

STUDY ON THE INCIDENCE OF GLUTEN INTOLERANCE ASSOCIATED DISEASES WITH CONSUMPTION OF AGLUTENIC FOODS

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Abstract

Celiac disease (CD) is an immune condition that patients have to deal for lifelong. It affects almost 1% of the general population and determines lifestyle and social changes due to diet control and restrictions. Gluten ingestion in patients with CD determines bloating, abdominal pain, constipation, nausea and vomiting conducting to anaemia, osteoporosis, neurological problems, herpetiform dermatitis can occur later in life. The incidence of CD increased especially for women (17.4 cases of 100,000 for one year); for men, the incidence is 7.8 per 100,000 people in one year. More and more children are also diagnosed with celiac disease, 21.3 per 100,000 person-years compared to 12.9 per 100,000 in adults. Wheat allergy, gluten sensitivity and celiac disease represent medical conditions that are correlated with cereal consumption and become of increased interest for consumers in order to have an appropriate diet or a preventive one. Gluten free diet (GFD) become more popular among consumers and its popularity is increasing, health practitioners started to question if there is a real health benefit for everyone or just a medical nutrition therapy for those in need.

Key words: allergy, celiac disease, gluten allergy, gluten sensitivity, gluten free diet.

INTRODUCTION

Wheat is the most cultivated and consumed cereals of all times; it was the first cultivated one and it determined the evolution of humankind. Some of the cultivars have been modified in order to meet new challenges in agriculture, but it seems that this has been altered the level of gliadin, the protein fraction that is responsible for gluten sensitivity diseases group.

Celiac disease is the result of both environmental (gluten) and genetic factors (HLA and non-HLA genes), and the distribution of these two components can probably be used to identify the areas of the world at risk for gluten intolerance (Cataldo et al., 2007).

MATERIALS AND METHODS

For this research we have analysed Scopus Elsevier database and SpringerLink Journals by specific key words like “celiac disease”, “gluten related diseases”, “symptoms”, “effect on social life”, “incidence”, “diagnosis and treatment”, “clinical studies”. We have also used the statistics found on statistica.com and other official information of different states. We

analysed and compared data from 2009 to 2020 in order to have an overview on the evolution.

RESULTS AND DISCUSSIONS

Gluten, the responsible factor

Gluten represents the main wheat, rye and barley storage proteins known as prolamins that have an important role in bakery. Gluten is essential for dough formation, elasticity, dough gas retention capacity, porosity and bread quality in the end. Biochemically, gluten is a mixture of gliadins (alcohol soluble) and glutenin (alcohol insoluble), proteins rich in glutamine and proline. The high level of proline determines a certain resistance of these proteins to the proteolytic activity of gastric and pancreatic enzymes; they are also resistant to the small intestinal brush border membrane enzymes. Due to this enzymatic resistance the formation of long gliadin peptides in the gastrointestinal tract is occurring and this induces a detrimental immune response in patients with celiac disease. The most studied peptide is known as the “33mer” and it is considered the main initiator of the inflammatory response to gluten; it was found in all food grains that are toxic to celiac

disease patients and absent in other nontoxic cereals. Shan et al. (2002) found that this peptide can be hydrolyzed *in vitro* by a *Flavobacterium meningosepticum* prolyl endopeptidase. They observed that in vivo study using the rat intestinal perfusion model, enzyme can break down the “33mer” with the diminishing of its toxic effects and also the decrease of the T cell stimulatory potential with important positive effect on detoxifying gluten in celiac disease patients by peptidase therapy; this would suggest a strategy for a therapy with oral peptidase for celiac disease patients. Furthermore, the effect of undigested peptides reaches the gut, become available as good nurture for intestinal bacterial gluten metabolism which can change the gut microbiota (Caminero et al., 2016).

Genetic factors

There are two factors that might concur celiac disease development: ingestion of gluten and genetic predisposition. The latter is evidenced by the fact that the prevalence of celiac disease among first degree relatives of patients is 8%, higher than that of general population (Singh P. et al, 2015). Regarding the genetic factors that might determine a risk for celiac disease, there were identified HLA- DQ haplotypes HLADQ2 and HLA- DQ8 with the highest risk, contributing with 25-40% of the genetic risk. Almost 40% of the North American and European populations also carry these haplotypes but they do not develop coeliac disease, which can conclude that HLA- DQ2 or HLA-DQ8 is necessary but not sufficient for coeliac disease to develop (Lindfors et al., 2019).

