CELIAC DISEASE PREVALENCE IN TURKEY: A POPULATION BASED CROSS-SECTIONAL STUDY

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ABSTRACT

Introduction*: Celiac disease affects 0.6 to 1.0% of the population worldwide. Undiagnosed CD has been significantly linked with a nearly 4-fold increase in all-cause mortality. The present study was designed to investigate the prevalence of undiagnosed Celiac Disease (CD) and to study the characteristics of these patients in the adult population in Mersin, Turkey.*

Materials and methods*: This study was undertaken through the time frame of June 2011- January 2013. Adults aged 18 and older living in Mersin are included in the study. Family physicians and volunteers registered to these family physicians were selected district-wide through random sampling method, stratified sampling method, respectively. Participants were tested for anti-tissue transglutaminase (anti-tTG) and anti-Deaminated Gliadin Peptide(DGP) IgA and IgG Enzyme-Linked ImmunoSorbent Assay (ELISA). Small intestinal biopsies were obtained from the seropositive patients, and they were examined according to the Marsh classification.*

Results*: 1.554 people participated in the study. Mean age was 42 years and 50,4% were female. 12 (0.77%) of the participants showed anti-tTG/DGP IgA or IgG positivity. The mean age of seropositive participants was 41 years and 83% of them were female. All seropositive participants were either human leukocyte antigen (HLA)-DQ2 or DQ8 positive.*

Conclusion*: This study is the first population-based prevalence study of CD in Turkish adult population. We found that seroprevalence of CD as 0.77% and biopsy proven CD prevalence as 0.39%. Patients with iron deficiency anemia or with relatives diagnosed as CD must be evaluated closely.*

Key words*: Celiac Disease, Prevalence, Population, Mersin, Turkey.*

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Introduction

Celiac Disease (CD) is a small intestinal autoimmune inflammatory enteropathy induced by dietary gluten in genetically susceptible individuals[(1)]. Peptides comprising the gliadin fraction of the gluten protein, trigger an immune response that leads to small intestinal mucosal inflammation and damage[(2)]. Celiac disease affects 0.6 to 1.0% of the population worldwide[(3)].The frequency of celiac disease is increasing in many developing countries because of westernization of the diet, changes in wheat production and preparation, increased awareness of the disease, or a combination of these factors[(3)]. Serologic screening studies have shown that only a small proportion of cases of celiac disease are clinically recognized (CD iceberg). Celiac disease can occur in people of any age and it affects both genders. The prevalence is 1.5 to 2 times as high among women as among men and is increased among persons who have an affected first-degree relative (10 to 15%), type 1 diabetes (3 to 16%), Hashimoto's thyroiditis (5%) or other autoimmune diseases (including autoimmune liver diseases, Sjögren's syndrome, and IgA nephropathy), Down's syndrome (5%), Turner's syndrome (3%), and IgA deficiency (9%)[(3)].

Typical gastrointestinal symptoms in CD include diarrhea, weight loss, postprandial abdominal pain, bloating, and flatus[4]. Long-term complications include osteoporosis, amenorrhea, infertility, and T-cell non-Hodgkin's lymphoma of the small intestine. Lower body mass index, family history of CD, and personal history of autoimmune conditions have been significantly associated with CD[5]. Iron deficiency and other nutrient deficiencies, including cobalamin, folic acid and fat-soluble vitamins, are common[5, 6]. The identification of CD patients who are at risk for specific nutritional deficiencies, complications including intestinal lymphoma, and associated familial disorders is critical[4].

Undiagnosed CD has been significantly linked with a nearly 4-fold increase in all-cause mortality as shown in a large US cohort study conducted over 45 years of follow-up[7]. CD has increased in prevalence over the last five decades[4], affecting up to 1% of the European[8] and US[9] populations with variable proportions worldwide[10].

In Turkey, which stands at an important transition point at the junction of Europe and Asia where the races mix; the prevalence of CD in adult population has been evaluated only in at-risk groups, those who applied to a hospital, blood donors and children. However, to best of our knowledge, an adult community-based prevalence study has not been conducted as yet[11-17]. Thus, the present study was designed to investigate the prevalence of undiagnosed CD in Turkish adult population in Mersin and to detect the characteristics of these patients.

