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Narrative Review

Prevalence and Diagnosis Method of Celiac Disease in Jordan: A Review Article

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Abstract

The Celiac Disease (CD) is an autoimmune enteropathy triggered by dietary gluten in genetically susceptible individuals. CD is considered one of the gluten-related disorders characterized by a small bowel enteropathy occurring in genetically susceptible individuals while exposed to the gliadin protein found in wheat, barley, and rye. This review has been conducted to create Jordanian customized recommendations for patient status, the prevalence of CD in Jordan. This review has been conducted employing Google Scholar, Medline, and PubMed. On these websites, we searched for articles on any date using critical terms related to celiac disease: "celiac disease", "celiac", "coeliac disease", "tissue transglutaminase antibody", "anti-endomysium antibody", "endomysial antibody", "prevalence", and "Jordan." In total, five research papers were retrieved. The results indicated that the total prevalence of CD is still unknown in Jordan due to the lack of research and the varying diagnosis methods. The available data is limited in order to build a comprehensive view of CD prevalence in Jordan. Nevertheless, minimal studies were carried out on a CD patient's awareness and education, and no intervention studies were available on CD patients among the Jordanian society. Therefore, a crude population prevalence study is needed.

Keywords: Celiac Disease (CD), Jordan, Prevalence, Diagnosis

Introduction

Celiac disease or "Coeliac Disease" (CD) is generally defined as a chronic immune-mediated enteropathy triggered by dietary gluten, which is present in grains including wheat, rye, and barley in genetically susceptible individuals. Two factors drive CD onset; genetic predilection and environmental exposure.[1-5] CD is developed within the susceptible patients who have a fraction of HLA-DQ2-positive and/or HLA-DQ8-positive, and those who are consuming a gluten-containing diet. Briefly, gluten (prolamin and glutelin proteins) is the viscoelastic protein with rheological properties that give highly flavored properties to food.[2] Gluten could be found in various cereals, including wheat, rye, barley, spelt, and kamut.[2] The main characteristic of the CD is malabsorption, which comes from the small intestine villous abnormalities. This malabsorption is the cause of nutritional deficiencies involving macro-and micronutrients. Therefore, there are many expected nutritional consequences secondary to CD, such as iron deficiency, vitamin B12 deficiency, and other water-soluble vitamin deficiencies.[6] Epidemiologic and prospective observational studies implicate a range of environmental factors that have an impact on disease development, such as mode of delivery, breastfeeding, amount and time of gluten exposure, early antibiotic therapy, enteral infection, and specific gut microbiome patterns.[3,7]

The genetic and immunological studies have revealed the importance of crucial HLA and non-HLA susceptibility genes in disease development and a long-lived pathogenic population of gluten-specific T cells targeting specific gluten peptides (T cell epitopes). Consuming gluten-containing-diet in genetically susceptible individuals shapes the immunologic context in which gluten is presented and shifting the balance from gluten tolerance to reactivity, and that this may be in part mediated through microbiome-host interactions.[1,8] CD is associated with the presence of other autoimmune diseases, including Hashimoto's thyroiditis, Graves' disease, and type 1 diabetes.[3,5]

It remains unclear whether CD directly leads to other

autoimmune diseases and whether early diagnosis and treatment with a Gluten-Free Diet (GFD) alter this risk. However, autoimmune diseases' co-occurrence supports the concept of shared genetic and immune pathways contributing to immune dysregulation and loss of self-tolerance.[1,8]

The diagnosis of CD depends on many factors but essentially requires the physician's awareness and knowledge. The diagnosis of this type of food allergy could happen at any age but mostly, it is performed between 9 and 24 months or in the third or fourth decade of life. Current diagnosis is based on demonstrating the enteropathy in small intestinal biopsies where histologic examination shows villous atrophy, crypt hyperplasia, and intraepithelial lymphocytosis, and the presence of circulating CD-specific antibodies to tissue transglutaminase (tTG), deamidated gliadin peptides (DGP), and endomysium (EMA). In children who have symptoms suggestive of CD, a strongly positive tTG antibody (tTGA) titer (ten times the upper normal level or higher),[9] and a CD-associated HLA genotype, the diagnosis of CD may be possible without the need for a small intestinal biopsy.[8] A strict and lifelong GFD is the only effective treatment[1] of this disease.[3] However, based on the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) guidelines 2019, HLA-DQ2 and DQ8 typing is not required in patients with positive TGA-IgA, if they qualify for CD diagnosis with biopsies or have high serum TGA-IgA (≥10xULN) and EMA-IgA positivity. If a patient's test is negative for HLA DQ2 and DQ8, the risk of CD is very low, while a positive result does not confirm the diagnosis.[9]

