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PROSPECTIVE STUDY

Seroprevalence of celiac disease among United Arab Emirates healthy adult nationals: A gender disparity

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Abstract

AIM: To determine celiac disease (CD) prevalence and associated manifestations or risk factors in healthy adult Emiratis.

METHODS: It is a cross-sectional prospective study, recruiting 1197 (573 women and 624 men) healthy Emiratis between September 2007 and April 2008

among those who went to Al Ain Hospital to undertake the prenuptial examination. Test for anti-tissue transglutaminase (tTG) IgA antibodies was used for CD diagnosis. Subjects with positive results in the anti tTG antibodies assay were also tested for anti-endomysial (EMA) IgA antibodies. A structured interview was used to collect basic demographic and clinical recall data including: information on name, contact address, age, gender, education status, previous diagnosis of CD, diagnosis of CD in 1st degree relatives and history of "chronic diarrhea, anemia, headache, hepatitis, diabetes, tumor, and thyroid disorder".

RESULTS: Fourteen blood samples (1.17%; 14/1197) were seropositive for CD. The latent CD seropositive patients were 13 women and 1 man and therefore the seroprevalence of CD was 1:86 (14/1197) for adult Emiratis: 1:44 (13/573) for women and 1:624 for men. Binary logistic regression revealed that history of chronic anemia (crude OR = 7.09; 95%CI: 2.32-21.61; P = 0.003) and being a woman (OR = 14.46; 95%CI: 1.89-110.91; P = 0.001) were associated with CD seropositivity. Whereas, the thyroid disorder showed a positive association with CD seropositivity that approach statistical significance (OR = 11.30; 95%CI: 1.32-96.95; P =0.09) and therefore was included in the multiple logistic regression analysis, which showed that CD seropositivity is independently associated only with history of chronic anemia (OR = 4.58; 95%CI: 1.45-14.48; P = 0.01) and being a woman person (OR = 10.47; 95%CI: 1.33-82.14; P = 0.026).

CONCLUSION: Compared to men the CD seroprevalence among women was remarkably higher. The CD association with women and chronic anemia is of importance from a public health perspective.

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Key words: Celiac disease; Epidemiology; Serology; Prevalence; Gender; United Arab Emirates



Core tip: Celiac disease (CD) prevalence is unknown in United Arab Emirates. Screening for CD among adult Emiratis was done by using anti TtG antibodies and anti-endomysial antibodies (EMA) confirmed those positive. A structured interview was used to collect demographic data and clinical history. Eleven hundred ninety seven subjects were included in the study; the seroprevalence was 1:86 for all adults; 1:44 for women; 1:624 for men. Chronic anemia and being a woman independently associated significantly with CD seropositivity. To our knowledge, this is the first study on CD prevalence among Emiratis; reporting the highest gender difference in CD seroprevalence worldwide.

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INTRODUCTION

Celiac disease (CD) is a chronic inflammatory condition in the small intestine, as a response to eating gluten in genetically susceptible individuals. Many symptoms are associated with CD including chronic diarrhea, anemia, and iron/vitamins deficiencies; but what is called as silent or latent CD is also common. Therefore, CD is considered as one of the less diagnosed diseases and affected persons are mostly unaware of having the disease. Moreover, diagnosis of CD often is required for extraintestinal manifestations, including psychiatric [1], skin [2], and autoimmune diseases^[3]. Those who remain undiagnosed are at risk of many long-term complications including but not limited to infertility, osteoporosis, and lymphoma. The basis of treatment of CD is abiding to a diet free of gluten^[4]. Therefore, timely diagnosis is essential not just to enable proper treatment of symptoms but also to avoid possible complications^[5].

The early epidemiological studies of CD in Europe were based on clinical presentation followed by intestinal biopsies led to undervaluing the prevalence of the disease. Development of highly sensitive and specific serological tests on which subsequent epidemiological studies were based upon, resulted in reporting higher CD prevalence and revealing many clinical features of the disease^[6]. Although intestinal biopsy is considered as the gold standard in diagnosis, serological tests are needed to screen for people who need the biopsy. Serology is also useful in distinguishing between the disease and the other causes of intestinal villi atrophy. The recommended test for CD screening is anti-tissue transglutaminase (tTG) antibodies. The test detects both IgA and IgG antibodies. The sensitivity of anti tTG antibodies test is more than 90% but the specificity is less compared with

anti-endomysial antibody (EMA) test^[7]. The tTG test is based on ELISA which is from a cost and time perspective superior to EMA test^[8].

