



## Celiac disease in Kuwait, is there a difference than other populations?

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### Abstract

Celiac disease is showing a different epidemiological pattern in the last few years where the Middle East is involved now in its prevalence, not just Europe.

#### **Aim of the study:**

Evaluate the difference between Kuwaitis and non-Kuwaitis in the seroprevalence and histopathological pattern of celiac disease.

#### **Patients and methods:**

This retrospective study included 182 patients diagnosed as celiac disease in Mubarak Al-kbeer hospital divided into 91 Kuwaitis and 91 non-Kuwaitis who were retrieved from the archives.

#### **Results:**

Females showed to have the upper hand in being diagnosed as celiac disease representing 67% of the patients. Diabetes Mellitus type 1 was the main associated disease with diagnosed patients and was more in the Kuwaitis population. There was no statistical significant difference between both studied groups considering serological findings, pathological results or gender.

#### **Conclusion:**

Kuwaitis population is similar to other populations in the prevalence of celiac disease.

#### **Keywords:**

Celiac disease; Seroprevalence; Diarrhoea; Anemia; Diabetes Mellitus type 1

## Introduction:

For years, Celiac disease was considered a disease that is mainly prevalent in Europe but now it is well established as a worldwide disease (1-5). There are many causes of small bowel villous atrophy and/or malabsorption as Agammaglobulinaemia or hypogammaglobulinaemia, AIDS enteropathy, amyloidosis, autoimmune enteropathy, Crohn's disease, graft versus host disease, Tuberculosis and others. Celiac disease is one of these causes. In genetically predisposed individuals, dietary gluten causes an inflammatory response resulting in small intestinal villous atrophy. The prevalence of the disease is increasing worldwide for many reasons (6,7). The true increased prevalence is one cause. Also, the awareness of the disease and the invention of more serological markers increased the detection of the disease (8, 9, 10, 11.).

The diagnosed group of patients represents the iceberg of the diseased population as many individuals are asymptomatic (12, 13, 14 ). It is classified into "classical " type where symptoms and signs of malabsorption are found and "non- classical" type where this is not found.(15) Still, there are a significant group of patients who are diagnosed by the complications they develop as anemia or osteoporosis (16).

From a global perspective, the incidence of celiac disease differs from 1 : 132 in Switzerland to 1 : 1000 and 1 : 2000 in other European countries. (17). It usually affects one in a hundred among the general population, being more prevalent in the Middle East and North Africa. (18) In Arabic countries, according to a meta-analysis, the highest prevalence of celiac disease among otherwise healthy individuals was reported in Saudi Arabia at 3.2%, and the lowest was in Tunisia at 0.14% (19).

Screening on large scale for Celiac disease requires tests with high sensitivity, specificity and positive predictive values and negative predictive values. Anti-gliadin antibodies were the used tests in 1980s to 1990s, but they showed low positive predictive values. They were replaced by endomysium (EMA) and tissue transglutaminase

antibodies (TTG) with sensitivity and specificity seemed to be at least 90–95%. Another test that was added to the panel and gained some popularity is for deamidated gliadin peptide antibodies (DGP) (20).

Sometimes, small intestinal biopsies are required regardless of the result of serological testing. This happens in cases with severe gastrointestinal symptoms, children with stunted growth, the association with other autoimmune diseases as type 1 DM, Addison disease or thyroid disease (21).

This study is done to investigate the epidemiology of celiac disease in Kuwaitis population in regards to serological and histopathological examination.

## Patients and methods:

This is a retrospective study done in Mubarak Al-kabeer hospital where we retrieved the date of patients diagnosed as having celiac disease from the archives of the hospital.182 patients were diagnosed as having celiac disease as sure diagnosis, divided as 91 Kuwaitis and 91 non-Kuwaitis. Serological testing and endoscopic biopsy results were all revised and recorded. Biopsy results were categorized according to Marsh classification (22) .

