The global village of celiac disease.* In: Fasano A, Troncone R, Branski D, eds. Frontiers in celiac disease. Volume 23-31. Basel: Switzerland Karger, 2008.
http://dx.doi.org/10.1159/000128610

21. Murray JA, Van Dyke C, Plevak MF, et al. *Trends in the identification and clinical features of celiac disease in a North American community, 1950-2001.* Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2003; 1: 19-27.
http://dx.doi.org/10.1053/jcgh.2003.50004
PMid:15017513

22. McGowan KE, Castiglione DA, Butzner JD. *The changing face of childhood celiac disease in north america: impact of serological testing.* Pediatrics. 2009; 124: 1572-8.
http://dx.doi.org/10.1542/peds.2008-2373
PMid:19948628

23. Kochhar R, Sachdev S, Kochhar R, et al. *Prevalence of coeliac disease in healthy blood donors: a study from north India.* Dig Liver Dis. 2012; 44: 530-2.
http://dx.doi.org/10.1016/j.dld.2012.01.004
PMid:22497903

24. Garcia Novo MD, Garfia C, Acuña Quiros MD, et al. *Prevalence of celiac disease in apparently healthy blood donors in the autonomous community of Madrid.* Rev Esp Enferm Dig. 2007; 99: 337-42.
PMid:17883297

25. Melo SB, Fernandes MI, Peres LC, et al. *Prevalence and demographic characteristics of celiac disease among blood donors in Ribeirao Preto, State of Sao Paulo, Brazil.* Dig Dis Sci. 2006; 51: 1020-1025.
http://dx.doi.org/10.1007/s10620-006-9340-9
PMid:16758312

26. Shamir R, Lerner A, Shinar E, et al. *The use of a single serological marker underestimates the prevalence of celiac disease in Israel: a study of blood donors.* Am J Gastroenterol. 2002; 97: 2589-94.
http://dx.doi.org/10.1111/j.1572-0241.2002.06028.x
PMid:12385444

27. Ghozzi M, Sakly W, Mankai A, et al. *Screening for celiac disease, by endomysial antibodies, in patients with unexplained articular manifestations.* Rheumatol Int. 2014; 34: 637-42.

http://dx.doi.org/10.1007/s00296-013-2906-x
PMid:24292850

28. Carroccio A, Iannitto E, Di PL, et al. *Screening for celiac disease in non-Hodgkin's lymphoma patients: a serum anti-transglutaminase-based approach.* Dig Dis Sci. 2003; 48: 1530-1536.

http://dx.doi.org/10.1023/A:1024811707311
PMid:12924648

29. Vancikova Z, Chlumecky V, Sokol D, et al. *The serologic screening for celiac disease in the general population (blood donors) and in some high-risk groups of adults (patients with autoimmune diseases, osteoporosis and infertility) in the Czech republic.* Folia Microbiol (Praha). 2002; 47: 753-8.

http://dx.doi.org/10.1007/BF02818684

30. Al Attas RA. *How common is celiac disease in Eastern Saudi Arabia?* Ann Saudi Med. 2002; 22: 315-9.

PMid:17146251

31. Volta U, Ravaglia G, Granito A, et al. *Coeliac disease in patients with autoimmune thyroiditis.* Digestion. 2001; 64: 61-5.

http://dx.doi.org/10.1159/000048840
PMid:11549838

32. Cuoco L, Certo M, Jorizzo RA, et al. *Prevalence and early diagnosis of coeliac disease in autoimmune thyroid disorders.* Ital J Gastroenterol Hepatol. 1999; 31: 283-7.

PMid:10425571

33. Freeman HJ. *Risk factors in familial forms of celiac disease.* World J Gastroenterol. 2010; 16: 1828-31.

http://dx.doi.org/10.3748/wjg.v16.i15.1828
PMid:20397258 PMCid:PMC2856821

34. Farre C, Humbert P, Vilar P, et al. *Serological markers and HLA-DQ2 haplotype among first-degree relatives of celiac patients. Catalonian Coeliac Disease Study Group.* Dig Dis Sci. 1999; 44: 2344-9.

http://dx.doi.org/10.1023/A:1026685527228
PMid:10573385

35. Maki M, Mustalahti K, Kokkonen J, et al. *Prevalence of Celiac disease among children in Finland.* N Engl J Med. 2003; 348: 2517-24.

http://dx.doi.org/10.1056/NEJMoa021687
PMid:12815137

36. Book L, Zone JJ, Neuhausen SL. *Prevalence of celiac disease among relatives of sib pairs with celiac disease in U.S. families.* Am J Gastroenterol. 2003; 98: 377-81.

http://dx.doi.org/10.1111/j.1572-0241.2003.07238.x
PMid:12591058

37. Hansen D, Bennedbaek FN, Hansen LK, et al. *High prevalence of coeliac disease in Danish children with type I diabetes mellitus.* Acta Paediatr. 2001; 90: 1238-43.