CD affects all ages and races worldwide and its prevalence varies from 0.5%-3%. Initially the disease was thought to be largely confined to northern Europe and Australasia and not common in North America and the Middle East, but CD is now known to be prevalent in all those regions^[9]. The published prevalence for CD varies between 1:150-1:300 in UK and 1:80-1:122 in Ireland^[4], while it was 1:200 among Italian school children which is much more than earlier prevalence based on clinical findings^[10]. Hotmeier and Caspary reported that; for each diagnosed CD patient there are approximately 7-10 undiagnosed patients [11]. The above-mentioned findings suggested an analogy to what is called CD iceberg. A study reported a prevalence of 1:96 in north India and the study concluded that CD is more common than expected^[12], while the prevalence was 1:50 in Shiraz, Iran^[13]. There are few reports from the Middle East and the Gulf on the prevalence of CD, and to our knowledge no study exists on the prevalence of CD in UAE nationals. Therefore, this study aims at estimating the prevalence of CD among healthy adult Emiratis.

MATERIALS AND METHODS

Study design

This study was a prospective cross sectional concerning CD prevalence in Al Ain city among adult Emiratis who were undergoing the tests of prenuptial examination. Sample size calculation was based on an estimated CD prevalence of 1%, and a lower 95% confidence limit of 0.58%. The estimated minimum number of subjects to be included was 1150; and was adjusted to around 1200 to include about 4% more than the required number.

Study area

Al Ain is the second largest city in the Emirate of Abu Dhabi, it is located inland on the country's eastern border with Oman about 165 km from Abu Dhabi and about 140 km from Dubai. The area of this city covers over 1.17 million hectares mostly of sand dunes, the temperature during the year ranges between 10 °C up to 48 °C. Al Ain city is the country hub for learning, harboring the UAE University and is famous as a tourist destination. The city is divided into 35 districts with a total population of 0.63 million, 30.8% of whom were Emiratis (estimation of mid 2012).

Al Ain Hospital is one of two major governmental hospitals in Al Ain city and at the time of sampling, it was the only place in the city performing the prenuptial examination tests for UAE nationals.

Study population and blood sampling

The study population is Emiratis who visited Al Ain Hospital for the prenuptial examination between September 2007 and April 2008. The inclusion criteria were:



being an adult (16 years of age or more), not previously diagnosed as a CD patient and willing to participate in the study. The exclusion criteria were: Emiratis less than 16 years of age, Emiratis who were diagnosed as having CD, Emiratis with serological equivocal results for CD diagnosis and all non-Emiratis. Blood sampling was carried out at Al Ain Hospital; 5 mL was obtained from each subject. Sera were separated on the same day and stored at -80 °C. Sera were tested for anti-tissue transglutaminase (tTG) IgA antibodies, total IgA measurement was carried out for sera which were negative in tTG IgA. Seropositive sera in anti tTG IgA antibodies were tested for anti EMA IgA antibodies and the following criteria were used to define a serum as CD positive: positive in both anti tTG IgA and anti EMA IgA antibody tests; or in sera with total IgA deficiency, positive in both anti tTG IgG and anti EMA IgG antibodies. The criteria for a serum sample to be designated as CD seronegative were if sufficient in total IgA to be negative in anti tTG IgA, or if deficient in total IgA to be negative in anti tTG IgG.

Demographic and clinical recall data

For each subject a structured interview was done and included information on name, contact address, age, gender, education status, knowledge about CD, if he/she was previously diagnosed as CD patient, diagnosis of CD in 1st degree relatives, history of: chronic diarrhea, anemia, headache, diabetes, tumor, hepatitis and thyroid disorder.