In regards to the epidemiology of CD in the world in the past, the prevalence of CD was underestimated globally. In the present, it is considered one of the most common genetically inherited disorders in the West, with a 1% prevalence.[10] The global prevalence of CD based on a recent systematic review and meta-analysis reported that the pooled result of the prevalence was 1.4% ranging between 1.1% and 1.7% of the total population (275.818 individuals). This prevalence is based on positive results from tests for anti-tissue transglutaminase and/or anti-endomysial antibodies. The pooled results indicated that the prevalence of CD was 0.4%, 0.5%, 0.6%, and 0.8% in South America, Africa, North America, Asia, and Europe and Oceania, respectively.[11]

Upon several systematic reviews,[11-13] the CD prevalence is rising in many countries. Reports from systematic review and meta-analysis published in 2017 stated that the incidence of CD ranges from 1:132 in Switzerland to 1:1000 and 1:2000 in other European countries.[12] In the Nordic countries, a frequency of CD was estimated by the results of serological screening of blood donors (in some cases supplemented with biopsy and based on ESPGHAN guidelines 2019, screening blood donors does not reflect trur prevalence as they are most of the time healthy individuales), of about 1/300 of that in the rest of Europe (especially that of Ireland and Italy) and around 1/250 of some areas in the United States. In some regions, the prevalence of CD is 1/100.[9] The meta-analysis pooled estimated about 1.6% in 47.873 individuals based on positive anti-tissue transglutaminase and/or anti-endomysial antibodies in Asia. The pooled prevalence of biopsy-proven CD was 0.5% in 43.955 individuals.[13] The pooled CD's prevalence was 0.3% in Iran, 0.5% in Turkey, and 0.6% in India. In Aragón, the estimated prevalence of CD ranged from 0.24 to 0.81%.[14] In 2012, Barada et al. mentioned that the prevalence of CD is underestimated in developing countries due to the lack of awareness among the population.[15,16] Many studies reported that CD affects both genders with reported female predominance; on the other hand, more children were diagnosed compared to adults.[10,11,13,17]

An older review in the Middle Eastern and North African (MENA) reported that the prevalence of CD in the MENA is similar to that of Western countries among the low-risk populations but is higher in high-risk populations (for example, in those with type 1 diabetes) with the diagnosis variation method. A very recent systematic review reported that the prevalence of CD in the Arab countries ranged from 0.14% to 3.2% among the healthy adult populations; Tunisia had the lowest range (0.14%) while Saudi Arabia has the highest. Among the children, the prevalence ranged from 0.6% to 1.5%.[1]

Among the high-risk population, Egypt had the highest prevalence of CD (44%), whereas Turkey had the lowest prevalence percentage, 2.45%. The prevalence among the low-risk population was high in Turkey (1%), where the lowest prevalence was in Tunisia (0.3%).[15]

In Jordan, some systematic reviews and meta-analyses included one or two of the Jordanian studies in the analysis, but there was no systematic review

focusing on the prevalence of CD in Jordan while including all the available references. In Jordan CD is underdiagnosed; moreover, information regarding the prevalence and the diagnosis method are not available.

Therefore, this study aimed to review the prevalence of CD and to discuss the related issues to CD in Jordan. This article could be valuable for stakeholders to build any recommendations to support the CD status in Jordan. Furthermore, this study could help standardize the recommendations related to the diagnosis based on the European Society of Paediatric Gastroenterology.

Materials and Methods

Studies Selections

In the present review, a systematic review research approach was used. The manuscripts were collected by conducting a comprehensive search of multiple electronic databases such as Google Scholar, Medline, PubMed and local journal (such as Journal of the Royal Medical Services) with the following Medical Subject Headings (MeSH) terms and keywords "celiac disease", "celiac", "coeliac disease", "tissue transglutaminase antibody", "anti-endomysium antibody", "endomysial antibody", and "prevalence". Each one was cross-referenced with mainly "Jordan". The inclusion criteria included original research studies published in peer-reviewed journals, mainly focusing on epidemiology, burden, prevalence, risk factors, incidence, or CD prognosis in Jordan. The articles were also identified using a hand search of the studies' references whose full texts were accessed in the local journals. No language restrictions were on the search. Complete local journal searching and cross-referencing were undertaken by all authors and two reviewers who agreed on the last search. The point prevalence of CD in (Altamimi 2019) was calculated after the study was published.