http://dx.doi.org/10.1111/j.1651-2227.2001.tb01568.x
PMid:11808892

38. Larsson K, Carlsson A, Cederwall E, et al. *Annual screening detects celiac disease in children with type 1 diabetes.* Pediatr Diabetes 2008; 9: 354-9.

http://dx.doi.org/10.1111/j.1399-5448.2008.00367.x
PMid:18774995

39. Bonamico M, Pasquino AM, Mariani P, et al. *Prevalence and clinical picture of celiac disease in Turner syndrome.* J Clin Endocrinol Metab. 2002; 87: 5495-8.

http://dx.doi.org/10.1210/jc.2002-020855
PMid:12466343

40. Smukalla S, Lebwohl B, Mears JG, et al. *How often do hematologists consider celiac disease in iron-deficiency anemia? Results of a national survey.* Clin Adv Hematol Oncol. 2014; 12: 100-5.

PMid:24892255

41. Kavimandan A, Sharma M, Verma AK, et al. *Prevalence of celiac disease in nutritional anemia at a tertiary care center.* Indian J Gastroenterol. 2014; 33: 114-8.

http://dx.doi.org/10.1007/s12664-013-0366-6
PMid:23996798

42. Hjelle AM, Apalset E, Mielnik P, et al. *Celiac disease and risk of fracture in adults-a review.* Osteoporosis international: a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2014; 25: 1667-76.

http://dx.doi.org/10.1007/s00198-014-2683-8
PMid:24691647

43. Stobaugh DJ, Deepak P, Ehrenpreis ED. *Increased risk of osteoporosis-related fractures in patients with irritable bowel syndrome.* Osteoporosis international: a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2013; 24: 1169-75.

http://dx.doi.org/10.1007/s00198-012-2141-4
PMid:22993020

44. Troncone R, Discepolo V. *Celiac disease and autoimmunity.* J Pediatr Gastroenterol Nutr. 2014; 59 Suppl 1: S9-S11.

http://dx.doi.org/10.1097/01.mpg.0000450394.30780.ea
PMid:24979198

45. Liu E, Lee HS, Aronsson CA, et al. *Risk of pediatric celiac disease according to HLA haplotype and country.* N Engl J Med. 2014; 371: 42-9.

http://dx.doi.org/10.1056/NEJMoa1313977
PMid:24988556 PMCid:PMC4163840

46. Virta LJ, Kolho KL. *The risk of contracting pediatric inflammatory bowel disease in children with celiac disease, epilepsy, juvenile arthritis and type 1 diabetes-a nationwide study.* J Crohns Colitis. 2013; 7: 53-7.

http://dx.doi.org/10.1016/j.crohns.2012.02.021
PMid:22445838

47. Mehrdad M, Mansour-Ghanaei F, Mohammadi F, et al. *Frequency of celiac disease in patients with hypothyroidism.* J Thyroid Res. 2012; 2012: 201538.

http://dx.doi.org/10.1155/2012/201538
PMid:22545223 PMCid:PMC3321550

48. Megiorni F, Pizzuti A. *HLA-DQA1 and HLA-DQB1 in Celiac disease predisposition: practical implications of the HLA molecular typing.* J Biomed Sci. 2012; 19: 88.

http://dx.doi.org/10.1186/1423-0127-19-88
PMid:23050549 PMCid:PMC3482388

49. Ludvigsson JF, Kampe O, Lebwohl B, et al. *Primary Hyperparathyroidism and Celiac Disease: A Population-Based Cohort Study.* J Clin Endocrinol Metab. 2012; 97: 897-904.

http://dx.doi.org/10.1210/jc.2011-2639
PMid:22238405 PMCid:PMC3319223

50. Efe C, Wahlin S, Ozaslan E, et al. *Autoimmune hepatitis/primary biliary cirrhosis overlap syndrome and associated extrahepatic autoimmune diseases.* Eur J Gastroenterol Hepatol. 2012; 24: 531-4.

http://dx.doi.org/10.1097/MEG.0b013e328350f95b
PMid:22465972

51. Krishnareddy S, Lewis SK, Green PH. *Dermatitis herpetiformis: clinical presentations are independent of manifestations of celiac disease.* Am J Clin Dermatol. 2014; 15: 51-6.

http://dx.doi.org/10.1007/s40257-013-0051-7
PMid:24293087

52. Plotnikova N, Miller JL. *Dermatitis herpetiformis.* Skin therapy letter. 2013; 18: 1-3.

PMid:23674144

53. Iqbal T, Zaidi MA, Wells GA, et al. *Celiac disease arthropathy and autoimmunity study.* J Gastroenterol Hepatol. 2013; 28: 99-105.

