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REVIEW

Celiac disease in Middle Eastern and North African countries: A new burden?

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Abstract

Celiac disease (CD) is now recognized as a common disorder among Middle Eastern (ME) and North African (NA) populations. The aim of this review is to assess the available data regarding CD in the ME and NA and to compare this information with that of Western countries. A literature review was performed using the electronic databases PubMed and Medline (1950-2008) as search engines, and "celiac disease" was used as a Mesh term. The search was limited to ME and NA countries. The prevalence of CD in ME and NA countries among low risk populations is similar to that of Western countries, but is higher in high risk populations such as those with type 1 diabetes. It is underestimated because of lack of clinical suspicion and lack of patient awareness. Clinical presentations in term of gastrointestinal, hematologic, skeletal, and liver manifestations are similar between both populations except for a high prevalence of short stature in some ME and NA countries. Few studies have addressed atypical or silent CD. As in the West, diagnosis is initially made by serological tests and is confirmed by small intestinal biopsies. Gluten-free diet is the main mode of treatment with a higher apparent adherence rate than in the West. Most disease complications result from malabsorption. The disease is strongly associated with HLA DQ2 and to a lesser extent with HLA DQ8 alleles. In conclusion, CD prevalence is underestimated, with little data available about its malignant complications. Disease parameters in the ME and NA are otherwise similar to those in Western countries.

Key words: Celiac disease; Gluten-free diet; Insulin dependent diabetes mellitus; Iron deficiency anemia; Middle East

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INTRODUCTION

Celiac disease (CD) is an autoimmune disorder which affects genetically predisposed individuals upon the ingestion of gluten. Its prevalence has been underestimated, but it is now considered one of the most common genetic disorders in the West with a prevalence of 1%-2.67%[1-3].

In Middle Eastern (ME) and North African (NA) countries, the literature regarding CD has expanded signif-

icantly. The number of original articles published from the region during the last 30 years is about 120 with around 30, 29, 16, and 10 articles coming from Israel, Turkey, Tunisia, and Iran, respectively. Most studies are epidemiological. The true prevalence of the disease is underestimated and its clinical features have not been fully determined due to small sample size, selection bias, limited knowledge about CD and limited funds available for research.

The aims of this review of CD in ME and NA countries are to compare the disease parameters to those in Western countries, namely its epidemiology in low and high risk populations, its most common clinical presentations, the diagnostic tests used and their reported sensitivity and specificity. In addition, we determine the efficacy of the treatment modalities used, compliance with a gluten-free diet (GFD) and disease complications.

EPIDEMIOLOGY OF CD IN THE MIDDLE EAST AND NORTH AFRICA

Until the 1990s, the prevalence of CD in ME and NA countries was considered low. However, with the introduction of anti-endomysial antibodies (AEA) and anti-gliadin antibodies (AGA) testing, CD has been more readily reported from developing countries[4], and its prevalence seems similar to that of Western countries[4-7]. However, this prevalence varies from 0.14% to 1.17% in low risk, and from 2.4% to 44% in high risk populations (Tables 1 and 2). This difference is attributed to the heterogeneity of the studied populations, subject selection, diagnostic strategies used, and whether confirmatory biopsies were performed or not. For example, two studies from Tunisia reported a five-fold difference in CD prevalence, probably due to the use of different screening methods[8,9].

CD in low risk populations

Prevalence of CD among low risk populations ranges from 0.14% to 1.3% as assessed by serological markers and from 0.033% to 1.17% assessed by biopsies (Table 1). The prevalence was found to be > 1% in two studies from Turkey[5,6], 0.5%-1% in six reports from Turkey, Egypt, Iran, Tunisia and Israel[7,8,10-13], and < 0.5% in five reports from Jordan, Lebanon, Tunisia, and Kuwait[9,14-17].