Results

The Prevalence of CD

A total of 39 articles were found on CD in Jordan. After removing the duplicates, seven studies were included in this review (Figure 1). Two articles were excluded from the discussion. The first one was a case series report from south of Jordan,[18] and the second study did not study the CD prevalence, it was actually an investigation of the frequency of HLA-DQA1*0501 and DQB1*0201 alleles in Jordanian patients with CD and their first-degree relatives.[18] A summary of the prevalence of CD in Jordan has been presented in Table 1. As results show, the diagnosis confirmation endpoint for five articles[4,19-22] was different in each study, but they were similar in the antibody testing. The participant number in all studies ranged from 34[19] to 1985[21] patients. The age ranged from 4.6 to 12.2 years in all included studies, except in one study[20] which the participants were adults with an age mean of 51.5 years. Two studies were looking for CD prevalence in high-risk populations (patients with autoimmune hypothyroidism[20] and patients with type 1 diabetes.[4] The rest of the study populations were unselected (low-risk populations).

Related to the diagnosis issue, as shown in Table 1, the diagnosis method was different between the studies. For example, a study[19] depended on the appearance of subtotal or severe partial hyperplastic villous atrophy of the small-intestinal mucosa and a full clinical remission after starting GFD. Whereas in 2017, another study[22] used the small intestinal biopsy, (tTG-IgA) and (EMA-IgA) to confirm the CD diagnosis. Furthermore, no study used the clinical presentation to assess CD's presence except one study[22] as Altamimi described the clinical symptoms among the study population.

Discussion

The recent systematic review and meta-analysis considered the seroprevalence of CD (the availability of a positive anti-tissue transglutaminase) is the availability of a positive anti-tissue transglutaminase (tTG) antibody (Ab) and/or anti-endomysial antibodies (AEAs). Whereas, Antigliadin Antibody (AGA) is no longer recommended in CD's diagnostic algorithm.[11]

As shown in Table 1, the diagnosis method varied among studies to determine the prevalence of CD in Jordan. The oldest study's diagnosis was in 1996[19] based on the appearance of subtotal or severe partial hyperplastic villous atrophy of the small-intestinal mucosa and a full clinical remission after removing gluten from the diet. The serology screening for CD was not available in this study. Four patients ha three small-intestinal biopsies, nin had two biopsies, and the remaining 21 patients had one pathological biopsy on a gluten-containing diet, followed by a clinical and anthropometric response after gluten withdrawal. In a

Table 1. Prevalence and Incidence of Celiac Disease in Jordan

Study	Study aim	City(s)	No. of cases	Population age /risk degree	Diagnosis method	Small intestinal biopsy	Result
19	To determine the incidence and clinical presentation of CD.	Northern Jordan	34 (35.% boys)	Age mean 4.6 years. unselected (low risk) populations	Appearance of subtotal or severe partial hyperplastic villous atrophy of the small-intestinal mucosa and a full clinical remission after removal of gluten from the diet	Yes	The crude incidence rate of CD of ≈ 1:2,800 live births The point prevalence of 7:100,000
21	To investigate the prevalence of CD using serological markers in apparently healthy schoolchildren	Northern Jordan. Irbid city	16 Children (7 boys)	Age median: 8 years. unselected (low risk) populations	(tTG) and (EmA)	No	The serological prevalence was estimated to be 1:124
20	The prevalence of coeliac disease among patients with autoimmune hypothyroidism	N. A	914 (11.8% male)	Age mean: 51.1 Autoimmune hypothyroidism patients	(tTG-IgA) and (EMA-IgA)	Yes	Overall rate of CD among autoimmune hypothyroidism patients was estimated to be 12.8%
22	To evaluate CD presentation in clinically diagnosed children	South Jordan	35 (51.4% male)	Age mean: 6.7 years. unselected (low risk) populations	(tTG-IgA) and (EMA-IgA)	No	*Estimated point prevalence = 46/100,000
4	Determine the prevalence of biopsy-proven CD (BPCD) among pediatric patients with type one diabetes	N.A	538 (51.7% boys)	Age mean: 12.02 Type 1 diabetes patients	IgA (tTG IgA)	Yes	positive celiac serology 16.6% and 47% were diagnosed with CD at onset of T1D

*calculated from the numbers of population census and the number of cases at the point of data collection.