Materials and methods

Determination of the study group

This cross-sectional study was undertaken in the city of Mersin during the June 2011 - January 2013 period. Official permissions for the study were obtained from the Local Health Authority and approval of the ethics committee was taken from the Local Ethics Committee of Mersin University, Faculty of Medicine.

Mersin is a cosmopolitan city in the South of Turkey, which has 10 different districts. Adults aged 18 and older living within the boundaries of Mersin formed the target population of the study. According to Turkish Statistical Institute 2009 population census results, there are 1.133.935 people in this age group living in Mersin. The minimum sample size has been calculated as 1.519 using Epi info 3.5.2 (Epi Info™ Help Desk Centers for Disease Control and Prevention, Atlanta), assuming the relevant population is 1.133.935, an expected prevalence of 1.0% with a degree of accuracy desired set at ±0.5% and a confidence interval of 95%. It was planned to include 1.600 people in the study group. The study group was sorted based on age, gender and district via stratified sampling method according to the districts' age and sex distribution.

52 family physicians were selected district-wide through random sampling method. Family physicians were working at 36 different family health centers. Respondents to be sampled in this study were chosen from those registered to each family physician by using stratified sampling method. The chosen respondents and volunteers were included in the study. Those that would participate in the study were invited to the family health center and informed about the study. Informed consent form was obtained from the voluntary participants, and they were clearly informed about the objectives of the study and the eventual necessity of small intestinal biopsy sampling. A data form consisting of two parts was used in order to collect data. While the first part gathered information on the demographic and socio-economic status of the participant such as age, gender, educational and economic background, the second part investigated gastrointestinal symptoms such as diarrhea, constipation, abdominal pain and other symptoms. A pilot study of the data form was done on 20 people outside of the study group and necessary arrangements were made. The data form was filled by the family physician by using face-to-face question-answer technique. After the data forms were filled 10 cc venous serum samples obtained from participants were stored at -20°C until performing the procedure.

Diagnostic Procedure: Serological evaluation and endoscopy

The serum samples of all participants were tested for antitTG and antiDGP immunoglobulin (Ig) A and IgG using a commercially available enzyme linked immunosorbent assay (IMMCo Diagnostics, ImmulisaTM Celiac FusionTM tTG/DGP ELISA, USA). The test kits were stored at a temperature between +2 and +8◦C and reached room temperature before use. The manufacturers' recommended cut-off values were used to calculate the diagnostic performance. The cutoff was 20 U/mL for the assays. A level higher than 20 U/mL was accepted as positive.

Finally, participants who had positive test result were informed about the disease and small intestinal biopsy was performed. Endoscopic biopsies were obtained from the second part of the duodenum. A pathologist, blinded to the serology results, examined all biopsy specimens according to the Marsh classification[18].

Those diagnosed with CD were followed up by the Mersin University Faculty of Medicine Gastroenterology clinic. Respondents with diagnosis of CD were subjected to tests for HLA-DQ2 and DQ8 genotype determination, hemogram, liver functions, bone mineral density and thyroid functions. Abdominal ultrasonography was also performed.

Statistical analysis

Data obtained from the forms was inputted. Descriptive statistics such as mean, proportion and percentage were used in the analysis of the quality-controlled data. Data were calculated by using SPSS v11.0 (Statistical Package for Social Science, SPSS Inc., Chicago, IL).

Results

The current study had 1.554 participants and the participation rate was 97.1% (Table 1).

The mean age was 42,1 years. Of the 1.554 donors, 772 (49,6%) were male and 782 (50,4%) were female. Twelve of the participants showed anti-tTG/DGP IgA or IgG positivity. Thus, the total seropositivity was 0,77%. The mean age of participants who had anti-tTG/DGP IgA or IgG positivity was 41,0 (minimum, 19 years, maximum, 62 years). Of the seropositive participants, 2 (16,7%) were male and 10 (83,3%) were female. Figure 1 shows the distribution of antibody screening for CD in adults in Mersin. One participant refused further genetic investigation (HLA genotyping). All tested participants were (11/12) either HLA-DQ2 or DQ8 positive.