Anti tTG IgA antibodies

Anti tTG IgA antibodies were measured using an ELISA method based on human recombinant transglutaminase (IBL International, Hamburg, Germany). The test was carried out according to the manufacturer instruction. Interpreting the results for tTG IgA qualitatively was based on OD cutoff ratio values as described in the footnote of Table 1.

Total human serum IgA

Quantitative determination of human IgA in serum was carried out using an ELISA method. The test was carried out according to the manufacturer recommendation (XEMA, Medica Co., Moscow, Russia). Sera with IgA level < 0.05 g/L are considered IgA deficient.

Anti-endomysial IgA antibody

The test is based on indirect immunofluorescence assay for semi-quantitative assessment of endomysial antibodies. The test was carried out according to the manufacturer instruction (Immco diagnostics, New York, United States).

Ethical aspects

Al Ain Medical District Human Research Ethics Committee approved the ethical application in July 2007. Upon fully explaining the objectives and the expected benefits from participating in the study, each subject included in the study gave his/her consent for the blood sample and to provide the required information for the structured interview.

Statistical analysis

Data analysis was carried out on personal computer using SPSS (version 15, SPSS Inc., Chicago, IL, United States). The difference in age between "men and women" and between "diabetics and non-diabetics" was assessed by the student's t-test. The linear by linear (for ordinal variables), the Pearson χ^2 test and the Fisher exact test were used to compare dichotomous nominal variables between women and men. Binary and multiple logistic regressions were used to analyze the association between the variables obtained from the structured interview with CD serology.

RESULTS

Study population attributes

Fourteen hundred and thirty persons were requested to participate in the study and 1211 (84.7%) approved. Fourteen were excluded due to grossly hemolyzed samples (11) or equivocal CD serology (3). Therefore, 1197 Emiratis (573 women and 624 men) were included in the study. The age range was 16-70 years with a mean \pm SD of 24.87 ± 6.35 . The mean age for men 26.36 ± 7.413 was higher (P < 0.001) compared to women 23.247 \pm 4.427. The distribution according to age of the study population into 6 groups (16-20, 21-25, 26-30, 31-35, 36-40 and > 40 years of age) and according to gender, showed that most men and women (87.4%) were between 16 and 30 years and there were more men in all the age groups except in the age group 16-20 years (data not shown).

Serological data

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All sera tested for total IgA antibodies were IgA sufficient (data not shown). Fourteen blood samples (1.17%; 14/1197) were seropositive for anti tTG IgA and anti EMA IgA and fulfilled the CD seropositive definition and therefore their donors were considered serologically as CD patients (Table 1). The 14 seropositive patients were 13 women and 1 man and therefore the seroprevalence of CD was 1:86 (14/1197) for adult Emiratis: 1:44 (13/573) for women and 1: 624 for men.

Association of variables with CD serology

In order to test for any association between variables obtained through the structured interview and CD serology, results of binary logistic regression analyses are presented in Table 2. The History of chronic anemia (OR = 7.09, 95%CI: 2.32-21.61, P = 0.003) and being a woman (OR = 14.46; 95%CI: 1.89-110.91, P < 0.001) were associated with CD seropositivity. Whereas, the thyroid disorder showed a positive association with CD serology that approach statistical significance (OR = 11.30; 95%CI: 1.32-96.95, P = 0.09) and therefore was included



Table 1 Demographic, serology and clinical history data in adult Emiratis diagnosed serologically with celiac disease

Subject	Gender	Age	tTG IgA ¹	EMA IgA	Clinical history
1	M	24	7.6	+++	a
2	F	28	1.27	+	t
3	F	22	2.42	+++	n
4	F	24	3.6	++	n
5	F	23	8.25	+++	a
6	F	20	3.15	++	n
7	F	20	6.6	+++	n
8	F	22	4.87	+++	a
9	F	25	9.1	+++	n
10	F	18	9.89	+	a
11	F	24	9.13	+++	n
12	F	27	7.6	+	n
13	F	24	4.25	+++	n
14	F	22	6.78	++	a

¹Using qualitative evaluation ratio for tissue transglutaminase (tTG) IgA the cutoff for the positive > 1.2, equivocal 0.85-1.2, and negative subjects < 0.85. a: Anemia; t: Thyroid disorder; n: No complain; M: Male; F: Female; EMA: Anti-endomysial antibodies.

in the multiple logistic regression analysis. Using multiple logistic regressions (for the statistically significant variables in binary logistic regression in addition to the variable thyroid disorder) revealed that only history of chronic anemia and being a woman were independently associated with CD serology (Table 2). Five out of the 14 CD patients reported a history of chronic anemia and one patient reported a thyroid disorder. None of the remaining eight CD patients complained from diarrhea or any symptoms or signs of any disease (Table 1).

