

The Prevalence of Celiac Disease in Patients with Diabetes Mellitus

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ABSTRACT

Aim: To determine the prevalence of celiac disease related autoantibodies in patients with type 1 and 2 diabetes mellitus (DM), and to compare these results with the general population. **Methods:** In total, 137 consecutive patients with type 1 DM, 172 with type 2 DM and 113 age-sex matched control subjects were included into the study. Antigliadin-autoantibodies (AGA) IgG and IgA, and endomysial-antibodies (EMA) IgG and IgA antibodies were determined. Patients who were positive for one or more were offered a gastroduodenoscopic examination. **Results:** AGA IgG positivity was detected in 38.7% (53/137) patients with type 1 DM in 26.2% (45/172) patients with type 2 DM and in 16.8% (19/113) control subjects (significant differences). AGA IgA positivity was detected in 24.8% (34/137) patients with type 1 DM, in 9.3% (16/172) patients with type 2 DM and in 3.5% (4/113) control subjects (significant differences). EMA IgG positivity was detected in 10.2% (14/137) patients with type 1 DM in 0.6% (1/176) patients with type 2 DM and 0.9% (1/113) control subjects (significant differences). EMA IgA positivity was detected in 11.7% (16/137) patients with type 1 DM in 0.6% (1/172) patients with type 2 DM and in none of control subjects. EMA IgA positivity was significantly higher in patients with type 1 DM as compared with patients with type 2 DM and controls. **Conclusions:** High prevalence of celiac disease at the diagnosis of type 1 DM is observed. Serological markers are useful for identifying celiac disease patients with type 1 DM.

Keywords: Celiac Disease, Diabetes Mellitus, AGA IgA, AGA IgG, EMA IgA, EMA IgG

1. Introduction

Celiac disease (CD) is proved to be a T-cell mediated gluten intolerance in genetically predisposed individuals and it is made distinct and recognizable by villus atrophy and malabsorption of small intestine. In some people who are genetically apt to CD, it becomes visible after ingestion of foods containing gluten and related proteins (Alaedini and Green, 2005). CD shows a noticeable regional frequency. Western Europe is the region where CD is known to be prevalent. That CD is widespread with an incidence of nearly 1% [1], has been unveiled by serological screening studies.

It has been confirmed that in patients with type 1 DM has the high ratio of general existence of CD. This existence of relation is declared as 2.3% to 7% [2] which are higher than general population. Originally, both of the diseases are known as autoimmune and as a result of an interaction between genetic and environmental factors,

they could be obvious. However, in patients with type 2 DM, CD related autoantibodies are not so common [3,4].

Short stature, sideropenic anemia, or hypertransaminasemia are several symptoms which are non-classical forms of the disease that most patients who have diabetes and CD. In many cases, patients are completely symptom-free [5]. The risk of ever-evolving autoimmune diseases, malignancy, osteoporosis, infertility, and intestinal lymphomas is proportional to the time of exposure to gluten in CD patients [6,7]; thus, for the early diagnosis of silent celiac disease, using serologic screening tests is vital. AGA has merely 80% sensitivity and specificity. [8] EMA has been proved to be a more trustworthy marker than AGA since it has 90% of sensitivity and specificity [10]. In screening purposes for CD in diabetic patients, the united detection of anti gliadin and antiendomysium antibodies is being used because its a sensitivity and specificity is 100%. In order to uncover silent celiac disease in diabetic patients, these

antibodies are a reliable method.

As we scanned the literature, we did not encounter any data about the frequency of CD related autoantibodies in patients with DM in the Southeastern population of Turkey. For this reason, in this study, we evaluated the prevalence of CD related autoantibodies in patients with type 1 and 2 DM and found a higher frequency of AGA IgA, IgG and EMA IgA, IgG positivity in patients with DM compared with the general population.

2. Materials and Methods

The study was performed in Dicle University, Department of Endocrinology between January 2002 and December 2008. In total, consecutive 137 patients with type 1 DM, 172 patients with type 2 DM and 113 age-sex matched control subjects were included into the study.