http://dx.doi.org/10.1111/j.1440-1746.2012.07272.x
PMid:22988822

54. Malt EA, Dahl RC, Haugsand TM, et al. *Health and disease in adults with Down syndrome.* Tidsskr Nor Laegeforen. 2013; 133: 290-4.

http://dx.doi.org/10.4045/tidsskr.12.0390
PMid:23381164

55. Grossi A, Palma A, Zanni G, et al. *Multiorgan autoimmunity in a Turner syndrome patient with partial monosomy 2q and trisomy 10p.* Gene. 2013; 515: 439-43.

http://dx.doi.org/10.1016/j.gene.2012.12.007
PMid:23262341

56. Giannotti A, Tiberio G, Castro M, et al. *Coeliac disease in Williams syndrome.* J Med Genet. 2001; 38: 767-8.

http://dx.doi.org/10.1136/jmg.38.11.767
PMid:11694549 PMCid:PMC1734770

57. Dirks MH. *Practical considerations for the identification and follow-up of children with celiac disease.* Paediatr Child Health. 2004; 9: 714-8.

PMid:19688081 PMCid:PMC2724146

58. Ruuskanen A, Kaukinen K, Collin P, et al. *Gliadin antibodies in older population and neurological and psychiatric disorders.* Acta Neurol Scand. 2013; 127: 19-25.

http://dx.doi.org/10.1111/j.1600-0404.2012.01668.x
PMid:22494246

59. Bukulmez A, Dalgic B, Gunduz B, et al. *The evaluation of hearing loss in children with celiac disease.* Int J Pediatr Otorhinolaryngol. 2013; 77: 175-9.

http://dx.doi.org/10.1016/j.ijporl.2012.10.012
PMid:23137854

60. Hadjivassiliou M, Aeschlimann P, Strigun A, et al. *Autoantibodies in gluten ataxia recognize a novel neuronal transglutaminase.* Ann Neurol. 2008; 64: 332-43.

http://dx.doi.org/10.1002/ana.21450
PMid:18825674

61. Crosato F, Senter S. *Cerebral occipital calcifications in celiac disease.* Neuropediatrics. 1992; 23: 214-7.

http://dx.doi.org/10.1055/s-2008-1071345
PMid:1407390

62. De Maddi F, Pellegrini F, Raffaele CG, et al. *Celiac disease and juvenile idiopathic arthritis: a still enigmatic crossover.* Scand J Gastroenterol. 2013; 48: 511-2.

http://dx.doi.org/10.3109/00365521.2013.772232
PMid:23448357

63. Zelnik N, Pacht A, Obeid R, et al. *Range of neurologic disorders in patients with celiac disease.* Pediatrics. 2004; 113: 1672-6.

http://dx.doi.org/10.1542/peds.113.6.1672
PMid:15173490

64. Welander A, Sundelin B, Fored M, et al. *Increased Risk of IgA Nephropathy Among Individuals With Celiac Disease.* J Clin Gastroenterol. 2013; 47: 678-83.

http://dx.doi.org/10.1097/MCG.0b013e318284792e
PMid:23442839

65. Smerud HK, Fellstrom B, Hallgren R, et al. *Gluten sensitivity in patients with IgA nephropathy.* Nephrol Dial Transplant. 2009; 24: 2476-81.

http://dx.doi.org/10.1093/ndt/gfp133
PMid:19332868

66. Prasad D, Khara HS, Gupta M, et al. *Celiac disease associated membranous nephropathy - a rare cause or coincidence? A case report.* Cases J. 2009; 2: 7018.

http://dx.doi.org/10.1186/1757-1626-0002-0000007018
PMid:19829897 PMCid:PMC2740114

67. Collin P, Syrjanen J, Partanen J, et al. *Celiac disease and HLA DQ in patients with IgA nephropathy.* Am J Gastroenterol. 2002; 97: 2572-6.

http://dx.doi.org/10.1111/j.1572-0241.2002.06025.x
PMid:12385441

68. Tursi A, Giorgetti G, Brandimarte G, et al. *Effect of gluten-free diet on pregnancy outcome in celiac disease patients with recurrent miscarriages.* Dig Dis Sci. 2008; 53: 2925-8.

http://dx.doi.org/10.1007/s10620-008-0242-x
PMid:18368491

69. Martinelli P, Troncone R, Paparo F, et al. *Coeliac disease and unfavourable outcome of pregnancy.* Gut. 2000; 46: 332-5.

http://dx.doi.org/10.1136/gut.46.3.332
PMid:10673293 PMCid:PMC1727862

70. Volta U, Bellentani S, Bianchi FB, et al. *High prevalence of celiac disease in Italian general population.* Dig Dis Sci. 2001; 46: 1500-5.

http://dx.doi.org/10.1023/A:1010648122797
PMid:11478502

71. Sjoberg K, Eriksson S. *Regional differences in coeliac disease prevalence in Scandinavia?* Scand J Gastroenterol. 1999; 34: 41-5.

