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RESEARCH ARTICLE

THE WORLD INCIDENCE OF CELIAC DISEASE IS INCREASING: A REVIEW

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ABSTRACT

Background: Currently, we are witnessing a diffused ongoing epidemic of CD of great scale. Epidemiological data provide strong evidence of a steady rise in celiac disease (CD) throughout westernized societies over the last six decades. Multiple publications exist, describing past or actual incidences/prevalence of CD, however, long term studies follow-up, on selected populations are scarce.
Aims: To calculate the % increases per year of CD incidence worldwide and analyze the differential longitudinal increases of CD per country, and identify geoepidemiological trends.
Methods: A systematic review was performed to identify incidences of CD. Studies from the last 6 decades were identified using Medline, Google, and Cochrane Library databases. Only long-term regional or national long-term follow-ups are reported.
Results: The mean ± s.d. of the net increase in %/year incidence of CD worldwide is 9.77±8.27. In all of these studies, differences between old vs new frequencies were highly significant ($p< 0.0001$). Geoepidemiologically, Netherland/USA had the highest/lowest net %/year CD incidence increases: 9.23±9.64, 5.0±2.09 respectively. The mean ± s.d. net %/year increases in children was comparable to that depicted in adult populations: 6.6±7.9, 5.2±4.0, respectively $p=0.664$.The increases were higher in northern/western countries than in southern/eastern countries.
Conclusions: Reviewing available literature, it can be deduced that incidences of CD have increased significantly over the last 60 years. In Canada, Scotland, and Spain the %/year incidence surges were highest while in Estonia, USA and New Zealand it was the lowest. These observations point to a stronger influence of environmental factors as opposed to genetic factors on CD development.

INTRODUCTION

Epidemiological data provide strong evidence of a steady rise in autoimmune disease throughout westernized societies over the lastdecades[1]. Celiac disease (CD), being an autoimmune disease [2], is not an exception. Currently, we are witnessing a diffused ongoing epidemic of CD of great scale[3]. The prevalence of the disease is increasing constantly and has increased over fourfold in the last half-century [4]. The prevalence of "suspected" celiac disease varies from 1 in 87 to 1 in 500 individuals in western countries. The majority of patients are undiagnosed since diagnosed cases of CD have a much lower prevalence being somewhere between 1 in 500 and 1 in 9000 individuals. In high risk populations, the average risk of CD can reach 5-10%. The generally reported incidence of CD in the western world is around 1%, however, 2 to 5.6% were reported in Northern European countries and in the Sahara desert region in North Africa, respectively[5-7]. Even in the Far East, where rice is the main staple food, increased incidence of CD is being reported, whereby India is a good example [8].

The geoepidemiological distribution of the autoimmune diseases , the world-wide North-South gradient and the West-East gradient in Europe related to the socioeconomic status, the rapid increase in developed countries and population migration observations are indicative of an environmental impact, rather genetic factors, driving these rapid and recent evolutionary processes [1,9,10]. Among others, two major environmental factors, strongly related to socioeconomical status are suspected to drive these phenomena: infections and nutrition[11]. Nutrition plays a pivotal factor in CD induction. Gluten, which is the storage protein of wheat, and its alcohol-soluble gliadins, are the primary offending inducers of the disease[12]. Most recently, the hypothesis that the industrial food additive enzyme microbial transglutaminase, used in the food processing as a protein glue, is a newly recognized environmental inducer of CD, was forwarded[13,14].

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Multiple publications exist, describing past or actual incidences/prevalence of CD, at single points in time, however, long term longitudinal follow-up studies, on selected populations are scarce. The present review will concentrate on such studies. The aims being to calculate the % increases per year of CD incidence worldwide, analyze the differential increases of CD per country and identify geoepidemiological trends.

METHODS

A systematic review was performed to identify incidences of CD. Studies from the last 6 decades (1950-2011) were identified using Medline, Google, and Cochrane Library databases. Only long-term regional or national long-term follow-up studies are reported. Studies on high risk populations and material from hospital archives, were excluded. A diploid statistical analysis was employed: Assessments were made using the reported incidences and used to calculate the average annual percent changes in incidence rates. Diploid statistical analysis used the Software MedCalc® and involved performing a t-test for the comparison of two independent means ($p<0.05$ was considered statistical significant)