The endoscopic findings observed in 5 of the patients including a nodular pattern to the mucosa, a paucity of the mucosal folds or cracked-mud appearance was concordant with CD. All of the 5 patients had Marsh type-III histopathology. Endoscopic findings were normal in Marsh type-II patients and other patients.

Biopsy of small intestinal mucosa was performed in all patients. Five of them had enteropathy of Type III-c according to Marsh's criteria, and one was Type II. The other 6 patients had mucosal histology concordant with chronic non specific duodenitis. We considered these patients as latent CD correlated to Marsh type 0 (elevated autoantibody titers without histologic abnormality) and recommended follow-up.

				Age 18-29		Age 30-39		Age 40-49		Age 50-59		Age 60-69		Age 70+	
Provinces	**M**	**F**	**T**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Mersin	416	418	834	139	128	94	97	80	79	56	58	31	32	16	24
Tarsus	140	145	285	41	42	32	32	28	28	20	21	11	12	8	10
Erdemli	59	59	118	16	16	14	14	12	12	8	8	5	5	4	4
Silifke	55	58	113	13	14	12	13	12	12	9	8	5	6	4	5
Anamur	31	31	62	7	8	7	7	7	6	5	4	3	3	2	3
Mut	31	30	61	8	8	7	6	6	6	4	4	3	3	3	3
Gülnar	16	14	30	4	3	3	3	3	2	2	2	2	2	2	2
Bozyazı	11	14	25	3	3	3	3	2	3	1	2	1	2	1	1
Aydıncık	6	7	11	1	1	1	2	1	1	1	1	1	1	1	1
Çamlıyayla	7	6	11	2	1	1	1	1	1	1	1	1	1	1	1
Total	772	782	1554	234	224	174	178	152	150	107	109	63	67	42	54

Table 1: The distribution of the study participants according to age, gender, and location.
M: male, F: female, T: total

All participants were screened for tTG/DGP IgA and IgG antibodies for CD. The age of the participants ranged from 18 and 82 years.

All seropositive adults were completely asymptomatic; 5 adults had iron deficiency anemia, 4 had duodenal pathology of Marsh type III-c and 1 had Marsh type-II. Four of the patients who had duodenal pathology of Marsh type-0 were HLA-DQ2 positive and 2 were HLA-DQ8 positive. Deficiency of vitamin B12 and osteoporosis were detected in one patient. This 38-years-old pre-menopausal patient had histology of Marsh type-III. One adult had the IgA deficiency; his test results were 33U/L. One was diagnosed with Hashimoto's thyroiditis (Figure 1).

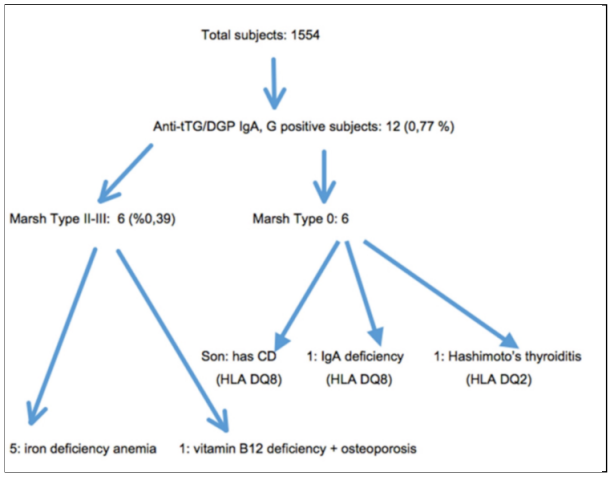

Figure 1: Summary results of the study.
Abbreviations: CD: Celiac Disease, HLA: Human leucocyte Antigen, Anti-tTG: Anti-tissue transglutaminase, DGP: Deamidated gliadin peptide

Abdominal ultrasonography was performed in all patients diagnosed with CD. Eight were completely normal (3 with Marsh type-III and 1 with Marsh type-II), minor secretion in small intestine was observed in 2 (both with Marsh type-III) and significant secretion in small intestine was observed in 2. These had normal endoscopy results and duodenal histology of Marsh type-0. The seroprevalence of CD was 0,77%, whereas the biopsy proven prevalence was 0,39%. Detailed characteristics of the patients diagnosed with CD are shown in table 2.