http://dx.doi.org/10.1080/00365529950172817
PMid:10048731

72. West J, Fleming KM, Tata LJ, et al. *Incidence and prevalence of celiac disease and dermatitis herpetiformis in the UK over two decades: population-based study.* The American journal of gastroenterology. 2014; 109: 757-68.

http://dx.doi.org/10.1038/ajg.2014.55
PMid:24667576 PMCid:PMC4012300

73. Biagi F, Trotta L, Alfano C, et al. *Prevalence and natural history of potential celiac disease in adult patients.* Scand J Gastroenterol. 2013; 48: 537-42.

http://dx.doi.org/10.3109/00365521.2013.777470
PMid:23506211

74. Dickey W, Hughes D. *Prevalence of celiac disease and its endoscopic markers among patients having routine upper gastrointestinal endoscopy.* Am J Gastroenterol. 1999; 94: 2182-6.

http://dx.doi.org/10.1111/j.1572-0241.1999.01348.x
PMid:10445547

75. Rostami K, Mulder C, Werre J, et al. *High prevalence of celiac disease in apparently healthy blood donors suggests a high prevalence of undiagnosed celiac disease in the Dutch population.* Scand J Gastroenterol. 1999; 34: 276-9.

http://dx.doi.org/10.1080/00365529950173681
PMid:10232872

76. Schweizer JJ, von Blomberg BM, Bueno-de Mesquita HB, et al. *Coeliac disease in The Netherlands.* Scand J Gastroenterol. 2004; 39: 359-64.

http://dx.doi.org/10.1080/00365520310008503
PMid:15125468

77. Rutz R, Ritzler E, Fierz W, et al. *Prevalence of asymptomatic celiac disease in adolescents of eastern Switzerland.* Swiss Med Wkly. 2002; 132: 43-7.

PMid:11953905

78. Cataldo F, Pitarresi N, Accomando S, et al. *Epidemiological and clinical features in immigrant children with coeliac disease: an Italian multicentre study.* Dig Liver Dis. 2004; 36: 722-9.

http://dx.doi.org/10.1016/j.dld.2004.03.021
PMid:15571002

79. Lohi S, Mustalahti K, Kaukinen K, et al. *Increasing prevalence of coeliac disease over time.* Aliment Pharmacol Ther. 2007; 26: 1217-25.

http://dx.doi.org/10.1111/j.1365-2036.2007.03502.x
PMid:17944736

80. Mustalahti K, Catassi C, Reunanen A, et al. *The prevalence of celiac disease in Europe: results of a centralized, international mass screening project.* Ann Med. 2010; 42: 587-95.

http://dx.doi.org/10.3109/07853890.2010.505931
PMid:21070098

81. Kondrashova A, Mustalahti K, Kaukinen K, et al. *Lower economic status and inferior hygienic environment may protect against celiac disease.* Ann Med. 2008; 40: 223-31.

http://dx.doi.org/10.1080/07853890701678689
PMid:18382888

82. Fasano A, Berti I, Gerarduzzi T, et al. *Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study.* Arch Intern Med. 2003; 163: 286-92.

http://dx.doi.org/10.1001/archinte.163.3.286
PMid:12578508

83. Rubio-Tapia A, Ludvigsson JF, Brantner TL, et al. *The prevalence of celiac disease in the United States.* Am J Gastroenterol. 2012; 107: 1538-44.

http://dx.doi.org/10.1038/ajg.2012.219
PMid:22850429

84. Catassi C, Kryszak D, Bhatti B, et al. *Natural history of celiac disease autoimmunity in a USA cohort followed since 1974.* Ann Med. 2010; 42: 530-8.

http://dx.doi.org/10.3109/07853890.2010.514285
PMid:20868314

85. Teresi S, Crapisi M, Vallejo MD, et al. *Celiac disease seropositivity in Saharawi children: a follow-up and family study.* J Pediatr Gastroenterol Nutr. 2010; 50: 506-9.

http://dx.doi.org/10.1097/MPG.0b013e3181bab30c

86. Coton T, Grassin F, Maslin J, et al. *Celiac disease: special features in Africa. Description of 8 cases in Djibouti (horn of Africa).* Med Trop (Mars). 2008; 68: 144-8.

87. Fleming AF. *Iron deficiency in the tropics.* Clin Haematol. 1982; 11: 365-88.

PMid:7042157

88. Honar N, Karamizadeh Z, Saki F. *Prevalence of celiac disease in patients with type 1 diabetes mellitus in the south of Iran.* Turk J Gastroenterol. 2013; 24: 122-6.