RESULTS

The mean ± s.d. of the net increased %/year in the overall incidence of CD worldwide is 9.77±8.27. Allocating these annual net % increases in individual countries, in a decreasing order: The Netherlands had the highest increase while the USA exhibited the lowest one, as shown in figure No 1[6,7,15-41].Table No 1 summarizes the past and the more recent incidences of CD, and the time gap between the surveys, in specific countries, where follow up studies were available. The highest/lowest %/year increased incidences were depicted in Canada/Estonia (33.3, 2.5, respectively)[15-41]. Comparing the differences between the overall mean± s.d. of the old vs new calculated incidences, the surge was highly significant ($p< 0.0211$). In order to normalize for the periods of time, so as to minimize environmental influences, all the incidence surveys carried out between 1976-2001,in countries where more than 2 or more comparative studies were performed, were compared(shown in Figure 2[15-30,32,33,35-39,41]).A clear upward trend of CD incidence is shown, throughout these 2.5 decades ($r^2=0.968$ $p<0.019$). The mean ± s.d. net %/year increases in children were comparable to those depicted in adult populations: 6.6±7.9, 5.2±4.0, respectively, $p=0.664$.

Country	Old incidence/100000	New incidence/100000	Time interval (years)	Incidence net increase	Incidence net increase %/year
Estonia	0.1	3.1	34	3.0	2.9
New Zealand	1.4	12.9	28	11.5	3.6
USA	3.3	12.0	20.0	8.7	5.0
Sweden	6.7	29.0	18.3	22.3	5.5
Finland	4.6	8.8	15.5	4.2	6.5
Denmark	1.0	4.1	15.0	3.1	6.7
UK	3.5	10.0	11.3	6.6	8.8
Israel	1.2	4.2	11.0	3.0	9.1
Netherlands	0.9	1.9	10.8	1.0	9.2
Spain	6.9	16.0	10.0	9.2	10.0
Scotland	1.8	11.7	6.0	9.9	16.7
Canada	10.4	15.7	3.0	5.3	33.3

Figure No 1 the annual net % increases/year, in individual countries, in an increasing order. (adapted from references:6,7,15-41)

The North/South and West/East trends in CD incidence surges are shown in Fig 3[15-41]. The increases were higher in Northern/Southern countries than in Western/Eastern ones, reaching significant levels. (11.3±9.0, 5.2± 3.4,11.8± 9.3, 6.4 ±3.7, $p<0.002$, $p<0.007$, respectively).

DISCUSSION

Population-based estimates of the incidence of CD in different countries are crucial for investigating possible etiologies or influencing environmental factors or underlining risk factors. Quantification of the likely healthcare burden and the planning of future strategies to face the ongoing epidemic of CD is of no less importance.

The beneficial aspects of early recognition of CD are well known. The CD related complications of stunted growth, failure to thrive, nutritional deficiencies, osteoporosis, anemia, increased risk of malignancy, infertility, hepatic transaminasemia and association with other autoimmune diseases are all potentially reversible on a gluten free diet, when the disease is diagnosed early enough. The increased awareness responsible for the surge in diagnosed patients' needs to continue together with a lower threshold for screening high risk populations using a cheap, non-invasive and reliable antibody biomarker to prevent delays in diagnosing such a common but preventable disease[42].

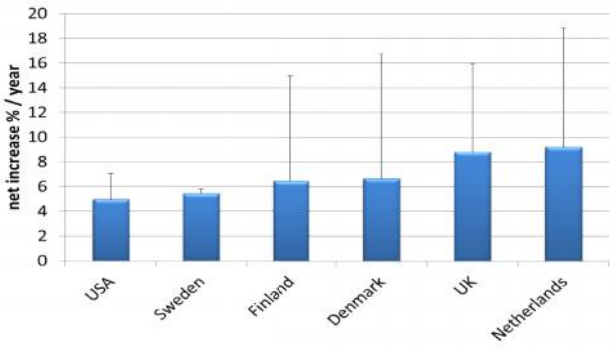

Figure No 2 A comparison of the net % increase/year in incidences, performed between 1976-2001. (Including studies from: Netherland, USA, Finland, Israel, Estonia, New Zealand, Sweden, UK, Denmark and Scotland). (adapted from references:15-30,32,33,35-39,41)

In the present review the increased incidences of CD world-wide, in the last decades are described. The mean of the net increased %/year incidence of CD worldwide is quite high at 9.77%. Differences between old vs new frequencies, in the counties where the information was available, were highly significant.