Most studies screened healthy blood donors[6,9-11,17], of whom young males represented > 70%. One study screening healthy individuals for CD in Iran, 50% of whom were females, reported a similar disease prevalence of 1% among both men and women[7]. On the other hand, Green *et al*[2] reported that the disease was 2 to 3 times more common in women. Another study from Tunisia on healthy blood donors, 30% of whom were females, reported a disease prevalence of 0.4% among women compared to 0.22% among men[17]. Exclusion of subjects with iron deficiency anemia (IDA), abnormal liver function tests (LFTs) and the low percentage of participating females may have led to the underestimation of disease prevalence. In addition, low suspicion among physicians may have contributed to the low reported incidence of CD[8,14]. Finally, studies restricted to patients presenting with severe symptoms might have underestimated the true prevalence of the disease by missing asymptomatic and mildly symptomatic individuals[15].

CD in high risk populations

High risk populations include patients with positive family history, insulin dependent diabetes mellitus (IDDM) and/or thyroiditis, and those with symptoms of malabsorption such as chronic diarrhea, refractory IDA and weight loss. Among these, the prevalence of CD ranges from 2.4% to 44% assessed by serological markers and biopsies (Table 2).

In Western countries, the prevalence of CD among patients with IDDM is 1%-12% assessed by serological markers and 1%-11% by biopsies[1]. The disease is more common in children than adults with IDDM. In nine reports from ME and NA countries, the prevalence of CD among IDDM patients was 2.4%-20% assessed by serological markers and 2.4%-16.4% by biopsies (Table 2). Small sample size and a high rate of consanguinity may have contributed to the high prevalence. CD and IDDM share many genetic factors including HLA DR3-DQ2 and HLA DR4-DQ8 haplotype[18,33].

CD is common in patients with autoimmune thyroid diseases. In Western countries a prevalence of 4%-5% is reported[34,35], with an average of 1.5%-6.7% as assessed by serological markers and 3% by intestinal biopsies[1]. The prevalence of CD among Tunisian patients with Grave's disease was 3.7% by serological markers and 2.5% by biopsies[19]. An increased prevalence of autoimmune thyroid antibodies among CD patients on a GFD[36] has also been reported. In Turkey, 5.9% of patients with autoimmune thyroiditis had positive CD serology[20]. Autoimmune thyroid disease and CD share a common genetic background (HLA DQ2 and HLA DQ8)[20].

Prevalence of CD in relatives

In the US, the prevalence of CD was found to be 4.5% and 2.5% in first and second-degree relatives of patients with the disease, respectively[3]. The National Institutes of Health (NIH) estimates the prevalence of CD among first degree relatives to be 4%-12%, assessed by biopsy.

In two studies from Algeria and Turkey, the prevalence of CD in patients' first degree relatives was 3.4% and 1.7%, respectively[21,33]. Among 381 first degree relatives, 26 had positive serology, and villous atrophy was present in 13 of 16 who had biopsies performed[21]. Also, clustering of CD within families has been reported from Jordan and Algeria[14,21]. There are no twin studies of CD in ME and NA countries. The high rate of consanguinity in these countries might contribute to a higher prevalence of CD and provides an opportunity for studying genotype-phenotype correlations.

CLINICAL PRESENTATION

The clinical presentation of CD varies from silent disease to full-fledged severe intestinal and extra-intestinal manifestations[1,2,37]. A study comparing Turkish and US

Table 1 Prevalence and incidence of celiac disease in Middle Eastern and North African countries among low risk populations