PMid:23934458

89. Shahbazkhani B, Malekzadeh R, Sotoudeh M, et al. *High prevalence of coeliac disease in apparently healthy Iranian blood donors.* Eur J Gastroenterol Hepatol. 2003; 15: 475-8.

http://dx.doi.org/10.1097/00042737-200305000-00003
PMid:12702902

90. Elsurer R, Tatar G, Simsek H, et al. *Celiac disease in the Turkish population.* Dig Dis Sci. 2005; 50: 136-142.

http://dx.doi.org/10.1007/s10620-005-1291-z
PMid:15712651

91. Gursoy S, Guven K, Simsek T, et al. *The prevalence of unrecognized adult celiac disease in Central Anatolia.* J Clin Gastroenterol. 2005; 39: 508-11.

http://dx.doi.org/10.1097/01.mcg.0000165664.87153.e1
PMid:15942437

92. Imanzadeh F, Sayyari AA, Yaghoobi M, et al. *Celiac disease in children with diarrhea is more frequent than previously suspected.* J Pediatr Gastroenterol Nutr. 2005; 40: 309-11.

http://dx.doi.org/10.1097/01.MPG.0000154012.10420.08
PMid:15735484

93. Ertekin V, Selimoglu MA, Kardas F, et al. *Prevalence of celiac disease in Turkish children.* J Clin Gastroenterol. 2005; 39: 689-91.

http://dx.doi.org/10.1097/01.mcg.0000174026.26838.56
PMid:16082278

94. Akbari MR, Mohammadkhani A, Fakheri H, et al. *Screening of the adult population in Iran for coeliac disease: comparison of the tissue-transglutaminase antibody and anti-endomysial antibody tests.* Eur J Gastroenterol Hepatol. 2006; 18: 1181-6.

http://dx.doi.org/10.1097/01.meg.0000224477.51428.32
PMid:17033439

95. Tatar G, Elsurer R, Simsek H, et al. *Screening of tissue transglutaminase antibody in healthy blood donors for celiac disease screening in the Turkish population.* Dig Dis Sci. 2004; 49: 1479-84.

http://dx.doi.org/10.1023/B:DDAS.0000042250.59327.91
PMid:15481323

96. Makharia GK, Mulder CJ, Goh KL, et al. *Issues associated with the emergence of coeliac disease in the Asia-Pacific region: a working party report of the World Gastroenterology Organization and the Asian Pacific Association of Gastroenterology.* J Gastroenterol Hepatol. 2014; 29: 666-77.

http://dx.doi.org/10.1111/jgh.12514
PMid:24783246

97. Gupta R, Reddy DN, Makharia GK, et al. *Indian task force for celiac disease: current status.* World J Gastroenterol. 2009; 15: 6028-33.

http://dx.doi.org/10.3748/wjg.15.6028
PMid:20027674 PMCid:PMC2797658

98. Yachha SK, Poddar U. *Celiac disease in India.* Indian J Gastroenterol. 2007; 26: 230-7.

PMid:18227574

99. Catassi C, Anderson RP, Hill ID, et al. *World perspective on celiac disease.* J Pediatr Gastroenterol Nutr. 2012; 55: 494-9.

http://dx.doi.org/10.1097/MPG.0b013e318272adf4
PMid:22983371

100. Agrawal S, Srivastava SK, Borkar M, et al. *Genetic affinities of north and northeastern populations of India: inference from HLA-based study.* Tissue Antigens. 2008; 72: 120-30.

http://dx.doi.org/10.1111/j.1399-0039.2008.01083.x
PMid:18721272

101. Shanmugalakshmi S, Balakrishnan K, Manoharan K, et al. *HLA-DRB1*, -DQB1* in Piramalai Kallars and Yadhavas, two Dravidian-speaking castes of Tamil Nadu, South India.* Tissue Antigens. 2003; 61: 451-64.

http://dx.doi.org/10.1034/j.1399-0039.2003.00061.x
PMid:12823769

102. Makharia GK, Verma AK, Amarchand R, et al. *Prevalence of celiac disease in the northern part of India: a community based study.* J Gastroenterol Hepatol. 2011; 26: 894-900.

http://dx.doi.org/10.1111/j.1440-1746.2010.06606.x
PMid:21182543

103. Sood A, Midha V, Sood N, et al. *Prevalence of celiac disease among school children in Punjab, North India.* J Gastroenterol Hepatol. 2006; 21: 1622-5.

http://dx.doi.org/10.1111/j.1440-1746.2006.04281.x
PMid:16928227

104. Masood N, Ali Shaikh I. *Clinical presentations and biochemical profile in adult celiac disease patients in Hyderabad: Pakistan.* Pak J Med Sci. 2014; 30: 287-90.

PMid:24772128 PMCid:PMC3998995

105. Rashid M, Khan AG. *Celiac disease in Pakistan: challenges and opportunities.* J Ayub Med Coll Abbottabad. 2009; 21: 1-2.