Environmental factors

The main environmental factor responsible for celiac disease is dietary gluten. Despite the fact that all humans are exposed to gluten, only some of them develop celiac disease, which means that there must be another factor that is involved in the mechanism of celiac disease development. Microorganisms effect was investigated (Forsberg et al., 2004; Ou et al., 2009; Wacklin et al., 2014) as being linked to celiac disease. Unbalanced gut microbiota, dysbiosis, increased levels of *Prevotella*, *Clostridium* and *Actinomyces*, increased prevalence of viruses,

including rotavirus, bacteria have been found in celiac disease patient’s gut.

Other environmental factors might be the changes in the quantity and quality of ingested gluten, infant feeding patterns, the spectrum of intestinal infections, gut microbiota colonization, etc. (Lionetti et al., 2015). Smoking might be also considered involved in the inflammatory bowel disease and as being responsible for modulation of celiac disease (Snook et al., 1996).

In Sweden, a study indicated that the disease risk was substantially lower in infants introducing small amount of gluten when still breast-fed (Ivarsson et al., 2013). The protective role of breastfeeding was also suggested by Akobeng et al. (2006) and the increased risk of getting celiac disease by introducing gluten in weaned children before 4-month-old or after 6 months (Norris et al., 2005). These data were challenged by Stordal et al. (2013) in an epidemiological study performed in Norway on mother and child cohort study (on 107000 children); they found an increased risk of developing celiac disease in those children consuming gluten after 6 months and higher risk in children breastfed after 12 months of age. Development of tolerance may be facilitated by timely introduction of gluten, but factors involved in loss of tolerance needs further studies. The results are unexpected because they show a low protection of breastfeeding for celiac disease, an increased risk associated to longer breastfeeding period and also the reduced risk of introduction of gluten before the age of 4 years old. Meanwhile, there are also two big national cohort studies that have underlined the influence of antibiotic use in the first year of life and the risk of developing celiac disease.

Two national cohorts (in Norway and Denmark) have highlighted the influence of antibiotics use in the first year of life on risk increasing for developing celiac disease, including a dose-gradient effect (Dydenborg et al., 2019). Bach JF. (2018) and Kondrashova et al. (2008) also found that the excessive hygiene and reduced exposure to different types of microbes in early life could overactive the immune response in later life and could be a factor for increasing the celiac disease risk.

Taken together, the development of coeliac disease requires a complex interplay between

the host, dietary gluten and other environmental factors that is currently far from being fully understood and that future research is necessary for a better understanding of this disease etiology (Lindfors et al., 2019).

Among the problematic disorders related to gluten, about 6% may be non-coeliac gluten sensitivity, 10% may be wheat allergy, and only 1% is celiac disease (Figure 1) (Gasbarrini et al., 2014).

Other related diseases

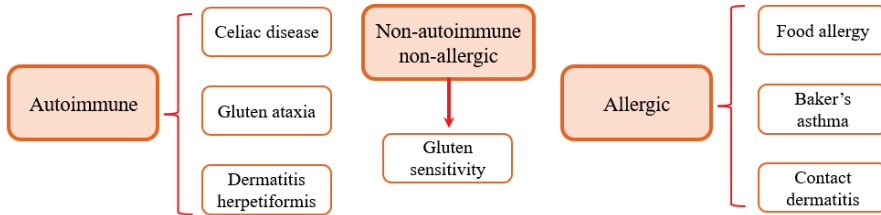


Figure 1. Classification of gluten related disorders

Wheat allergy. The main food allergies are milk, eggs, fish, crustacean shellfish, peanuts, tree nuts, soybeans, and wheat. Almost 5% people may have a true food allergy but only about 0.1% has a documented wheat allergy. Similar to celiac disease, wheat allergy is an immune-mediated reaction to the proteins found in wheat products, but it differs because is an IgE-mediated reaction to the water and salt-insoluble gliadins, particularly ω -5 gliadin. The symptoms of wheat allergy affect the mouth, nose, eyes, and throat (swelling, itching, and irritation); the skin (rash, hives, swelling); respiratory tract (wheezing, difficulty breathing, anaphylaxis); and gastrointestinal tract (cramps, nausea, emesis, gas, bloating, diarrhoea, and abdominal pain) (Pietzak et al., 2012).