Country	Population	Method	Confirmation by duodenal biopsy	Result
Central Anatolia, Turkey[5]	906 hospitalized adults	t-TG[1]	Yes	Prevalence 1%
Turkey[6]	2000 healthy blood donors	t-TG[1,2]	Yes (incomplete)	Prevalence by serology 1.3% and by histology 1.17%
Iran[7]	2799 healthy individuals	t-TG[1], AEA[1]	Yes	Prevalence 0.96%
Tunisia[8]	6286 school children	t-TG[1], AEA[1]	Yes (incomplete)	Prevalence 0.64%
Tunisia[9]	1418 healthy blood donors	AEA[1]	Yes	Prevalence 0.14%
Iran[10]	2000 healthy blood donors	AGA[1], AEA[1]	Yes	Prevalence 0.6%
Israel[11]	1571 healthy blood donors	AEA[1], t-TG	Yes (incomplete)	Prevalence 0.63%
Turkey[12]	1263 healthy school children	t-TG[1]	Yes (incomplete)	Prevalence by serology 0.87% and by histology 0.63%
Egypt[13]	1500 healthy children	t-TG[1,2], AEA[1]	Yes	Prevalence 0.53%
Jordan[14]	494 000 children	No serology done	Yes	Incidence 1 in 2800 live births, point prevalence 7:100 000
Kuwait[15]	60 000 newborn over 5 years	NR	Yes	1 in 3000 births
Lebanon[16]	42 600 hospitalized children	AGA, AEA	Yes	5 per 1000 hospital admissions
Tunisia[17]	2500 healthy blood donors	AGA[1,2], AEA[1]	No	Prevalence 0.3%

[1]IgA; [2]IgG. AEA: Anti-endomysial antibodies; AGA: Anti-gliadin antibodies; tTG: Tissue transglutaminase; NR: Not reported.

Table 2 Prevalence of celiac disease in Middle Eastern and North African countries among high risk populations

Country	Population	Method	Confirmation by duodenal biopsy	Prevalence (%)
Egypt[13]	150 children with diarrhea and failure to thrive	t-TG[1,2], AEA[1]	Yes	4.7
	250 children with IDDM	t-TG[1,2], AEA[1]	No	6.4
Saudi Arabia[18]	123 pts with IDDM	AGA[1], ARA[1]	Yes (incomplete)	4.9-8.1
Tunisia[19]	161 pts with Grave disease	AEA[1], t-TG[1]	Yes (incomplete)	3.7
Turkey[20]	136 pts with autoimmune thyroiditis	t-TG[1]	Yes (incomplete)	5.9
Algeria[21]	116 children with IDDM	AGA[1,2], AEA[1]	Yes	16.4-20
Iran[22]	100 pts with chronic diarrhea	AGA[1], AEA[1]	Yes	19
Iran[23]	825 children with chronic diarrhea	AGA[1], AEA[1]	Yes	6.5
Iran[24]	250 pts with IDDM	Total IgA, AEA[1]	Yes	2.4
North-Eastern Libya[25]	243 pts with high clinical suspicion	NR	Yes	31.7
Eastern Saudi Arabia[26]	145 pts with high clinical suspicion	AEA[1], ARA[1]	Yes	4-11
Egypt[27]	25 pts with refractory iron deficiency anemia	AGA[2], AEA[1], t-TG[2], ARA	Yes	44
Turkey[28]	100 pts with IDDM	AEA[1]	Yes	6
Iraq[29]	40 pts with IDDM	NR	Yes	15
Libya[30]	234 pts with IDDM	AGA, t-TG, ARA, AEA	Yes	10.3
Tunisia[31]	348 pts with IDDM	AEA[1], t-TG	Yes	2.6-4
Turkey[32]	122 pts with IDDM	Total IgA, AEA[1]	Yes	2.45

[1]IgA; [2]IgG. IDDM: Insulin dependent diabetes mellitus.

patients found that the former presented mostly with diarrhea and anemia and the latter with atypical symptoms such as fatigue, abdominal pain and bloating[38]. Whereas some reports from Turkey, Jordan and Iran address silent and atypical CD[5,14,39], little is known about the prevalence and the clinical, serologic and histopathologic features of patients with atypical or silent CD in this region, the so-called celiac iceberg.

GI manifestations

GI complaints are the most common presenting symptoms. They include diarrhea, abdominal pain, constipation, bloating, flatulence, nausea and vomiting. Lo *et al*[40] report a drop in the percentage of CD patients presenting initially with diarrhea to 43%, compared to 73% before 1993.

Among six studies assessing chronic diarrhea in ME and NA countries, CD prevalence was 6.5%-21%[22,23,41-44]. In Iran, Lebanon, Iraq, Saudi Arabia and Kuwait, CD was one of the most common causes of chronic diarrhea[22,41-44]. In Egypt, 4.7% of children presenting with diarrhea and failure to thrive had CD[13].