PMid:20929000

106. Perez Villavicencio A, Beirute Lucke C, Peña AS. *Perspectives to take into account when studying celiac disease in China and Central America.* In: Rodrigo L, Peña AS, eds. Celiac disease and non-celiac gluten sensitivity. Barcelona, Spain: OmniaScience, 2014: 61-64.

http://dx.doi.org/10.3926/oms.237

107. Yuan J, Gao J, Li X, et al. *The tip of the "celiac iceberg" in China: a systematic review and meta-analysis.* PLoS One. 2013; 8: e81151.

http://dx.doi.org/10.1371/journal.pone.0081151
PMid:24324669 PMCid:PMC3852028

108. Wu J, Xia B, von Blomberg BM, et al. *Coeliac disease in China, a field waiting for exploration.* Rev Esp Enferm Dig. 2010; 102: 472-7.

http://dx.doi.org/10.4321/S1130-01082010000800003
PMid:20670067

109. Wu J, Xia B, von Blomberg BM, et al. *Coeliac disease: emerging in China?* Gut. 2010; 59: 418-9.

http://dx.doi.org/10.1136/gut.2009.197863
PMid:20207652

110. Wang XQ, Liu W, Xu CD, et al. *Celiac disease in children with diarrhea in 4 cities in China.* J Pediatr Gastroenterol Nutr. 2011; 53: 368-70.

PMid:21701402

111. Sher KS, Fraser RC, Wicks AC, et al. *High risk of coeliac disease in Punjabis. Epidemiological study in the south Asian and European populations of Leicestershire.* Digestion. 1993; 54: 178-82.

http://dx.doi.org/10.1159/000201035
PMid:8359561

112. Watanabe C, Komoto S, Hokari R, et al. *Prevalence of serum celiac antibody in patients with IBD in Japan.* J Gastroenterol. 2014; 49: 825-34.

http://dx.doi.org/10.1007/s00535-013-0838-6
PMid:23754511 PMCid:PMC4019828

113. Cook HB, Burt MJ, Collett JA, et al. *Adult coeliac disease: prevalence and clinical significance.* Journal of gastroenterology and hepatology. 2000; 15: 1032-6.

http://dx.doi.org/10.1046/j.1440-1746.2000.02290.x
PMid:11059933

114. Tanpowpong P, Ingham TR, Lampshire PK, et al. *Coeliac disease and gluten avoidance in New Zealand children.* Arch Dis Child. 2012; 97: 12-26.

http://dx.doi.org/10.1136/archdischild-2011-300248
PMid:22075107

115. Chin MW, Mallon DF, Cullen DJ, et al. *Screening for coeliac disease using anti-tissue transglutaminase antibody assays, and prevalence of the disease in an Australian community.* Med J Aust. 2009; 190: 429-32.

PMid:19374615

116. Hovell CJ, Collett JA, Vautier G, et al. *High prevalence of coeliac disease in a population-based study from Western Australia: a case for screening?* Med J Aust. 2001; 175: 247-50.

PMid:11587254

117. Remes-Troche JM, Ramirez-Iglesias MT, Rubio-Tapia A, et al. *Celiac disease could be a frequent disease in Mexico: prevalence of tissue transglutaminase antibody in healthy blood donors.* J Clin Gastroenterol. 2006; 40: 697-700.

http://dx.doi.org/10.1097/00004836-200609000-00007
PMid:16940881

118. Remes-Troche JM, Nunez-Alvares C, Uscanga-Dominguez LF. *Celiac disease in Mexican population: an update.* Am J Gastroenterol. 2013; 108: 283-4.

http://dx.doi.org/10.1038/ajg.2012.408
PMid:23381082

119. Remes-Troche JM, Rios-Vaca A, Ramirez-Iglesias MT, et al. *High prevalence of celiac disease in Mexican Mestizo adults with type 1 diabetes mellitus.* J Clin Gastroenterol. 2008; 42: 460-5.

http://dx.doi.org/10.1097/MCG.0b013e318046ea86
PMid:18344893

120. Cromeyer M, Gutierrez RA, Zaldivar K, et al. *Celiac disease in El Salvador.* In: Rodrigo L, Peña AS, eds. Celiac disease and non-celiac gluten sensitivity. Barcelona, Spain: OmniaScience, 2014: 75-88.

http://dx.doi.org/10.3926/oms.231

121. Brenes-Pino F, Brenes A. *Small Intestine Biopsy and its Interpretation: Preliminary Results in Costa Rica.* In: Rodrigo L, Peña AS, eds. Celiac disease and non-celiac gluten sensitivity. Barcelona, Spain: OmniaScience, 2014: 203-218.

http://dx.doi.org/10.3926/oms.229

122. Modelli IC, Gandolfi L, Almeida RC, et al. *Serological screening for celiac disease in symptomatic 12 to 36 month-old children.* Arq Gastroenterol. 2010; 47: 61-5.

http://dx.doi.org/10.1590/S0004-28032010000100011
PMid:20520977

123. Almeida PL, Gandolfi L, Modelli IC, et al. *Prevalence of celiac disease among first degree relatives of Brazilian celiac patients.* Arq Gastroenterol. 2008; 45: 69-72.

http://dx.doi.org/10.1590/S0004-28032008000100013
PMid:18425232

124. Pereira MA, Ortiz-Agostinho CL, Nishitokukado I, et al. *Prevalence of celiac disease in an urban area of Brazil with predominantly European ancestry.* World J Gastroenterol. 2006; 12: 6546-50.