Researches have shown that about 0.3% of children under the age of 5 in Europe are allergic to wheat; 0.1% of all Europeans suffer from this allergy. In people over the age of 18, it can lead to a number of life-threatening factors.

Gluten sensitivity is a condition that imply the improvement of the symptoms when gluten is removed from diet. The patients have neither celiac disease nor wheat allergy, but it is important to eliminate those two diagnostics before labelling a patient as “gluten sensitive.” In Table 1 there is a comparison of symptoms for gluten sensitivity non celiac disease, celiac disease and wheat allergy.

Table 1. Comparison of symptoms for different gluten related diseases

| Symptoms | Gluten sensitivity non celiac disease | Celiac disease | Wheat allergy |
|--------------------------------|--|--|---|
| Gut manifestation | Diarrhea, abdominal pain, bloating, constipation, nausea and vomiting | Diarrhea, abdominal pain, bloating, constipation, nausea and vomiting | Diarrhea, abdominal pain |
| Other manifestations | Headaches, blurred mind, fatigue, eczema, inflammation of muscle tissue, numbness, mood swings | Anemia, osteoporosis, neurological problems, lymphoma, pubertal delay dermatitis herpetiformis | Rushes, asthma, caught, angioedema, nose flow, eczema |
| Duration of symptoms | Hours - days | Hours - days | |
| Intestinal membrane morphology | Intraepithelial lymphocytosis of the small intestine | Atrophy of the intestinal villi | |
| Diagnosis | Decision tree | Serological testing followed by small bowel biopsy | Allergy test, presence of IgE antibodies to wheat protein |
| Management | Gluten free diet, probiotic Aspergillus niger prolylendoprotease (AN-PEP). | Gluten free diet | Gluten free diet, subcutaneous epinephrine for acute episodes |

Prevalence in the world

It was observed a global increasing of celiac disease incidence: in US, the prevalence of celiac disease raised from 0.2% in 1075 up to 1% in 2000 (Catassi et al., 2010); in Scotland, in

20 years, the incidence of celiac disease raised 6.4 folds in children (White et al., 2013). The reason for this increasing of the reported celiac disease is still unclear, but must be related to the environmental factors.

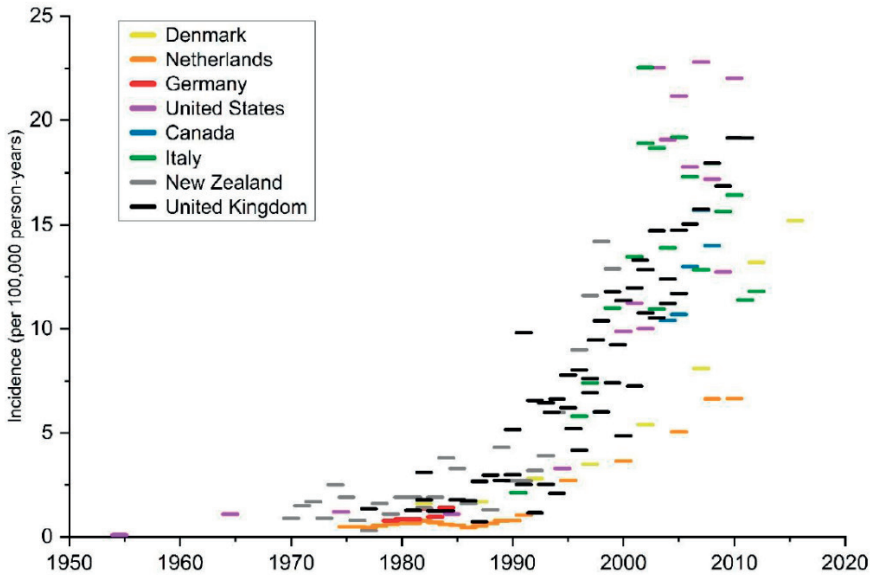


Figure 2. Evolution of the overall incidence of celiac disease in the world (King J.A et al, 2020)

In Africa, the prevalence of celiac disease in children is 5.6%, a tenfold higher than in most European countries; the most exposed are black-eyed, black-haired African population originated from Western Sahara maybe because of the genetic factors considering an increased level of consanguinity in this region and population (Lionetti et al., 2015). The incidence was estimated at 0.8% in Libya, 0.6% in Tunisia and 0.5% in Egypt (Cataldo et al., 2007).