The reported prevalence of GI manifestations has varied widely among different studies (Table 3). This may be due to the low number of patients evaluated or a delay in their presentation. For example, al-Hassany[45] reported 10 cases with advanced CD who all had diarrhea, abdominal distension and weight loss. Diarrhea and abdominal distension were significantly more common in younger children, whereas abdominal pain, failure to thrive and growth retardation were more common among those who were older. This is attributed to the predominance of classical CD among younger children versus atypical CD seen among older children[14,46].

About one third of children with CD in Western countries develop short stature[50]. In ME and NA countries, short stature was discovered to be the presenting symptom in 7.7% to 53% of patients. The highest prevalence of short stature was reported from Jordan where 26% of children with CD had rickets. In Turkey, 51% of patients had a

Table 3 Clinical presentation of celiac disease in the Middle East and North Africa

Country	Population	Abdominal distention/ flatulence (%)	Diarrhea (%)	Short stature (%)	Weight loss/failure to grow (%)	Abdominal pain (%)
Iran[7]	29 adults with CD detected by screening	55.5	22.2	NR	NR	18.5
Jordan[14]	34 pts with CD	44.0	65.0	53.0	NR	44.0
Kuwait[15]	20 children with CD	80.0	100.0	25.0 (rickets)	100.0	NR
Lebanon[16]	65 children with CD	26.2	60.0	NR	49.2	NR
Turkey[33]	60 Adults with CD	48.3	66.7	NR	50.0	NR
Iran[39]	52 pts with CD	32.7	48.1	23.1	78.8	NR
Iraq[45]	10 children with CD	100.0	100.0	NR	100.0	NR
Turkey[46]	104 children with CD	60.6	81.7	45.2	44.0-50.0	23.0
Turkey[47]	45 children with CD	NR	40.0	51.0	NR	NR
Libya[25]	77 children with suspected CD	49.0	53.0	23.0	100.0	15.0
Saudi Arabia[26]	10 children with suspected CD	NR	50.0	10.0	30.0	30.0
Egypt[27]	11 pts with anemia and CD	18.2	45.5	45.5	57.1	63.6
Saudi Arabia[48]	16 adults with CD	NR	37.0	18.5	NR	18.5
Libya[49]	39 pts with with CD	61.5	59.0	7.7	82.0	20.5

CD: Celiac disease.

height < 2.5 standard deviations below the mean[47].

Many CD patients are initially diagnosed as having irritable bowel syndrome (IBS). Green *et al*[51] reported that up to 36% of American patients with CD were previously diagnosed with IBS. In Iran, 12% of IBS labeled patients turned out to have CD[39].

Hematological manifestations

The prevalence of anemia at the time of CD diagnosis is 12%-69%[52]. IDA is the most common form and may be the only finding in 45% of patients with sub-clinical CD[53]. Worldwide prevalence of CD among patients with IDA is 2.8%-8.7% and may be as high as 15%[54,55]. Folate and B12 deficiency may contribute to anemia in CD, and surprisingly, anemia of chronic disease is relatively common[52]. In ME and NA countries, anemia occurs in 20%-80% of CD patients and the majority of cases are attributable to iron deficiency[14,15,22,24-26,33,45-47]. An Egyptian study found that 4% of young IDDM patients with anemia had CD[56]. Another paper reports a CD prevalence of 44% among 25 Egyptian patients evaluated for refractory IDA[27].

Osteoporosis

The prevalence of osteopenia and osteoporosis in CD patients is 30%-50% and 3.4%-14%, respectively[57,58]. In ME and NA countries, 5 studies of CD patients reported a prevalence of hypocalcemia of 3.3%-27.4%[33,45,46] and of osteoporosis of 13.5%-16.7%[33,39]. In Saudi Arabia, osteomalacia and IDA were the most common presenting symptoms, accounting for 43.5% of the clinical presentations[48]. In Tunisian children with CD diagnosed by screening, osteopenia prevalence was 34.7%[8]. Delay in the diagnosis of CD may account for the high prevalence of osteoporosis[33].