Discussion

CD has emerged as a public health problem with varying disease prevalence among different races and nations. The epidemiologic knowledge of CD has seen great changes during the last decade of the 20th century. The disease was considered relatively rare in most European countries before that date[19-21]. Since the availability of sensitive noninvasive serologic tests, has made screening for CD in general populations possible, the CD prevalence is increasing worldwide[22]. Several European studies have shown a population-based screening prevalence for the disease in the order of 1:150 to 1:300[22-24]. If silent and potential cases are also included, the prevalence rises to 0.8%[25, 26].

No	Age	Sex	tTTG ¹	Clinical	GIS symptoms	Family history	USG Findings	Endoscopic Findings	Histology	Education	HLA
1	62	F	26,19	-Hashimoto Tiroiditis	-	-	N	N	NSD	None	DQ2
2	47	F	151,47	-IDA	Bloating	-	N	S,D,C,A	M3	Primary school	DQ2
3	31	F	23	-Thalassemia Minor	Bloating	-	N	N	NSD	Primary school	DQ2
4	47	F	42,75	IDA	-	-	N	N	M2	university	DQ2
5	38	K	30,01	-Deficiency of vitamin B12 -Osteoporosis	-	Yes, her daughter	Minimally dilated SB	S,C	M3	Literate	DQ8
6	55	K	160	-IDA	-	Yes, Nephew	Minimally dilated SB	S,D,C	M3	Literate	DQ8
7	30	K	253,33	-IDA	-	-	N	S,D,C	M3	High school	-
8	19	K	179,12	-IDA	-	-	N	C	M3	High school	DQ8
9	41	M	25,56	-	-	Yes, his son*	N	N	NSD	university	DQ8
10	31	M	33,22	-	IBS Selective IgA Deficiency	-	Significantly dilated SB	N	NSD	university	DQ8
11	44	F	53,25	-	-	-	Significantly dilated SB	N	NSD	university	DQ2
12	48	F	20,00	HT, CAD, depression	-	-	N	N	NSD	Primary school	DQ2

Table 2: Detailed characteristics of the patients diagnosed as CD.
*Abbreviations: M: Male, F: Female, IDA: Iron Deficiency Anemia, HT: Hypertension, CAD: Coronary artery disease, IBS: Irritable Bowel Syndrome, SB:small bowel, N: Normal, M2: Marsh type 2, M3: Marsh type 3, NSD: Non specific duodenitis, S: scalloped configuration of folds D: the disappearance or reduction of Kerckring folds C: cracked-mud appearance A: Aphtous ulcer USG: Ultrasonography; 1: Anti-TTG/DGP IgA, G level: IU/ml; *: Newly diagnosed*

The values reported from the United States are in the range of 0.02% to 1.75%[27, 28]. In some of these studies, only patients with clinically diagnosed diseases were considered, whereas in others, screening with anti-gliadin antibody (AGA) IgA-G and anti-endomysial antibody (EMA) was performed. We detected 12 adults with positive anti-tTG/DGP IgA and IgG. Biopsy of small intestinal mucosa was performed in all serology positive patients. Seroprevalence of CD is 0,77%. Duodenal histology was correlated to Marsh type-II-III in half of the cases and correlated to Marsh type-0 in the other half. In general, the prevalence detected in the current study is similar to that of aforementioned studies. The prevalence of CD in the current study was 1:115 based on positive TTG, whereas the prevalence of biopsy proven CD was 1:158.

Previously, CD was considered a disease of childhood because the majority of the cases were less than 2 years of age. However, the disease is common in adults and can be diagnosed at any age[29, 30]. Gomez et al presented the prevalence of CD as 1:167 in an adult population[19]. In a study by Ivarsson et al., a population-based sample of Swedish adults was screened and the prevalence of biopsy-proven CD was reported to be 5.3/1000[31].