In Middle East, celiac disease incidence is 0.8% in Iran and 0.6% in Turkey (Lionetti et al. 2015). The frequency in India shows a difference between the north and the south part due to wheat-rice shift in diets (Catassi et al., 2014).

King et al. (2020) shown that in the 21st century, the female incidence for celiac disease was 17.4 per 100000 cases compared to 7.8 in males. Children have a bigger prevalence of celiac disease (20.1 in 100000 cases) compared to adults (13.2 in 100000 cases). Diagnosis of celiac disease increased annually up to 8.4%.

Fasano et al (2003) have shown that the incidence of celiac disease is 1 in 33 average

healthy people, 1 in 56 with related symptoms, 1 of 22 with first degree relatives, 1 in 236 prevalence for African- Hispanic and Asian-Americans. It was also found that only 35% of newly diagnosed patients had chronic diarrhoea, which contrary the fact that this symptom is mandatory for the celiac disease.

By early diagnosis of the celiac disease the risk of developing certain complication is decreasing. By screening the blood tests of all at risk subjects the diagnosis rate rose 40 times (Catassi et al., 2007).

The average time for a symptomatic person to be diagnosed with celiac disease is four years, which determines an increased risk for developing neurological problems, autoimmune disorders and even cancers (Green et al., 2001).

Gluten free diets: necessity versus fad

Patients dealing with celiac disease must have a lifelong gluten-free diet in order to avoid the harmful peptide from gluten, which basically means avoiding any food product containing wheat, rye, barley. Considering that there are a

wide range of wheat containing foods, it is very difficult to avoid gluten.

Many researches were done in the last years attempting to evaluate how much celiac patients could enjoy a safe, nutritious, tasty and affordable diet. There are some controversial issues that have emerged: the high cost of a gluten free diet, the widespread availability and variety of gluten free products, the possible lower nutritional value of this type of diet and also gluten free as a fad.

The nutritional quality of a gluten free diet is reported to be have higher content of fat, saturated fat, sugar, salt and lower content of proteins, fiber and vitamins. In the blood and urine of celiac patients with gluten free diet, was also observed higher concentrations of heavy metals, especially arsenic and mercury. Overall, a gluten free diet was associated with potential health risks like deficiency of micronutrients, coronary artery disease, hyperlipidaemia and hyperglycaemia (Gorgitano et al., 2019).

Even if the popularity of gluten-free dieting has increased considerably among the general population during recent years, owing to the

above-mentioned reasons, the promotion of a gluten-free diet among people without coeliac disease should not be encouraged.

In the context of a continuously increasing market of gluten free products, patients living with celiac disease experience the so called “double-edged sword” symptom. They are grateful for more palatable and available gluten free products, but they are also experimenting the misunderstandings about the severity of the illness as a result of many noncoeliac consumers having gluten free diets (King et al., 2018).

Under EU legislation (Commission Regulation (EU) No. 828/2014), food operators are only allowed to use the following claims regarding the absence or reduced presence of gluten in food: ‘gluten-free’ and ‘very low gluten’; this is providing they meet the relevant compositional requirements (Table 2).

Under certain conditions these claims may be voluntarily accompanied by specified statements (Table 3).

Table 2. Specifications and criteria for gluten-free and very low gluten claims

| Claim | Specification | Additional criteria |
|-------------------|--|--|
| “Gluten free” | No more than 20mg/kg of gluten as sold to the final consumer | |
| “Very low gluten” | No more than 20mg/kg of gluten as sold to the final consumer | Must consist or contain one more ingredient made from wheat, rye, barley, oats or their crossbred varieties which have been specially processed to reduce gluten content |

Table 3. Voluntarily statements and criteria for gluten free products labelling

| Optional statements | Specifications | Additional criteria |
|--|--|--|
| “Suitable for people intolerant to gluten” | Used only when accompanying a “gluten free” or “very low gluten” claim | |
| “Suitable for coeliacs” | | |
| “Specially formulated for people intolerant to gluten” | Used only when accompanying a “gluten free” or “very low gluten” claim | The food is specially produced, prepared and processed to: a) reduce the gluten content of one or more gluten containing ingredients; b) substitute the gluten-containing ingredients with other ingredients naturally free of gluten. |
| “Specially formulated for coeliacs” | | |

The most universally acknowledged symbol associated with gluten-free products is a crossed ear of wheat (Grabowicz et al, 2019). It is a

common practice for gluten-free foods producers in Europe to label their products with this symbol (Figure 3).