The net increased incidences of CD in the Northern and Western countries, compared to the Southern and Eastern ones follows the global geoepidemiological trends of autoimmune disease[43]. Reviewing available literature, it can be deduced that incidences of CD have increased significantly over the last 60 years. The recent outbreak of autoimmune diseases in industrialized countries has brought into question the factors contributing to this increased incidence. Given the constancy of genetics, growing attention has focused on environmental factors, and in particular, the western lifestyle[44]. Indeed, over the last few decades significant changes in western dietary

habits, environmental surroundings and pollution exposure, infectious habitat and stress load, have led to a parallel rise in autoimmune diseases. Thus, CD occupies an important place in this environmental mosaic of autoimmunity.

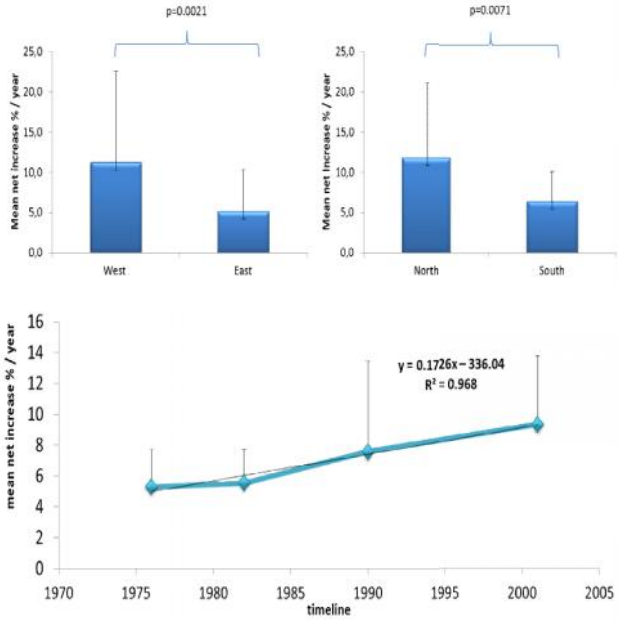

Figure No 3 The net increased %/year in the geographical distribution of the incidence of CD. (adapted from references:15-41)

A main question to ask is, what the reasons for such a documented CD surge are? Several explanations can be suggested:

A. Increased wheat intake

Increased production and consumption of high gluten containing prolamines. During the 20th century, global wheat output expanded by about 5-fold, whereby until about 1955 most of this reflected increases in wheat crop area, with limited (about 20%) increases in crop yields per unit area. Since 1955 however, there has been a dramatic ten-fold increase in the rate of wheat yield improvement per year, and this has become the major factor associated with increases in global wheat production. An average 2.5 tons of wheat was produced on one hectare of cropland in the world in the first half of 1990s, but this had increased to about 3 tons in 2009[45,46].

B. Higher gluten content in modern wheat.

During the evolution of wheat, genetic survival was essential for the wheat species to adapt to changing environmental conditions. In the modern age, extensive genetic natural selection, due to changing environment and breeding manipulations due to human intervention, have resulted in improved grain numbers, wheat survival and adaptation. Infact, multiple recent studies have documented the increased CD epitopes along the process of gluten gene enrichment in the passage of ancient diploid to modern tetraploid and hexaploid wheat species [47].

C. Genetic advantage and survival of CD patients

Interactions between environmental factors and predisposing genes could be involved in the development of CD, although the evolutionary burden can also evolve toward CD protection. It was suggested that the disadvantaged celiac patients survived the eco-catastrophes of the last two millennia by adapting to the extreme temperature changes and their consequences in Europe[47]. The hemochromatosis and SH2B3 genes, counteracting iron deficiency anemia and bacterial infections, respectively, are some examples [47,48].

D. Increased influence of environmental inducers of CD

Infections: CD is more prevalent in developed countries, higher socio-economic societies and higher hygienic environments, supporting the hygiene hypothesis[49]. However, the list of infections associated with CD is increasing constantly, as is the case with other autoimmune diseases [11,50,51]. Infections are major inducers of autoimmunity. Molecular mimicry, epitope spreading, bystander activation and stimulation of pattern recognition receptors, as well as persistent infection and polyclonal activation of B cells, are suggested as mechanisms [52]. Most recently light was shed on the interaction between host genetics and microbiota composition in relation to CD development.[53]. Expression of the HLA-DQ2 is a strong risk factor for the development of CD. Children with this haplotype have an altered microbiota composition prior to clinically apparent disease.