**Table 1: Modified Marsh Classification of histologic findings in celiac disease**

Marsh Type	IEL / 100 enterocytes - jejunum	IEL / 100 enterocytes - duodenum	Crypt hyperplasia	Villi
0	<40	<30	Normal	Normal
1	>40	>30	Normal	Normal
2	>40	>30	Increased	Normal
3a	>40	>30	Increased	Mild atrophy
3b	>40	>30	Increased	Marked atrophy
3c	>40	>30	Increased	Complete atrophy

IEL :intraepithelial lymphocytes

## Statistical analysis:

Data were verified, coded by the researcher and analyzed using IBM-SPSS 21.0 (IBM-SPSS Inc., Chicago, IL, USA) \*. Descriptive statistics: Means, standard deviations, medians, ranges and percentages were calculated. Test of significances: chi-square test was used to compare the difference in distribution of frequencies among different groups. A significant p value was considered when it is equal or less than 0.05.

## Results:

### Demographic data:

182 patients diagnosed as celiac disease were recruited in the study. The studied group has mean age of 23.4 + 16.9 to be divided into equal groups of Kuwaitis and Non-Kuwaitis, 91 patients in each group. Most of the studied groups were females representing 67% of the patients. Serological testing was

carried to the studied groups. Anti- tTG IgG was positive in 110 patients and negative in 70 patients. Anti tTG IgA was found positive in 120 patients and negative in 61. When examining anti- endomysial Ab, it was positive in 53 patients and negative in 78 ones. 28 patients were positive for anti DPG IgG and 26 recorded positive for anti DGP IgA.(Table 2)

Table 2: **Demography and serological findings of the studied sample**

Variables		No. = 182	(%)
Nationality	Kuwaitis	91	50.0
	Non-Kuwaitis	91	50.0
Age	Mean ± SD Min - Max	23.4 ± 16.9 2 - 76	
Gender	Male	60	33.0
	Female	122	67.0
Serology anti TTG IgG	Positive	110	60.4
	Negative	70	38.5
	Not available	2	1.1
Serology anti TTG IgA	Positive	120	65.9
	Negative	61	33.5
	Not available	1	0.5
Serology anti Endomysial Ab	Positive	53	29.1
	Negative	78	42.9
	Not available	51	28.0
Serology anti DGP IgG	Positive	28	15.4
	Negative	29	15.9
	Not available	125	68.7
Serology anti DGP IgA	Positive	26	14.3
	Negative	41	22.5
	Not available	115	63.2

Biopsy and medical conditions associated with Celiac disease:

Medical diseases of suspension as risk factors for association with celiac disease were reported in examined cases to show that DM type 1 has the upper hand in the studied patients being reported in 39 patients. Anemia was found to be the presentation in 14 patients and diarrhea was reported in 7 patients. Weight loss was found in 6 patients. 110 patients had no reported associated diseases. The histopathological results of endoscopic biopsies were revised. Different stages of Marsh classification were reported to show that G-3b was the highest group of the examined patients. The results of 116 patients were not available. (Table 3)

Table (3) **Biopsy & medical problems of the studied sample.**

Variables		No.= 182	(%)
Biopsy (Marsh Classification)	G-2	7	3.8
	G-3a	6	3.3
	G-3b	19	10.4
	G-3c	18	9.9

Medical Problems	Negative	16	8.8
	Not available	116	63.7
	DM -I	39	21.4
	Thyroid disease	1	0.5
	Anaemia	14	7.7
	Diarrhea	7	3.8
	Weight loss	6	3.3
	others	5	2.7
Not written	110	60.4	

Serological markers, biopsies and associated medical conditions:

Anti- tTG IgG, anti tTg IgA, anti endomysial Ab, anti DGP IgG and IgA were examined in Kuwaitis and Non- Kuwaitis patients. There was no statistical significant difference reported. The associated medical conditions showed very close values for both groups except for DM type 1 which was more in Kuwaitis than Non-Kuwaitis. Both studied groups didn't show statistical significant value. Examining the endoscopic biopsies showed no statistical significant difference with p value of 0.4 between Kuwaitis and Non- Kuwaitis groups. (Table 4)