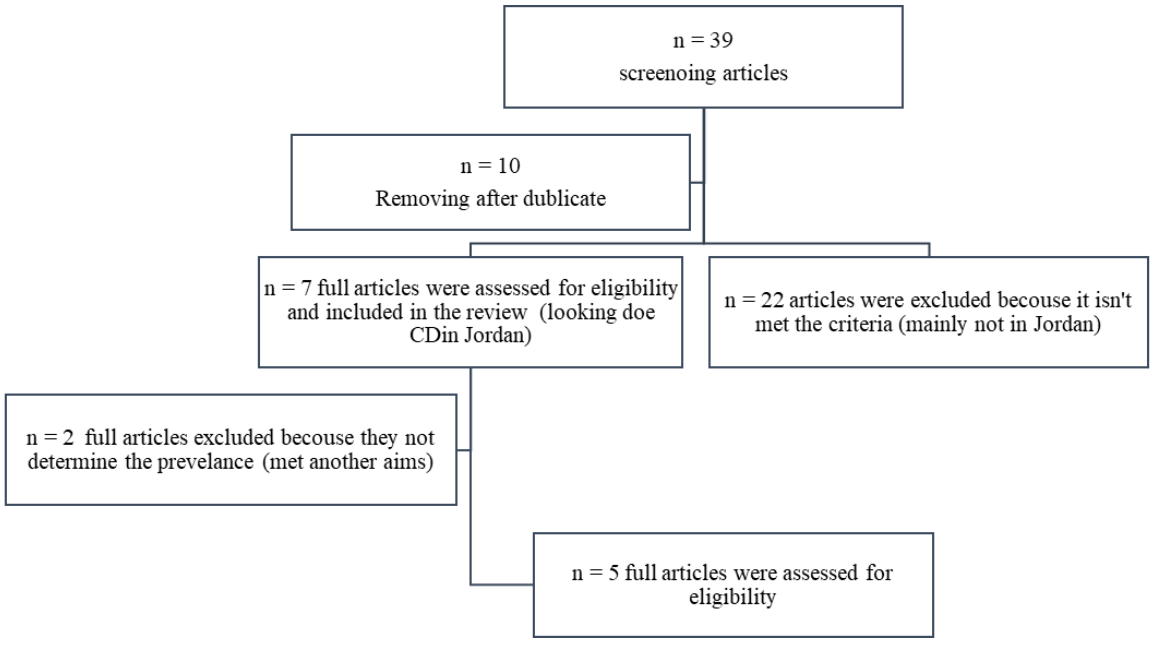

Figure 1. Retrieval of Articles and Screening Process.

study by Rawashdeh et al. (1996), the prevalence of CD was 0.03%. This rate was higher than that in the United States at that time, although the expected actual cases in Jordan was expected to be higher than this result due to the low level of suspicion and the delay in diagnosis. No other studies were published between 1996 and 2010 related to the prevalence of either crude or point prevalence. Nuseir et al. (2010) collected their sample from the same city as Rawashdeh et al. (Irbid city only). The result of the study[21] indicated that the serological prevalence of CD is 0.8% among children of a mean age of 8 years old, according to the analysis of IgA antibodies (tTG) and EmA as the next test for the positive IgA. Despite of the methodology's difference, between 1996 and 2010, CD's prevalence increased from 0.03% to 0.8% in northern Jordan. In 2014, two studies were published related to CD in Jordan; the first one was a cross-sectional record-based review[20] in regards to the prevalence of celiac disease among adult patients with autoimmune hypothyroidism and the second one[23] described the hematological findings among children with CD at the time of presentation.

The first study was a cross-sectional study on the seropositivity of anti-EMA immunoglobulin (IgA) and IgG among high-risk populations (autoimmune hypothyroidism). Whereas another study[23] described the hematological outcomes among children with CD without a prevalence estimation of CD Redundancy. They used a combination of symptoms, high antibody levels specific for CD, and HLA testing (HLA-DQ2 and/or HLA-DQ8), and they omitted the duodenal biopsy for the diagnosis based on ESPGHAN guidlines, 2012 to ensure the CD diagnosis. Farahid et al. found that the seroprevalence of CD was 12.8% (which is expected in high-risk populations). They also reported high rates compared to previous reports (3-7% prevalence of CD in patients with autoimmune thyroid disorders).[24] This might reflect a population-specific effect.

The sample size in Farahid et al.'s (2014) study was large and believed to represent the whole country. The samples were collected at the National Center for Diabetes, Endocrine, and Genetic Disorders, the primary referral center in Jordan for such disorders, which receives patients from all over the country.