GLUTEN FREE

Figure 3. Gluten free symbol for package labelling

Gluten free products consumption in Western societies has become very popular among the consumers not only those with different health conditions that need free gluten diet, but also those oriented to healthy eating and living. In Figure 4 it can be observed that the number of Americans on a gluten free diet without celiac

disease increased from 44% in 2009-2010 up to 72% in 2013-2014.

It can also be observed that the undiagnosed celiac disease decreased from 51% in 2009-2010 to 12% in 2013-2014. The level of gluten free diet among Americans increased from 1.3 to 2.4 in 4 years taken as reference.

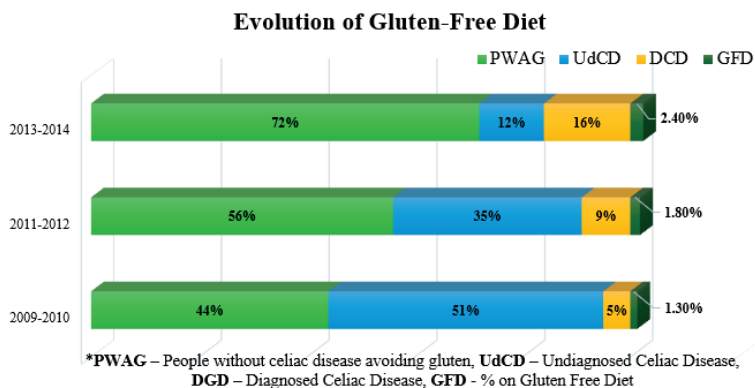


Figure 4. The rise of the gluten free diet (statista.com)

Gluten free foods consumption for non-celiac disease patients had increased among general population (Silvester et al., 2015). This might be due a behavioural cause by perceiving these products as being more healthy and more appropriate for a balanced way of living and eating (Faulkner et al., 2014). This is also known as “halo effect” which states that as a perception level, the products labelled as healthier, low-fat, low carbo, vegan can mislead the consumers about the total nutritional value of food.

57% of consumers eating gluten free foods are doing this because of medical reasons (Dunn et al., 2014), while the rest of 43% are preferring this type of products as part of a special lifestyle and positive image of the products.

The US Department of Agriculture stated that the gluten-free industries revenues reached \$1.7 Billion by 2010. In line with this trend, the

gluten free product market size was in 2020 up to 5.6 billion USD, from which 1.77 billion representing only US gluten free products market (<https://www.statista.com>).

There are more than 2,000 gluten free food items available in the United States, and consumers are more likely to find these foods in regular grocery stores. From 2004-2005, sales of gluten-free foods increased by 77.8 million dollars (a growth of 14.6%).

CONCLUSIONS

Celiac disease become a public health issue, with an increased prevalence worldwide in the last years. It still remains significantly underdiagnosed, especially in developing countries but important changes have been made in developing the decisional tree for diagnosis and differentiation among other gluten related

disease like non-celiac gluten sensitivity, wheat allergy, irritable bowel syndrome.

Non-celiac gluten sensitivity is a clinical feature under investigation: it is probably a heterogeneous group that overlaps with irritable bowel syndrome and celiac disease. More research is needed to establish the risk factors, the biomarkers, the definitive diagnostic criteria before patients can really benefit from results.

Continuous gluten ingestion is the major cause of persistent celiac disease, due to its influence on gut membrane healthy and functioning. This may determine serious health threat because of neurological problems, anaemia and osteoporosis that might occur due to intestinal absorption problems.

There is no treatment for celiac disease, but adopting a gluten free diet for lifelong for celiac disease patients.

Multiple potential new therapies are being studied at it can lead to paradigm shifts in the way gluten intolerance, celiac disease and wheat allergy are managed.

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