PMid:17072989 PMCid:PMC4100646

125. Mora M, Litwin N, Toca Mdel C, et al. *Prevalence of celiac disease: multicentric trial among pediatric population from five urban districts in Argentina.* Arch Argent Pediatr. 2012; 110: 490-6.

http://dx.doi.org/10.5546/aap.2012.eng.490

126. Gomez JC, Selvaggio GS, Viola M, et al. *Prevalence of celiac disease in Argentina: screening of an adult population in the La Plata area.* The American journal of gastroenterology. 2001; 96: 2700-4.

http://dx.doi.org/10.1111/j.1572-0241.2001.04124.x
PMid:11569698

127. Marine M, Farre C, Alsina M, et al. *The prevalence of coeliac disease is significantly higher in children compared with adults.* Aliment Pharmacol Ther. 2011; 33: 477-86.

http://dx.doi.org/10.1111/j.1365-2036.2010.04543.x
PMid:21166832

128. Greco L, Timpone L, Abkari A, et al. *Burden of celiac disease in the Mediterranean area.* World J Gastroenterol. 2011; 17: 4971-8.

http://dx.doi.org/10.3748/wjg.v17.i45.4971
PMid:22174546 PMCid:PMC3236588

129. Reunala T. *Dermatitis herpetiformis: coeliac disease of the skin.* Annals of medicine. 1998; 30: 416-8.

http://dx.doi.org/10.3109/07853899809002482
PMid:9814827

130. Meyer LJ, Zone JJ. *Familial incidence of dermatitis herpetiformis.* Journal of the American Academy of Dermatology. 1987; 17: 643-7.

http://dx.doi.org/10.1016/S0190-9622(87)70250-3

131. Reunala T. *Incidence of familial dermatitis herpetiformis.* The British journal of dermatology. 1996; 134: 394-8.

http://dx.doi.org/10.1111/j.1365-2133.1996.tb16220.x
PMid:8731659

132. da Silva Kotze LM, Nisihara R, Kotze LR, et al. *Celiac disease and dermatitis herpetiformis in Brazilian twins: a long-term follow-up and screening of their relatives.* Journal of pediatric endocrinology and metabolism. 2013; 26: 71-5.

http://dx.doi.org/10.1515/jpem-2012-0282
PMid:23329745

133. Hervonen K, Alakoski A, Salmi TT, et al. *Reduced mortality in dermatitis herpetiformis: a population-based study of 476 patients.* The British journal of dermatology. 2012; 167: 1331-7.

http://dx.doi.org/10.1111/j.1365-2133.2012.11105.x
PMid:22708883

134. Zhang F, Yang B, Lin Y, et al. *Dermatitis herpetiformis in China: a report of 22 cases.* Journal of the European Academy of Dermatology and Venereology : JEADV. 2012; 26: 903-7.

http://dx.doi.org/10.1111/j.1468-3083.2011.04204.x
PMid:22032403

135. Shibahara M, Nanko H, Shimizu M, et al. *Dermatitis herpetiformis in Japan: an update.* Dermatology. 2002; 204: 37-42.

http://dx.doi.org/10.1159/000051808
PMid:11834848

136. Daneshpazhooh M, Chams-Davatchi C, Payandemehr P, et al. *Spectrum of autoimmune bullous diseases in Iran: a 10-year review.* International journal of dermatology. 2012; 51: 35-41.

http://dx.doi.org/10.1111/j.1365-4632.2011.04946.x
PMid:22182376

137. Wong SN, Chua SH. *Spectrum of subepidermal immunobullous disorders seen at the National Skin Centre, Singapore: a 2-year review.* The British journal of dermatology. 2002; 147: 476-80.

http://dx.doi.org/10.1046/j.1365-2133.2002.04919.x

138. Adam BA. *Bullous diseases in Malaysia: epidemiology and natural history.* International journal of dermatology. 1992; 31: 42-5.

http://dx.doi.org/10.1111/j.1365-4362.1992.tb03519.x
PMid:1737688

139. Smith JB, Tulloch JE, Meyer LJ, et al. *The incidence and prevalence of dermatitis herpetiformis in Utah.* Archives of dermatology. 1992; 128: 1608-10.