Abnormal LFTs

Hypertransaminasemia is an early manifestation of liver involvement in CD. Five to 10% of patients with elevated serum aminotransferases end up being diagnosed with CD[59]. Liver biopsy may reveal lesions ranging from reactive hepatitis to cirrhosis, which may be partially or totally reversed with a GFD. In ME and NA countries, few studies have reported abnormal LFTs among patients with CD[21,46]. A Turkish study reported increased transaminases and hypoproteinemia in 38.3% and 4% of CD patients, respectively[46]. The latter may be attributed to protein-losing enteropathy and/or decreased hepatic synthetic activity[46]. An Iranian group reported increased transaminases among 25% of CD patients[22]. Transaminases levels normalized in all patients, except those with cirrhosis, on a GFD[22,46].

Prevalence of autoimmune diseases among patients with CD

About 30% of patients with CD have other autoimmune disorders such as IDDM and autoimmune thyroiditis[60,61]. In ME and NA countries, the prevalence of autoimmune diseases among CD patients was demonstrated to be as low as 1.9% in Turkish patients[46] and as high as 33% in Iranian patients[28]. Many of these patients were diagnosed with CD after substantial delays[39]. The prevalence of IDDM in CD patients is 6.7%-18.5% and affected patients are typically older than those with IDDM alone[33,39,48]. They are mostly females with longer duration of diabetes[24]. Autoimmune diseases are more common in patients with IDDM and CD than in those with CD or IDDM alone[28,33,62]. In a Turkish study, adult patients with IDDM and CD had a 33.33% prevalence of other autoimmune diseases such as autoimmune thyroiditis[28]. This may be an overestimation due to small sample size. Importantly, a French study demonstrated a reduction in the development of autoimmune diseases among CD patients adherent to a GFD compared to those not adherent to such a diet[63]. This highlights a major role of early diagnosis and therapy of CD in order to reduce the burden of autoimmunity.

DIAGNOSIS

The diagnosis of CD is challenging and requires a high

Table 4 Serological diagnosis of celiac disease in Middle Eastern and North African countries

Country	Population	AGA (%)		AEA (%)		t-TG Ab (%)	
		Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
Turkey[6]	2000 healthy individuals	NR	NR	NR	NR	90.0	NR
Iran[7]	2799 healthy individuals	NR	NR	19.0	100.0	100.0	99.0
Israel[11]	1571 healthy blood donors	NR	NR	20.0	100.0	50.0-60.0	25.0-38.0
Tunisia[17]	2500 healthy blood donors	100.0	84.0	NR	NR	NR	NR
Algeria[39][1]	116 children with IDDM	IgA AGA, IgG AGA, and IgA AEA					
		Sensitivity 80.0			Specificity 100.0		
Turkey[46]	104 children with CD	76.0 (IgA), 94.0 (IgG)	NR	90.0	NR	NR	NR
Saudi Arabia[26]	145 high risk patients	NR	NR	NR	100.0	NR	NR
Egypt[27]	11 children with CD	100.0	21.4	81.8	21.4	72.7	85.7
Israel[68]	39 children with CD and 22 healthy children	NR	NR	100.0	100.0	NR	NR

[1]Sensitivity and specificity of all tests simultaneously.

level of suspicion. All screening algorithms start with serological tests and include testing for IgA and IgG anti-gliadin antibodies (AGA), IgA and IgG anti-endomysial antibodies (AEA), IgA and IgG tissue transglutaminase (tTG) and a new generation of anti-gliadin antibodies to deamidated synthetic gliadin peptides (DGP)[64]. The AEA test is currently the gold standard because of its high sensitivity and almost 100% specificity[1,65]. Furthermore, high levels of both AEA and tTG have very high sensitivity and specificity[66]. Small intestinal biopsy remains the gold standard diagnostic test[1,67].