The laboratory evaluations of all patients and control subjects were performed according to standart methods at Dicle University Medicine Faculty Laboratory services. AGA IgG and IgA, and EMA IgG and IgA antibodies were determined by immunofluorescence method with Euroimmun immunofluorescence autoantibody determination kits. Total IgA level was detected by nefelometric technique by Beckmancoulter image to be able to exclude patients or control subjects with IgA deficiency. Specific questions were asked and laboratory examinations were performed by same physician to define signs or symptoms of CD; development of diarrhea, hypogonadism, anemia, weight loss, osteoporosis, dermatitis herpetiformis and elevation of transaminases.

Patients who were positive for (AGA Ig A, EMA IgG, and EMA IgA) one or more were offered a gastroduodenoscopic examination. In the intestinal histopathological analysis, more than three biopsy specimens were taken from the second part of duodenum during gastroduodenoscopy. Hematoxylineosin staining was used in these specimens. Slides were graded by conventional histology as normal, with partial villous atrophy, and with subtotal villous atrophy.

3. Statistical Analysis

Mean value, standard deviation (SD), minimum and maximum values were calculated. Independent t test was used to determine the mean values of the variables. The relation of categorical variables was analyzed with the Chi-square test. A p value <0.05 was accepted as statistically significant.

4. Results

In total 137 patients with type 1 DM, 172 patients with type 2 DM and 113 healthy subjects were included into

the study. Out of 137 patients with type 1 DM, 75 were female and 62 were male, and out of 172 patients with type 2 DM, 88 were female and 84 were male. Out of 113 control subjects, 62 were female and 51 were male. Median age of patients with of type 1 DM was 28 (ranged from 16 to 39), median age of patients with type 2 DM was 42 (ranged from 29 to 68) and the control subjects was 39 (ranged from 29 to 48). There was no statistically significant difference between patients with type 1 DM, type 2 DM and control subjects. Median age of patients with type 1 DM was lower than patients with type 2 DM and control subjects ($p < 0.0001$). There is no statistically significant difference between median age of patients with type 2 DM and control subjects. None of the patients and control subjects has IgA deficiency.

AGA IgG positivity was detected in 53 out of 137 (38.7%) patients with type 1 DM, in 45 out of 172 (26.2%) patients with type 2 DM and in 19 out of 113 (16.8%) control subjects. There was a statistically significant difference in terms of AGA IgG positivity between patients with type 1 DM and control subjects, and patients with type 1 DM and type 2 DM patients ($p = 0.000$ and $p = 0.019$, respectively). However, there was no statistically significant difference in terms of AGA IgG positivity between patients with type 2 DM and control subjects.

AGA IgA positivity was detected in 34 out of 137 (24.8%) patients with type 1 DM, in 16 out of 172 (9.3%) patients with type 2 DM, and in 4 out of 113 (3.5%) control subjects.

There was a statistically significant difference in terms of AGA IgA positivity between patients with type 1 DM and control subjects ($p = 0.000$), There was no statistically significant difference in patients with type 2 DM as compared with controls. There was a statistically significant difference in terms of AGA IgA positivity between patients with type 1 DM and type 2 DM ($p = 0.000$),

EMA IgG positivity was detected in 14 out of 137 (10.2%) patients with type 1 DM, in 1 out of 176 (0.6%) patients with type 2 DM and 1 out of 113 (0.9%) control subjects. EMA IgG positivity was statistically significantly higher in patients with type 1 compared with controls subjects and patients with types 2 DM ($p = 0.002$, $p = 0.000$). There was no statistically significant difference between types 2 DM and control subjects in terms of EMA IgG positivity.

EMA IgA positivity was detected in 16 out of 137 (11.7%) patients with type 1 DM, in 1 out of 172 (0.6%) patients with type 2 DM and in none of control subjects. EMA IgA positivity was statistically significantly higher in patients with type 1 DM as compared with patients

with DM type 2 and controls ($p = 0.000$, $p = 0.000$). There was no statistically significant difference in terms of EMA IgA positivity of patients between with type 2 DM and controls subjects. AGA-IgA and EMA-IgA positivity was found in 10 out 137 patients with type 1 DM, in out of 172 patients with type 2 DM and in none of control subjects. Characteristics of patients with type 1 DM, type 2 DM and control subjects were shown in **Table 1**.