http://dx.doi.org/10.1001/archderm.1992.04530010046006
PMid:1456754

140. Smecuol E, Sugai E, Niveloni S, et al. *Permeability, zonulin production, and enteropathy in dermatitis herpetiformis.* Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association. 2005; 3: 335-41.

http://dx.doi.org/10.1016/S1542-3565(04)00778-5

141. Salmi TT, Hervonen K, Kautiainen H, et al. *Prevalence and incidence of dermatitis herpetiformis: a 40-year prospective study from Finland.* The British Journal of Dermatology. 2011; 165: 354-9.

http://dx.doi.org/10.1111/j.1365-2133.2011.10385.x
PMid:21517799

142. Hadjivassiliou M. *Immune-mediated acquired ataxias.* Handb Clin Neurol. 2012; 103: 189-99.

http://dx.doi.org/10.1016/B978-0-444-51892-7.00011-5
PMid:21827889

143. Hadjivassiliou M, Grunewald R, Sharrack B, et al. *Gluten ataxia in perspective: epidemiology, genetic susceptibility and clinical characteristics.* Brain. 2003; 126: 685-91.

http://dx.doi.org/10.1093/brain/awg050
PMid:12566288

144. Hernandez-Lahoz C, Rodrigo-Saez L, Vega-Villar J, et al. *Familial gluten ataxia.* Mov Disord. 2014; 29: 308-10.

http://dx.doi.org/10.1002/mds.25783
PMid:24375771

145. Nanri K, Mitoma H, Ihara M, et al. *Gluten ataxia in Japan.* Cerebellum. 2014; 13: 623-7.

http://dx.doi.org/10.1007/s12311-014-0582-3
PMid:24997752

146. Wills A, Dale R, Giovannoni G. *Gluten Ataxia and Post-Streptococcal Central Nervous System Syndromes: Emerging Immune-mediated Disorders of the Central Nervous System?* Curr Treat Options Neurol. 2005; 7: 183-189.

http://dx.doi.org/10.1007/s11940-005-0011-5
PMid:15814071

147. Leonard MM, Vasagar B. *US perspective on gluten-related diseases.* Clin Exp Gastroenterol. 2014; 7: 25-37.

PMid:24493932 PMCid:PMC3908912

148. Czaja-Bulsa G. *Non coeliac gluten sensitivity - A new disease with gluten intolerance.* Clin Nutr. 2014.

PMid:25245857

149. Peña AS, Rodrigo L. *Celiac disease and non-celiac gluten sensitivity.* In: Rodrigo L, Peña AS, eds. Celiac disease and Non-Celiac Gluten Sensitivity. Volume. Barcelona: OmniaScience, 2014: 25-43.

http://dx.doi.org/10.3926/oms.223

150. Di Sabatino A, Corazza GR. *Nonceliac gluten sensitivity: sense or sensibility?* Ann Intern Med. 2012; 156: 309-11.

http://dx.doi.org/10.7326/0003-4819-156-4-201202210-00010
PMid:22351716

151. Spence D. *Bad medicine: food intolerance.* BMJ. 2013; 346: f529.

http://dx.doi.org/10.1136/bmj.f529
PMid:23364064

152. Aziz I, Lewis NR, Hadjivassiliou M, et al. *A UK study assessing the population prevalence of self-reported gluten sensitivity and referral characteristics to secondary care.* Eur J Gastroenterol Hepatol. 2014; 26: 33-9.

http://dx.doi.org/10.1097/01.meg.0000435546.87251.f7
PMid:24216570

153. Ho MH, Wong WH, Chang C. *Clinical spectrum of food allergies: a comprehensive review.* Clin Rev Allergy Immunol. 2014; 46: 225-40.

http://dx.doi.org/10.1007/s12016-012-8339-6
PMid:23229594

154. Morita E, Chinuki Y, Takahashi H, et al. *Prevalence of wheat allergy in Japanese adults.* Allergol Int. 2012; 61: 101-5.

http://dx.doi.org/10.2332/allergolint.11-OA-0345
PMid:22377522

155. Dey D, Ghosh N, Pandey N, et al. *A hospital-based survey on food allergy in the population of Kolkata, India.* Int Arch Allergy Immunol. 2014; 164: 218-21.

http://dx.doi.org/10.1159/000365629
PMid:25138428

156. Lee AJ, Thalayasingam M, Lee BW. *Food allergy in Asia: how does it compare?* Asia Pac Allergy. 2013; 3: 3-14.

http://dx.doi.org/10.5415/apallergy.2013.3.1.3
PMid:23403837 PMCid:PMC3563019

157. Green PH. *The many faces of celiac disease: clinical presentation of celiac disease in the adult population.* Gastroenterology. 2005; 128: S74-8.

http://dx.doi.org/10.1053/j.gastro.2005.02.016
PMid:15825130