Diagnosis of CD in ME and developing countries

In 24 out of 28 studies of prevalence of CD in ME and NA countries, patients were initially screened with serological tests. In those testing positive, confirmation of the diagnosis by duodenal biopsy was performed in the majority of cases. In 7 out of 24 studies, confirmation by biopsy was incomplete (Tables 1 and 2). In 4 studies, intestinal biopsies were the initial mode of diagnosis because of the unavailability of serological tests[14,15,25,29]. Serological marker sensitivity and specificity varied widely because of difference in the choice of gold standard, bias in patient selection, population differences and methodology used, including number of biopsies (Table 4). AEA sensitivity ranges from 20%[7,11] to > 90%[17,46,68], with a specificity reaching 100%[7,11,26,68]. The low AEA sensitivity reported from 2 studies conducted in Iran and Israel is attributed to improper intestinal mucosal sampling, the low power of AEA-immunofluorescence in detecting early CD, and the poor performance of the AEA in the presence of milder degrees of villous atrophy[11,69]. These factors may have resulted in missing many cases of CD[7,11]. tTG IgA sensitivity is 70%-100%[6,7,57], and specificity is 99%[7]. The sensitivity of IgA AGA is about 80%, while that of IgG AGA is 90%-100%[17,27,46]. AEA testing was used in 19 out of 24 studies, while t-TGA and AGA testing were used in 12 and 9 studies, respectively (Tables 1 and 2). While the serological tests have shown high sensitivity and specificity for the diagnosis of CD, there are problems including differences in test kit sensitivity and specificity[70], as well as an apparent lower performance in the clinical setting compared to research laboratories[71].

The Marsh classification is a histologic grading system that reflects the varying degrees of intestinal mucosal villous atrophy and inflammatory changes that occur in patients with CD[1]. March classification is used by almost all investigators in the histological diagnosis and classification of CD severity.

TREATMENT

A GFD remains the mainstay of CD treatment. Adherence to a GFD in Western countries is reported to be less than 50%[72]. Treatment with a GFD results in improvement of many clinical and serological parameters[1,73]. Also, adherence to a GFD for five consecutive years or more significantly reduces the incidence of malignancies such as cancer of the mouth, pharynx, esophagus and lymphoma[74]. Moreover, adherence to a GFD has a protective effect on the development of many autoimmune diseases such as IDDM, inflammatory bowel diseases, hepatitis and hematologic disorders[63].

Adherence to a GFD in ME and NA countries ranges from 50% to 100%[10,14,15,18,22,23,39,59,62]. The vast majority of adherent patients have good response ranging from 60% to 100%[10,14-16,18,22,23,28,39,48,49]. Moreover, patients' level of compliance and response were used interchangeably in some studies[14,15,48]. The higher level of adherence to a GFD in comparison to Western countries may be due to the limited number of patients studied and the use of less rigorous parameters to assess adherence.

The reasons for poor compliance are not clear. Wheat and barley are major diet constituents with few acceptable alternatives[22], rendering the convincing of parents that bread is the cause of diarrhea very hard[15]. Also, convincing patients with atypical CD to adhere to a GFD is difficult[4]. Finally, lack of information about CD manifestations, lack of benefit from a GFD and lack of encouragement to adhere to such a diet may contribute. More than 10% of adults with CD do not adhere strictly

to long term GFD and more than 30% who believe they are, are actually consuming grams of gluten daily[4]. Diabetic patients adhering to a GFD will have fewer episodes of hypoglycemia and better diabetes control[26]. Demir *et al*[46] report improvement in growth velocity and rapid catch up of height and weight in children with CD who adhere to a GFD. Moreover, adherence to a GFD resulted in improvement of hepatic histopathological changes. In addition to a GFD, supplementation of calcium, vitamin D and iron may accelerate normalization of serological markers and reduce the rate of fractures and complications resulting from anemia[39].

There are no reports regarding refractory CD or its treatment from ME or NA countries. In addition, no trials of immunosuppressive or immune-modulator drugs have been described. Currently, both a permeability blocker and oral enzyme preparations are in clinical trials in the US and Europe[75-77]. While the safety and effectiveness of these potential therapies need to be determined, the financial burden of the addition of drugs to a GFD may be prohibitive in developing countries.