CD serology and structural interview variables in men and women

The distribution of gender in relation to CD serology and the structural interview data was analyzed. Most of the CD seropositive were women (P = 0.0006) and most of the anemic persons were women (P < 0.001), whereas, most of the diabetics were men (P < 0.005). The difference in diabetes between the two sexes is most likely due to age. Diabetics (mostly men) had significantly higher (P < 0.001) age (35.76 \pm 12.454) than non-diabetics (24.67 \pm 6.028). No other significant difference in the studied variables was found between the two sexes (Table 3).

DISCUSSION

The epidemiological pattern of CD in the world has changed due to many factors *e.g.*, more awareness to the wide variation in the clinical presentations of CD and discovering new serological tests which are simpler, inexpensive and led to increase in the power of detection and hence increase in the reported prevalence of CD^[6]. The new serological tests have helped in diagnosis of CD and reporting a higher disease prevalence (1:133) in some countries^[14]. However, the actual prevalence of CD is still not clear in spite of these efforts to detect the disease.

In the Middle East, there are few studies on the prevalence of CD in the general population, most of the studies focus on populations at risk, such as those having autoimmune disease e.g., diabetes mellitus type I and autoimmune thyroiditis^[15]. Generally CD prevalence is undervalued and its clinical features have not been fully determined due to small sample size, selection bias, limited knowledge about CD and insufficient research funds^[6,16]. In Libya, as an example of a Middle East country, CD prevalence among school students was (1:41) much higher than those reported in Europe or North America [17]. In Saudi Arabia, CD prevalence among healthy adolescents was (1:45) for both sexes; (1:33) for females and (1:68) for males. The investigators concluded that the CD prevalence in their study may be among the highest worldwide^[18].

To our knowledge, this is the first study on CD prevalence in UAE. This study is prospective cross-sectional concerning CD prevalence among adult UAE nationals who were in the course of undertaking the prenuptial examination. The prenuptial tests include screening for HIV, hepatitis B, syphilis and anemia. The only targeted population was men and women who were apparently healthy at time of recruitment. Choosing this population is satisfactory because the aim of the study is to detect silent/latent CD in healthy adult UAE nationals. Furthermore, from a logistic point of view, those Emiratis were in the process of giving blood for the prenuptial tests, therefore, there was no need for much effort to persuade them to participate in the study. Moreover, the choice of the study population may be reason for the nearly equal gender ratio in this study. The slight men majority in our study can be explained in part that women refused more to participate in the study compared to men; also, some men came alone because their intention was to marry foreigners and the prenuptial tests for foreigners is not carried at the test center at Al Ain Hospital.

In this study, the overall prevalence of CD is 1:86 among UAE nationals of Al Ain city is higher than the CD prevalence in the general population of Western Europe; in Denmark (1:330), Finland (1:130), Germany (1:500), Italy (1:184) and Netherland (1:198)^[8]. The CD high prevalence among healthy adult Emiratis emphasize the CD iceberg terminology (that refers to many undiagnosed CD patients in the general population).

Chronic anemia is a major manifestation of CD; it was shown to be associated with seropositivity for CD. Five seropositive subjects have a history of chronic anemia. Several studies reported anemia as the most common sign of CD among adults. In a study of 200 CD patients, 5% of them were anemic due to nutritional deficiency^[19]. Thus, it is suggested that all patients who have anemia or iron deficiency should be examined for CD. Iron deficiency usually affects 2%-5% of adolescents, adult girls and women^[20]. Most of the anemic subjects in this study were women, which is in agreement with the fact that anemia is more common in women compared with men.