In the last decades, most people in the region have considered this disease a chronic disorder that makes the child or the patient, in general, feel shame in the society. This is due to the fact that it is a hereditary disease and can be passed to the next generations. the social stigmta serounding the diagnosis of CD as a chronic diseas that cab be passed down to offsprings had a major role in underdiagnosing it.[25,26]

The mean age of the onset of symptoms in the study of Altamimi was 5.02 ± 3.09 years, while in the Rawashdeh study (1996), the duration of symptoms before diagnosis ranged from 1 month to 11 years.[19] This duration to the diagnosis may lead to late estimation of the true crude prevalence of CD in Jordan. Also, lack of knowledge among pediatricians, especially in regards to older children, increases the barriers to obtain precise estimations of the prevalence of this disease.

The typical gastrointestinal symptoms were the main clue to the diagnose of CD, and the next step was confirmation by the small intestinal biopsy. The availability of very sensitive and specific serologic tests, such as EMA and t-TG, made it possible to evaluate the prevalence of CD in the general unselected populations in Jordan and other countries.[16] The serological screening results have altered the perception of CD from a rare disorder into a relatively common condition because it is confirming the incidence of CD as serological testing are confirmatory.[21] Nusier et al. conducted the first study that estimated the prevalence of CD using serological markers among a group of children in one of the northern cities in Jordan.[21]

This review included studies depend on the antibody tests more than the diagnosis of the disease by the clinical symptoms. Rawashdeh (1996) depends on the small-intestinal biopsy and a full clinical remission after just removing gluten from the dietand not using either the serological testing or the clinical symptoms. Whereas another study[21] mainly depended on serological testing. In Farahid et al.'s study (2014), the authors looked at the association between the seropositivity of CD among patients with autoimmune hypothyroidism, and they concluded that there was a significant association between the autoimmune hypothyroidism of CD patients and anemia and vitamin b12 deficiency. A number of the clinical symptoms were reported in a study,[22] such as mainly chronic diarrhea (44%) and short stature, abdominal distention (8.8%), constipation /encopresis (8.8%), recurrent abdominal pain (14.7%) and 5.9% had oral ulcers.[22] In Rwalah et al.'s study, the researchers based on the positive serology and histological changes suggestive of CD in addition to the clinical presentation. Rwalah et al. reported that 4.5% of the

patients had thrived, 13.5% had short stature, 18.9% had chronic diarrhea, 7.2% had abdominal distention, 10.8% had constipation, 11.7% had iron deficiency anemia and the other related diseases such as type 1 diabetes mellitus (17.1%), and the down syndrome (1.8%).[23]

From another point of view, if we focus on the inversional factor rather than the clinical issues, another factor could explain this increase in the CD cases; the high consumption of wheat (cereals) in Jordan. Jordan has one of the world's highest wheat consumption rates as the primary food item on the Jordanian dishes is the wheat bread in different shapes and types.[27] Besides, there was not enough awareness among the families, especially the new mums, regarding the right time to introduce wheat to the kids and the awareness of the infant feeding guidelines in the first 12 months.[28]

Conclusion

CD has been raised as a significant public health problem over the past two decades. Unsurprisingly, CD is heavily underdiagnosed worldwide due to the lack of awareness and low suspicion of the disease. The number of published research is limited on CD in Jordan, although the number of patients have increased in the past 10 years. The first prevalence study conducted in 1996 estimated the point prevalence at 7:100,000. Two decades later, the point prevalence increased almost seven times. Some old studies have been published on the prevalence of CD in the Middle East and developing countries includig Jordan, based on some relevant published data. However, no recent comprehensive epidemiological review was found in Jordan. This review recommends the need for extensive prospective studies to assess the true incidence, the clinical course, the efficacy of treatment modalities employed, patient compliance, disease complications, and response to treatment in Jordan. The association of CD with other autoimmune diseases and the presence of specific genetic markers would be areas of interest in future research. The outcomes of the previous studies in Jordan recommend the need to emphasize the recent diagnosis method in Jordan at-risk groups for early identification of patients with CD.

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None.

Conflict of Interest

The authors declare that they have no conflicts interest.

Abbreviation List

CD: Celiac Disease

ESPGHAN: The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition

MENA: Middle Eastern and North African

IgA: Immunoglobulin A

tTg-IgA: Tissue Transglutaminase IgA

EMAIgA: The Anti-endomysial Antibody Test

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