In Italy, subjects from the population of Campogalliano were screened for CD and the prevalence of biopsy-proven CD was 4.9/1000, which increased to 5.7/1000 when the potential cases with normal villous architecture but increased levels of γ/δ intraepithelial lymphocytes (IEL) were included[32]. The estimated prevalence of CD in Australia and Spain are 2.3-3.9/1000 and 2.6/1000, respectively[33, 34]. The disease prevalence is estimated to be 56/1000 in the people of Sahara and 6/1000 in Iran[35, 36].

Our findings suggest that CD is an important health problem in Turkey. The classic symptoms of CD include chronic diarrhea, fatigue, iron deficiency anemia, and failure to thrive. Our clinical assessment showed that all patients were asymptomatic. These results showed that celiac iceberg could be projected to our newly diagnosed celiac population. The tip of the iceberg represents clinical cases, but the larger submerged portion represents the silent and subclinical cases[37]. The "water line" depends on the awareness of the disease, availability of diagnostic facilities, and variation of the clinical picture at both the population and the individual levels[38]. Five of our patients (5/12) had iron deficiency anemia, all of which had obvious duodenal pathology concordant with CD. One patient had premenopausal osteoporosis and vitamin B12 deficiency (Marsh type-III). One was diagnosed with Hashimoto's thyroiditis, with positive anti-thyroid peroxidase (TPO) and thyroglobulin (Tg) antibodies. IgA deficiency was detected in one of the patients, who had an antibody titer level of 33 U/L, hence could be diagnosed. This patient had duodenal pathology of Marsh type-0. Our patient group had a meaningful family history. One patient's daughter and one other's niece were diagnosed with CD earlier and unfortunately they were not screened from this aspect. After a patient's diagnosis of CD, his son, who was primarily diagnosed with IBS, was reevaluated and diagnosed with CD as well.

The disease is more common in women than men, but some studies have shown that both sexes might be equally affected[39]. The majority of our patient group were female (n=10/12, 83%). All patients were followed up regularly and a gluten-free diet was implemented. Screening for their families was advised.

The wide spectrum of the disease may be attributed to interaction of various environmental, genetic, and immunologic factors in the pathogenesis[39].

Early diagnosis of the disease depending on the clinical findings is difficult and the disease may manifest with severe complications including infertility, osteoporosis, and lymphoma[38, 40]. Mortality in CD is increased two to fourfold. An important issue is that mortality is not increased in cases with minor symptoms or in CD cases diagnosed by means of serological screening. Serologic screening of the population not only prevents the increased mortality but also results in an improved quality of life with a gluten-free diet even in asymptomatic individuals[41]. Therefore, an increasing number of experts are in favor of mass screening for early diagnosis of CD[38]. Early treatment with gluten-free diet precludes most of these complications[42-45].

Confirmation of CD is based on a combination of factors: clinical examination, celiac-specific serology, and upper endoscopic findings with histologic analysis of duodenal biopsy samples. Histopathologic features of CD include increased intraepithelial lymphocytes, crypt hyperplasia, and villous atrophy as categorized by the Marsh, Marsh-Oberhüber, or Corazza classifications. Six out of 12 patients showed positive (Marsh type-II, and III) histopathologic results in the current study. The remaining 6 patients were evaluated as Marsh

type-0. Only 5 patients with Marsh type-III showed endoscopic findings that were concordant with CD. Duodenum had normal look in the endoscopic screening of other cases.

These results indicate the importance of serologic assays for the diagnosis of CD. Half of the patients would have been missed, if the diagnosis relied merely on endoscopic or histopathologic findings. Specific CD autoantibodies include the AGA, anti-tTG, EMA, and DGP. Currently, IgA-tTGA is the favored single serologic test for identifying CD in patients aged over 2 years, but is false-negative in patients with a selective IgA deficiency. Selective IgA deficiency is more common in CD patients (1 in 40) than in the general population (1 in 400)[46, 47]. In order to avoid false-negative results in patients with selective IgA deficiency, it is recommended to measure total IgA. A second drawback of the detection of IgA anti-tTG is that hemolysis can cause false-negative results by sequestration of anti-tTG antibodies, especially in patients with low IgA anti-tTG titers[48]. IgG antibodies against DGP are a new valuable tool for the diagnosis of CD, which are reported to be comparable to IgA anti-tTG in adults and children[49-52]. Determining IgA anti-tTG and IgG anti-DGP in all patients is better than the other strategies. Given the good specificity of IgG anti-DGP, it has been suggested that IgG anti-DGP could be used in combination with IgA anti-tTG in all patients suspected of CD instead of first measuring total IgA in all patients to identify patients with a selective IgA deficiency[53].