COMPLICATIONS

Complications of CD range from malabsorption to cerebellar ataxia, dilated cardiomyopathy[78], infertility, lymphoma, as well as oropharyngeal, gastrointestinal and thyroid malignancies[45,79]. Metabolic bone disease, malignancies and autoimmune conditions may develop if treatment is delayed[80].

In the ME and developing countries, most complications result from malabsorption. Mortality in hospitalized patients with CD is relatively increased in the first 3 years after diagnosis, particularly in patients with malabsorption, those with delayed diagnosis, and those poorly adherent to a GFD[33]. Prolonged INR due to Vit K malabsorption is found in 25% of patients and improves on a GFD[81]. However, low levels of serum cholesterol, HDL, LDL and phospholipids in 46 Algerian patients with CD did not improve on a GFD[82]. Hypocalcemia and hypovitaminosis D contribute to osteoporosis which occurs in 16.7%[43] of CD patients, similar to what is reported in Western countries[57,83]. There have been case reports of hepatic vein thrombosis in North African subjects with CD[84,85].

A mortality rate of 3.3% was reported in 60 Turkish patients with CD, mainly due to malignancies[33]. In Turkey and Iran, non-Hodgkin lymphomas are the most common CD-associated malignancies[33,39]. Similar to Western countries, there is an increased prevalence of gastrointestinal malignancies and of non-Hodgkin lymphoma in CD patients. Oropharyngeal malignancies, as well as neurological, cardiac and cutaneous complications of CD, have been described in Western countries[1,2,37,78,79], but have not been well documented in ME countries. Left ventricular subclinical systolic dysfunction has been reported in Turkish children with CD, with a negative correlation between myocardial systolic wave and serum IgA AEA level[86].

Mortality rate among hospitalized patients with CD in Turkey was found to be increased 2-fold[33], although it is not clear what the control group was in this study. While increased mortality in CD patients has been well documented in the West using standardized mortality ratio (SMR)[1], which is the ratio of observed deaths in patients with celiac disease to expected deaths on the basis of age- and sex-specific rates in the region under study, no such data has been published from the Middle East.

GENETICS

Most CD patients have HLA DQ2 or HLA DQ8 alleles, which account for 40% of the total genetic predisposition to CD[1,2]. Moreover, HLA DQ2 and DQ8 are expressed in 30% of the general population, suggesting the presence of additional factors for CD development. One such factor is *CTLA-4* gene polymorphism, a non HLA gene thought to regulate T-cell immune function[87]. As in the West, CD is found in ME and NA countries to be strongly associated with HLA DQ2 (DQA1*0501 and DQB1*0201)[88-93]. HLA DQ8 (DQA1*0301 and DQB1*0302) is less strongly associated with CD[92]. *HLA B8*, a gene expressed in MHC I antigen presenting cells, is found to be associated with CD in Algeria[89], Iraq[94,95] and Turkey[91]. Carriers of this gene are at increased risk of developing CD[91]. In addition, Saharawi patients with atypical CD were found to over-express the MHC class I chain-related gene A (MICA) allele 5.1[89]. These associations have been reported in Western countries[96]. Increased prevalence of HLA-A25(10) in Turkish children with CD is reported, suggesting that this genotype is particularly encountered among this population[91]. No such association has been described in Western countries.

CONCLUSION

The prevalence of CD disease in ME and NA countries may be underestimated due to lack of awareness and low suspicion of the disease. Whether mass screening for the disease should be done in high risk populations, such as patients with short stature, chronic diarrhea, IDA, IDDM, and those with a positive family history is not clear. The best screening modality is not yet determined, though tTG IgA is probably the most economic.

Large prospective studies are needed to assess the true incidence, the clinical course, the efficacy of treatment modalities employed, patient compliance, disease complications and response to treatment in ME and NA countries. The association of CD with other autoimmune diseases and the presence of specific genetic markers would be areas of interesting future research. The high rate of consanguinity among people of the same ethnic background in this part of the world might provide an opportunity for establishing genotype-phenotype correlations in CD.

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