Of the 309 patients and 113 controls, 55 (13.4%) were positive for at least one of the three antibodies (AGA IgA, EMA IgG, and EMA IgA), and 41 accepted to undergo an endoscopy. Sixteen patients 10.9% of the DM1 patients, 0.6% ($n = 1$) of DM2 patients were histologically diagnosed with CD. Most of these patients had no symptoms of CD.

5. Discussion

CD accounts for one of the best-understood examples of an environmentally activated autoimmune disease, with genetic risk factors (HLA-DQ2/DQ8), environmental triggers gliadin, and autoantigenic targets tissue transglutaminase being well defined [11]. Villous atrophy and crypt hyperplasia, which ranges from silent asymptomatic forms to active malabsorption syndromes are the abnormalities in the small intestinal mucosa that show us CD is a heterogeneous disorder. Among patients with celiac sprue, a large number of diseases such as Dermatitis herpetiformis, type 1 DM, autoimmune thyroid disease happen to be more frequent.

In patients with type 1 DM, its clinical and pathologic manifestations, and typical gastrointestinal symptoms are rare [12]. That screening is necessary to detect CD in patients with type 1 DM is suggested by the increasing numbers of reports of milder, less symptomatic forms of CD without overt signs of malabsorption.

Undoubtedly, modern serology has become a reliable method for better targeting patients to biopsy although small intestinal biopsy has been the value test for diagnosis [13]. In order to screen high risk groups and the general population, both IgG and IgA AGA anti-bodies have been extensively used. They are cheap, easy to measure, and have reasonably high sensitivity

and specificity [14]. On the other hand, the positive foretelling value of this test is low for population screening [15]. In contrast, with high predictive value [15,16], EMA IgA is a highly sensitive (93% - 98%) and specific (99% - 100%) test. Some investigators suggested that in the presence of a positive EMA, a duodenal biopsy is not necessary for diagnosis by the use of this high specificity [17]. Since the majority of reports indicating approximately 90% sensitivity, we understand that generally the sensitivity of the EMA is excellent [18]. The degree of mucosal damage is correlated with the titer of EMA [19].

Two recent screening programs for CD in a cohort of American type 1 DM patients, found a prevalence of 6.4% [20,21], just as the same with European patients [22]. In an adult Turkish population with type 1 DM, the prevalence of CD is reported as 2.45% [23]. When we compare Turkish type 1 diabetes mellitus patients with American and European patients, the high prevalence of EMA antibodies (EMA IgG positivity 10.2%, EMA IgA positivity 11.7%) may be caused by excessive bread consumption in our region and the prevalence of gastrointestinal infection in children.

It is suggested by the previous studies that an independent trigger effect on the development of CD might be implemented by type 1 diabetes [24]. The reaction to gliadin in susceptible individuals could be triggered by immunoregulatory disturbances in type 1 DM. Both type 1 DM and CD are associated with certain HLA alleles of the DQB1 and DQA1 locus. Some of the co-existence of the two diseases may be explained by the HLA alleles; however, the reason why type 1 DM diagnosis precedes CD diagnosis is still unknown. It has been assumed that there may be a nonspecific activation of the immune system directed toward several dietary proteins attributable to defective immunoregulation or loss of immunologic tolerance of a variety of ingested antigens in patients newly diagnosed with type 1 DM [25].

We found a high prevalence of CD at the diagnosis of type 1 DM in the region. It is important to treat sub-clinical CD, because patients with undiagnosed CD are at risk of long-term CD complications, such as infertility, anemia, osteoporosis, and malignancy. It has been revealed that untreated celiac disease is associated with high morbidity and increased mortality [25,26]. Although the presentation of patients with celiac disease may be protean, serological markers are a cheap and non-invasive method for clinicians in primary care and secondary care to identify patients with this disease.

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Table 1. Characteristics of patients and control subjects.

	DM type 1 ($n = 137$)	DM type 2 ($n = 172$)	Controls ($n = 113$)
Female/male	66/62	88/84	62/51
Median age (year)	28(16 - 39)	42(29 - 68)	39(29 - 48)
AGA IgG positive	53(38.7%)	45(26.2%)	19(16.8%)
IgA positive	34(24.8%)	16(9.3%)	4(3.5%)
EMA IgG positive	14(10.2%)	1(0.6%)	1(0.9%)
IgA positive	16(11.7%)	1(0.6%)	0

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