Table (4) **Relation between serological findings, biopsy & medical problems and nationality of the studied sample**

Variables		Nationality		P-value 1
		Kuwaitis (No.=91) No. (%)	Non-Kuwaitis (No.=91) No. (%)	
Serology anti TTG IgG	Positive	54 (59.3)	56 (61.5)	0.954
	Negative	36 (39.6)	34 (37.4)	
	Not available	1 (1.1)	1 (1.1)	
Serology anti TTG IgA	Positive	58 (63.7)	62 (68.1)	0.527
	Negative	32 (35.2)	29 (31.9)	
	Not available	1 (1.1)	0 (0.0)	
Serology anti Endomysial Ab	Positive	28 (30.8)	25 (27.5)	0.668
	Negative	36 (39.6)	42 (46.2)	
	Not available	27 (29.7)	24 (26.4)	
Serology anti DGP IgG	Positive	15 (16.5)	13 (14.3)	0.584
	Negative	12 (13.2)	17 (18.7)	
	Not available	64 (70.3)	61 (67.0)	
Serology anti DGP IgA	Positive	14 (15.4)	12 (13.2)	0.656
	Negative	18 (19.8)	23 (25.3)	
	Not available	59 (64.8)	56 (61.5)	
Biopsy ( Marsh Classification)	G-2	2 (2.2)	5 (5.5)	0.486
	G-3a	4 (4.4)	2 (2.2)	
	G-3b	8 (8.8)	11 (12.1)	
	G-3c	7 (7.7)	11 (12.1)	
	Negative	10 (11.0)	6 (6.6)	
Medical Problems	Not available	60 (65.9)	56 (61.5)	0.607
	DM -I	24 (26.4)	15 (16.5)	
	Thyroid disease	0 (0.0)	1 (1.1)	
	Anaemia	6 (6.6)	8 (8.8)	
	Diarrhea	3 (3.3)	4 (4.4)	
	Weight loss	2 (2.2)	4 (4.4)	
	Others	3 (3.3)	2 (2.2)	
Not written	53 (58.2)	57 (62.6)		

### Effect of gender on serological markers:

Then, we investigated the effect of gender on the studied groups. We examined all the serological markers used to find if there is any distribution difference. Anti-tTG IgA had no significant difference statistically between males and females and the same was for anti-tTG IgG showed statistical significant difference. Anti DGP IgG and IgA showed no statistical significant difference in Kuwaitis and non-Kuwaitis between males and females. Anti- Endomysial Ab didn't show statistical significant difference in the studied groups. (Table 5)

**Table 5: Relation between serological findings and nationality & gender of the studied sample**

		Serology anti TTG IgA			P-value <sup>1</sup>
		Positive (No.=120) No. (%)	Negative (No.=61) No. (%)	Not available (No.=1) No. (%)	
Kuwaitis	Male	18 (15.0)	10 (16.4)	0 (0.0)	-
	Female	40 (33.3)	22 (36.1)	1 (100.0)	
Non-Kuwaitis	Male	18 (15.5)	14 (22.9)	0 (0.0)	0.099 <sup>1</sup>
	Female	44 (36.7)	15 (24.6)	0 (0.0)	
		Serology anti TTG IgG			P-value <sup>1</sup>
		Positive (No.=110) No. (%)	Negative (No.=70) No. (%)	Not available (No.=2) No. (%)	
Kuwaitis	Male	16 (14.5)	12 (17.1)	0 (0.0)	0.745
	Female	38 (34.5)	24 (34.3)	1 (50.0)	
Non-Kuwaitis	Male	25 (22.7)	7 (10.0)	0 (0.0)	0.052
	Female	31 (28.2)	27 (38.6)	1 (50.0)	
		Serology anti Endomysial Ab			P-value <sup>1</sup>
		Positive (No.=53) No. (%)	Negative (No.=78) No. (%)	Not available (No.=51) No. (%)	
Kuwaitis	Male	8 (15.1)	12 (15.4)	8 (15.7)	0.909
	Female	20 (37.7)	24 (30.8)	19 (37.3)	
Non-Kuwaitis	Male	9 (17.0)	14 (17.9)	9 (17.6)	0.939
	Female	16 (30.2)	28 (35.9)	15 (29.4)	
		Serology anti DGP IgG			P-value <sup>1</sup>
		Positive (No.=28) No. (%)	Negative (No.=29) No. (%)	Not available (No.=125) No. (%)	
Kuwaitis	Male	4 (14.3)	6 (20.7)	18 (14.4)	0.299
	Female	11 (39.3)	6 (20.7)	46 (36.8)	
Non-Kuwaitis	Male	4 (14.3)	5 (17.2)	23 (18.4)	0.767
	Female	9 (32.1)	12 (41.4)	38 (30.4)	
		Serology anti DGP IgA			