Table 2 Distribution and association of variables according to celiac disease serology in Emiratis distribution n (%)

Variable		CD-ve	CD+ve	¹OR (95%CI) [P value]	² OR (95%CI) [<i>P</i> value]
CD in family	No ³	1181 (99.8)	14 (100)	0.998 (0.99-1.00)	-
	Yes	2 (0.2)	0 (0.0)	[0.828]	
Anemia	No^3	1097 (92.7)	9 (64.3)	7.09 (2.32-21.61)	4.58 (1.45-14.48)
	Yes	86 (7.3)	5 (35.7)	[0.003]	[0.01]
Headache	No^3	1171 (99.0)	14 (100)	0.997 (0.99-1.00)	-
	Yes	12 (1.0)	0 (0.0)	[0.594]	
Diarrhea	No^3	1178 (99.6)	14 (100)	0.99 (0.98-1.00)	-
	Yes	5 (0.4)	0 (0.0)	[0.731]	
Diabetes	No^3	1162 (98.2)	14 (100)	0.996 (0.99-1.00)	-
	Yes	21 (1.7)	0 (0.0)	[0.480]	
Tumor	No^3	1182 (99.9)	14 (100)	0.98 (0.97-0.99)	-
	Yes	1 (0.1)	0 (0.0)	[0.878]	
Thyroid disorder	No^3	1175 (99.3)	13 (92.9)	11.30 (1.32-96.95)	-
	Yes	8 (0.7)	1 (7.1)	[0.09]	
Hepatitis	No^3	1172 (99.1)	14 (100)	0.998 (0.99-1.00)	-
•	Yes	11 (0.9)	0 (0.0)	[0.610]	
Sex	Man ³	623 (52.7)	1 (7.1)	14.46 (1.89-110.91)	10.47 (1.33-82.14)
	Woman	560 (47.3)	13 (92.9)	[0.001]	[0.026]

¹Crude odd ratio; ²Adjusted odd ratio; ³Reference group. CD: Celiac disease.

Table 3 Distribution of celiac disease serology and structural interview data in adult Emiratis men and women distribution n (%)

Parameter		Frequency	Men	Women	P value
CD Serology	-ve	1183 (98.8)	623 (99.8)	560 (97.7)	0.0006^{1}
	+ve	14 (1.2)	1 (0.2)	13 (2.3)	
CD in family	No	1195 (99.8)	624 (100)	571 (99.7)	0.229^{1}
	Yes	2 (0.2)	0 (0.0)	2 (0.3)	
Anemia	No	1106 (92.4)	601 (96.3)	505 (88.1)	< 0.001 ²
	Yes	91 (7.6)	23 (3.7)	68 (11.9)	
Headache	No	1185 (99.0)	618 (99.0)	567 (99.0)	1.000^{2}
	Yes	12 (1.0)	6 (1.0)	6 (1.0)	
Diarrhea	No	1192 (99.6)	621 (99.5)	571 (99.7)	1.0^{1}
	Yes	5 (4.4)	3 (0.5)	2 (0.3)	
Diabetes	No	1176 (98.2)	606 (97.1)	570 (99.5)	$< 0.005^2$
	Yes	21 (1.8)	18 (2.9)	3 (0.5)	
Tumor	No	1196 (99.9)	623 (99.8)	573 (100)	1.0^{1}
	Yes	1 (0.1)	1 (0.2)	0 (0.0)	
Thyroid disorder	No	1188 (99.2)	622 (99.7)	566 (98.8)	0.096^{1}
-	Yes	9 (0.8)	2 (0.3)	7 (1.2)	
Hepatitis	No	1186 (99.1)	617 (98.9)	569 (99.3)	0.642^{2}
-	Yes	11 (0.9)	7 (1.1)	4 (0.7)	

¹Fisher's Exact Test; χ^2 with continuity correction. CD: Celiac disease.