Stress: The brain gut axis is involved in many gastrointestinal conditions and stressful events affect multiple functions of the digestive tract [54]. The stress load is increasing alongside modern life, thus impacting gut physiology. Multiple animal studies have shown how stressful stimuli breach intestinal functional integrity [55-57]. Prior to diagnosis, the number of stressful events in celiac disease has been found to be more frequent than in the control group suggesting that life events may favor the clinical appearance of celiac disease or accelerate its diagnosis[58].

E. Gastrointestinal microbiome

Alterations in small intestinal microbial composition have recently been associated with autoimmune diseases including active CD, indicating a possible role for the microbiota in CD evolvement[53,59,60]. One of the potential mechanisms appears to be increased intestinal permeability. Since intestinal disbiosis is environmentally driven and heavily nutrient dependent, the changing environment in the later decades can explain the recent surge in CD incidence.

F. Increased intestinal permeability by disbiosis and food industrial additives

Various dietary components are also known to regulate epithelial permeability by modifying expression and localization of tight junction proteins[13,14,60]. More so, formula milk-feeding in conjunction with CD HLA-DQ genotype plays a role in establishing the infants gut microbiota, whereas, breast-feeding reduced the genotype-related differences in microbiota composition [61]. Recently, HLA-DQ2 was described as a high risk genetic factor in the altered microbiota composition prior to clinically apparent CD[53]. Chronic

inflammatory diseases of the intestine, such as celiac disease, are characterized by a leaky intestinal barrier[62].Tight junctions are not static barriers but highly dynamic structures that are constantly being remodeled due to interactions with external stimuli, such as food residues and pathogenic and commensal bacteria. In fact, commonly used industrial food additives abrogate human epithelial barrier function, thus, increasing intestinal permeability through the opened tight junction, resulting in entry of foreign immunogenic antigens and activation of the autoimmune cascade (14). The hypotheses that microbial transglutaminase, a common food industrial additive, is a new environmental inducer of CD, was recently suggesterd[13,14,63]. Taken together, the modern period surge in process food consumption, in conjunction with the dynamic CD disbiosis increasing intestinal permeability, can present one piece of the puzzle of CD incidence increase in the western world.

G. *Increased public and professional awareness.*

There has been a marked increase in both the public's, and physician's awareness (and also in the restaurant kitchen)of gluten related disorders [64-67]. Despite this, under awareness and under diagnosis are still prevalent. The studies emphasize the need for educating the public, patients, restaurant chefs and physicians in both the prevalence of celiac disease and the importance of early diagnosis, as well as the wide availability of serological tests on the market.

H. Improved diagnosis.

Multiple serological tests exist on the market. The first reliable one was found in the early 1980s[68] but the most frequently used one is IgA-tissue transglutaminase (tTG). Several combinations of CD related auto antibodies have been studied but not accurately compared with each other. The most frequently combined tests used are anti IgG-deaminated gliadin peptide and IgA-tTG, however, the new generation anti neo-epitope tTG combining tTg docked gliadin IgG+IgA is very reliable and is increasingly being used[42,69-73].Since only the tip of the CD iceberg is above the waterline and the much larger portion of the CD iceberg remains undetected underwater, it can be expected that the prevalence of the disease will continue to increase. An active case-finding strategy in the primary care setting was shown as an effective means to improve the diagnostic rate of CD in North America[67,74]. The need for a wider availability of the serological tests that can facilitate the diagnosis of celiac disease is obvious [66].

Several biases exist in the present review. Despite thorough review, some longitudinal follow ups could have been missed. The incidence analyses were done at large intervals, using different experimental designs, and different serological biomarkers and, during the last decades the knowledge, awareness, biomarkers, inclusion and exclusion criteria, as well as CD diagnostic guidelines, have changed extensively. These are the reasons why the present inclusion/exclusion criteria are so stringent. More specifically, in order to normalize for the periods of time, in order to diminish environmental influences, all the incidence studies done within a well-defined period, in countries where more than 2 or more comparative studies were performed, are displayed in Figure No 2.

In Summary, reviewing available literature, it can be deduced that incidences of CD have increased significantly over the last 60 years. The net increased incidences of CD in Northern and Western countries, compared to Southern and Eastern ones, were higher. No differences were observed between the adult and pediatric CD patients. The concrete explanation for the described surge of CD incidences is unknown, as multiple environmental changes have taken place over the last decades. These observations point to a stronger influence of environmental factors as opposed to genetic factors on CD development.

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