		Positive (No.=26) No. (%)	Negative (No.=41) No. (%)	Not available (No.=115) No. (%)	P-value <sup>1</sup>
Kuwaitis	Male	4 (15.4)	7 (17.1)	17 (14.8)	0.707
	Female	10 (38.5)	11 (26.8)	42 (36.5)	
Non-Kuwaitis	Male	4 (15.4)	8 (19.5)	20 (17.4)	0.987
	Female	8 (30.8)	15 (36.6)	36 (31.3)	

### Effect of gender on histopathological examination and associated medical conditions:

There was no statistical significant difference between males and females in relation to biopsy grading in Kuwaitis and in non-Kuwaitis with p value of 0.6 and 0.1 respectively. There was significant statistical difference between males and females in Kuwaitis population in regards to medical conditions associated with celiac disease with p value of 0.02. (tables 6,7)

**Table 6: Relation between biopsy classification and nationality & gender of the studied sample**

		Biopsy ( Marsh Classification)						P-value <sup>1</sup>
		G-2 No.=7 No. (%)	G-3a No.=6 No. (%)	G-3b No.=19 No. (%)	G-3c No.=18 No. (%)	Negative No.=16 No. (%)	Not available No.=116 No. (%)	
Kuwaitis	Male	1 (14.3)	0 (0.0)	3 (15.8)	1 (5.6)	3 (18.8)	20 (17.2)	0.642
	Female	1 (14.3)	4 (66.7)	5 (26.3)	6 (33.3)	7 (43.8)	40 (34.5)	
Non-Kuwaitis	Male	1 (14.3)	0 (0.0)	4 (21.1)	1 (5.6)	1 (6.3)	25 (21.6)	0.157
	Female	4 (57.1)	2 (33.3)	7 (36.8)	10 (55.6)	5 (31.3)	31 (26.7)	

**Table 7: Relation between medical problems and nationality & gender of the studied sample**

		Medical problems							P-value <sup>1</sup>
		DM-1 No.=39 No. (%)	Thyroid disease No.=1 No. (%)	Anaemia No.=14 No. (%)	Diarrhea No.=7 No. (%)	Wt loss No.=6 No. (%)	Others No.=5 No. (%)	Not written No.=11 No. (%)	
Kuwaitis	Male	12 (30.8)	0 (0.0)	0 (0.0)	1 (14.3)	2 (33.3)	1 (20.0)	12 (10.9)	0.023
	Female	12 (30.8)	0 (0.0)	6 (42.9)	2 (28.6)	0 (0.0)	2 (40.0)	41 (37.3)	
Non-Kuwaitis	Male	5 (12.8)	0 (0.0)	2 (14.3)	1 (14.3)	0 (0.0)	0 (0.0)	24 (21.8)	0.473
	Female	10 (25.6)	1 (100.0)	6 (42.9)	3 (42.9)	4 (66.7)	2 (40.0)	33 (30.0)	

### Discussion:

The awareness towards different presentations of Celiac disease has increased lately due to the changed epidemiology worldwide. The addition of more simple serological tests with more detection powers has increased this awareness also (23).