The women-to-men ratio of those who are sero-positive for CD in this study (13:1) is much higher than that reported in Finland (11:21)^[21], Sweden (7:3)^[22], and Argentina (2:1)^[23] but comparable to the ratio reported from eastern Switzerland (10:1)^[24]. In this study, the seroprevalence of CD in Emirati women was considerably higher compared with men; this dichotomy in gender-related CD prevalence was more remarkable compared to studies from other countries. Most of our subjects (87.4%) were in the young age category (16-30) which agrees with the conclusion of Dixit and coworkers^[25] 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". There are unknown factors that contribute to the high prevalence

of latent CD among women; two obvious factors are the amount of gluten consumption and the extent of intestinal damage^[26]. There is no study comparing the consumption of wheat in women and men in UAE and this study didn't include this variable in the structured interview. There are indications that autoimmune diseases have common genetic risk factors and many of these are gender-predisposed^[27]. Possibly women are genetically more susceptible to environmental exposure factors that affect the immunological processes leading to CD. Smoking may be protective against CD and in UAE men constitute the bulk of smokers^[28,29], also some endoscopy-confirmed CD patients who were smokers had negative CD serology^[30]. Therefore, smoking may partly explain why in this study the prevalence of celiac disease

in men was much lower compared with women. In support of this interpretation a retrospective study, from Sheikh Khalifa Medical City, Abu Dhabi, UAE, reported that only 48% of CD children patients were females^[31]. Therefore, on the assumption that those children were nonsmokers at the time of study, it is imperative to interpret the difference in CD prevalence between women and men in this study on epigenetic or environmental factors e.g., smoking rather than on inherent genetic susceptibility between the genders. On the other hand, the gender discrepancy may be related to the failure of the serological test to detect the disease in young men due to hormonal or environmental factors. Therefore, one may suggest that for young men with clinical symptoms suggestive of the disease, endoscopy and biopsy should be the basis for diagnosis with less emphasis on the serological tests.

There are some limitations in this study; most of the study population were at the age range of 16-30 years; therefore, compared to the general population older age groups were less represented. The diagnosis relied only on highly specific serological tests but was not proved by biopsy. There was no information on the diet of the sampled population, but it is well known that due to the modern lifestyle, the consumption of fast food (wheat-based diets) among Emiratis has increased considerably during the last decades^[32]. Finally, the study includes only the major risk factors for CD and does not include factors that may be protective against CD such as smoking.

In conclusion, as anemia is a major manifestation rather than a risk factor of CD, gender is the most important risk factor associated with CD seropositivity in this study, with much higher prevalence in women (1:44) compared with men (1:624). These findings are of importance from a public health perspective and should be conveyed to the health authority for raising the awareness of the disease among health workers and the general population. Health workers should know that there are many undiagnosed CD women patients among UAE nationals. Therefore, they should refer any patient with vague symptoms, complications or signs suggestive of CD to the healthcare specialists for further examination. Among the measures to diagnose latent/silent or unrecognized CD in the general population is the screening of all women who suffer from chronic anemia.

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COMMENTS

Background

Celiac disease (CD) can be easily mistaken for many other diseases due to its vast clinical symptoms and presentations. CD is a chronic inflammatory condition in the small intestine, in response to eating gluten in genetically susceptible individuals. It is a lifelong disease and the only treatment up-to-date is the complete abiding to a gluten-free diet. The highest prevalence of the disease worldwide has been reported in the Middle East. The aim of this study is to determine CD prevalence and associated manifestations or risk factors in healthy adult Emiratis.

Research frontiers

The lack of information on the prevalence of the disease from many countries is hindering the effort to draw a worldwide prevalence map of the disease. There is no previous report on the prevalence of CD in the United Arab Emirates.

Innovations and breakthroughs

The authors have reported for the first time the prevalence of CD among Emiratis. Furthermore, from public health perspective our findings of the highest worldwide gender disparity in the CD prevalence has great impact, the prevalence in women was 1:44 compared with 1:624 in men. The study points to the importance of considering CD as an etiological agent particularly in Emiratis women who suffer from chronic anemia.

Applications

The results suggest that CD is common among young Emiratis women in Al Ain; therefore, further studies on CD in UAE are warranted to determine the actual CD prevalence in UAE.

Peer review

CD prevalence is unknown in UAE and Screening for CD is very important. This is the first study on CD prevalence among Emiratis and it reports the highest gender difference in CD seroprevalence worldwide.

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