Since the measurement of anti-DGP is not affected by hemolysis[48], this strategy would also overcome the problem of hemolysis. IgG anti-DGP was recently shown to have a high diagnostic sensitivity in patients with a selective IgA deficiency[54], supporting the combined evaluation of IgA anti-tTG and IgG anti-DGP in all patients without the need for estimating total IgA. More recently, a screening assay that simultaneously detects IgA and IgG antibodies to tTG and DGP (tTG/DGP screen) was developed in an attempt to increase the sensitivity. The limited number of studies that have evaluated this screening assay found that the assay had a higher sensitivity and the highest likelihood ratio for CD, whereas double negative test results had the lowest likelihood ratio[55-59].

This method has been used in the current study, which enabled obtaining positive results even in the patient with IgA deficiency. In our study, we did not have EMA biopsy analysis which has been proved to be an extremely sensitive and specific method in diagnosis of coeliac disease[60]. This is a weakness of our study.

Immunogenicity against gliadin is controlled via HLA genes, and the HLA-DQ2 and/or HLA-DQ8 genotype is expressed in 99.4% of CD patients. Approximately 95% of CD patients carry the HLADQ2+ locus, while HLA-DQ8+/HLA-DQ2- individuals comprise only 5%[4, 61, 62]. Six of our patients were HLA-DQ2 positive whereas and 5 were positive for HLA-DQ8. HLA-DQ2/8 testing can be useful for its negative predictive value, whereby its absence can virtually exclude CD[63]. We performed it on all of our patients with positive serology for CD, considering their HLA-DQ2 and 8 genotyping, with the object of supporting the diagnosis or if necessary excluding it for patients whose endoscopic and histologic results were atypical.

Our institution is a University Hospital that serves patients from Mersin and neighboring cities in Mediterranean region of Anatolia. Mersin has the characteristics of a heterogeneously populated city that has witnessed population movements throughout history, where the races and religions have intersected and merged for centuries. It is possible that our results represent the status of the 18- to 70-year age group in our region and can give an idea on the prevalence of undiagnosed CD in adults in Southern Anatolia. The data on the prevalence of CD in Turkey is limited. In a risk group such as short-stature children, studies using EMA and endoscopic small intestinal biopsy, CD prevalence was found as 7 out of 84 (8.3%) and 26 out of 47 (55.3%), respectively[11, 12].

In a study on school children between 7 and 14 years of age in Eastern Turkey, AGA was positive in 23.6%, whereas EMA was not positive in any child[13]. Seroprevalence in primary school children from Erzurum was 0.8%[14]. In the study of Dalgıç et al., seroprevalence with anti-tTG IgA was 2,4%, biopsy proven CD prevalence was 0,47% in 20.190 primary school children, throughout Turkey[17]. In another study analyzing 2000 adult blood donors using the anti-TTG test, the prevalence was 1.3%(16). On 906 adults that applied to a hospital in Central Anatolia seroprevalence of anti-tTG IgA was found 0,9%[17]. The prevalence in our study is in accordance with the values reported from Europe. The absence of classic malabsorption symptoms in any of the patients is in accordance with the previous studies and the major constella-

tion of symptoms are nonspecific gastrointestinal related. Iron deficiency anemia was the most common symptom and positive family history stood out. Family members of 25% of the patients in the current study were also diagnosed with CD.

In conclusion, this study is the first population-based prevalence study of CD in Turkish adults, which demonstrated a high prevalence of CD in healthy adults. The findings of the current study indicate that adults with iron deficiency anemia and premenopausal osteoporosis, or positive family history for celiac disease should be evaluated more carefully with the understanding of the high CD prevalence in Turkey. The importance of serology for diagnosis should not be disregarded and it should be kept in mind that histopathologic and endoscopic findings can be negative in half of the cases.

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