Studies discussing the prevalence of celiac disease in the Middle East are mainly focusing on patients with associated autoimmune diseases as thyroiditis and DM (24). Saudi Arabia had a prevalence of (1:45) for both sexes; (1:33) for females and (1:68) for males according to a study conducted on 2013 by Aljebreen and his colleagues which is considered the highest prevalence worldwide. ( 25)

In our study, we investigated the serological and histopathological findings of celiac disease in Kuwaitis population and compared that to non-Kuwaitis patients. We were trying to find a difference between the two studied groups considering the serological markers, the histopathological examination and the association with other medical conditions. We tried also to investigate the gender distribution on the studied items between the two groups of patients.

Females in our study had the upper hand which is similar to the published literature with female predominance in celiac disease ( 26,27). Females, in general, are more than males in suffering from autoimmune diseases. Also, females seek medical help more than men. Beside, women report non gastrointestinal symptoms as menstrual disorders and infertility before other celiac related symptoms (28). This was also mentioned in the study done by Dixit and his colleagues with the conclusion that “gender disparity was most marked in young adults between the ages 18 and 29 years of whom only 18% of the patients diagnosed with CD were males” (29) .

Our age group was 23.4 + 16.9 which was near to the study carried in United Arab Emirates where the disease was mainly in the young age category (16-30) ( 30).

According to European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease (ESPGHAN) (31), screening of asymptomatic children and adolescents with an increased risk for CD such as type 1 diabetes mellitus (T1DM), Williams syndrome, Turner’s syndrome, autoimmune thyroid disease, autoimmune liver disease and selective IgA deficiency should be done for celiac disease. Our results showed that DM type 1 was the highest to be recorded in patients diagnosed as celiac disease.

Anemia was the second common finding in our patients which is not in concordance with the study carried out by

Wafaa Al Qabandi and her colleagues (32), where the study reported anemia as the major prevailing finding in the school children diagnosed by celiac disease. This may be contributed to the different age group studied. Also a study carried out by Yousif A Abu-Zeid and his co-workers (30) suggested that anemia was found in seropositive patients, indicating that patients with anemia or iron deficiency should be investigated for celiac disease. This was also emphasized by a study carried on 200 cases with celiac disease where 5% were diagnosed with anemia. (33)

We revised the results of anti tTG, anti endomysial antibodies and anti DPG antibodies for the patients diagnosed as celiac disease. This is in concordance with the ESPGHAN working group on CD which reported that IgA-tTG and EMA are the cornerstones of CD serology.( 34 ). We didn't find statistical significant difference between Kuwaitis and non- Kuwaitis in regards to serological testing. This is interpreted by the validity of the tests for all the populations worldwide and there will be no ethnic difference when tested. When we investigated the effect of gender on the serological markers in the studied groups, no statistical significant difference was detected.

The medical conditions associated with the diagnosis of celiac disease showed statistical significance in Kuwaitis population. Diabetes Mellitus type1 was the main associated condition. According to a study carried out by Shaltout et al , the incidence of type 1 diabetes in Kuwaiti children 0-14 years has doubled in the last 2 decades. (35 )

According to the pooled study performed by Parshant et al (36) documented that the prevalence of CD varies from 0.4% in South America to 0.8% in Europe and Oceania. The seroprevalence of CD was observed to be highest in Asia (1.8%) and lowest in Africa (1.1%). This difference was interpreted by a study carried out by Lebwohl and his colleagues where genetic factors, wheat consumption and age of its introduction, antibiotic and proton pump inhibitor use and even caesarian sections all are involved. ( 37 ) This was not the case in our study where there was no statistical difference between Kuwaitis and non-Kuwaitis in regards to Marsh Classification and serological markers in our study even when gender was added to the statistical analysis.

### **Conclusion:**

There is no statistical difference between Kuwaitis and non-Kuwaitis in distribution of celiac disease. Females have higher incidence of celiac disease and DM type 1 is more common in the Kuwaitis population.

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