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THE PREVALENCE OF CELIAC DISEASE AMONG ADULTS WITH TYPE 1 DIABETES

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ABSTRACT

Introduction: Celiac disease and type 1 diabetes are related together in terms of HLA markers and having the chromosomal places, and several studies have indicated that the prevalence of celiac disease in patients with type 1 diabetes is higher than in the general population. Therefore, screening for celiac disease is recommended for patients with type 1 diabetes.
Materials and Methods: This descriptive analytical study was carried out on 79 patients who had previously been diagnosed with type 1 diabetes and referred to the Adult Endocrine Clinic in Khorramabad, from April 2012 to October 2013. In case they met the inclusion criteria, patients were investigated in terms of the presence of the tTG-IgA Anti antibody. In those patients who had positive results in terms of the presence of antibodies, the anti-EMA IgA test and an upper endoscopy were performed, and a biopsies were obtained from the second part of the duodenum. The data was analyzed using SPSS software.
Findings: 79 type 1 diabetes patients with an average age of 21.4 ± 7.10, who were at least 11 and at most 39 years old were studied. 33 individuals were male (41.8%) and 46 individuals were female (58.2%). 14 patients (17.7%) were positive for tTG IgA, and among them 3 patients (21.42%) were positive for EMA IgA. Patients with positive tTG IgA test were considered appropriate for the endoscopy and biopsy. 4 patients with positive tTG IgA failed to show up for endoscopy and one person with positive tTG IgA had normal biopsy. Among 75 patients with type 1 diabetes that were present at all stages of the project, nine patients (12%) had celiac disease, among whom 6 patients were (66.66%) 10-20 years old and 3 patients were (33.33%) were older than 20. 6 patients were female (66.66%) and 3 patients were male (33.33%). None of them had a history of diabetes in their families. In the terms of having gastrointestinal symptoms in patients with diabetes type 1, 5 patients (6.3%) had gastrointestinal symptoms and 74 patients (93.7%) had no gastrointestinal symptoms. 100 percent of the patients with gastrointenstinal symptoms were tTG IgA positive and 40% were EMA IgA positive. There was a statistically significant relationship between serological results and gastrointestinal symptoms.
Discussion and Conclusion: Based on this study, the prevalence of celiac disease in patients with type I diabetes is 12%. Therefore, celiac screening tests are recommended as a routine test in these patients.

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Introduction

Celiac disease is a chronic inflammation of the small intestine which is engendered due to hypersensitivity to gluten (a protein found in wheat and barley) in genetically susceptible individuals. T-cell activation in the intestinal lamina propria by gliadin peptide via HLADQ8 and HLADQ2 [1, 2, 3] is an important event in the development of celiac disease. The prevalence in the general population in Iran is 6.0% [4].

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These manifestations varies based on the patient's age, duration of disease, and its severity. Some of the clinical and laboratory characteristics include: iron deficiency anemia, folate deficiency anemia, anorexia, bone pain, depression, diarrhea, infertility, weakness, nausea, vomiting, frequent abdominal pain, frequent oral ulcers, frequent abortions, short stature, weight loss, increased endomysial antibody titers, increased tissue transglutaminase, pathological fractures, and unjustifiably increased levels of liver enzymes [6, 7].

Use of antibody profiles, such as anti-gliadin antibodies (IgA, IgG), endomysial antibody, and tissue transglutaminase antibody,is a well-known method in the early diagnosis of celiac. Of course, nowadays, among the required serological tests for the diagnosis of celiac disease, the measurement of anti-gliadin antibody has been completely put aside, which is due to the low sensitivity and specificity of this test (50%) [8,38].

A combination of high sensitivity and specificity of the tTG test has led to the proposal that this test be used to evaluate patients suspected of having celiac or for screening as the first choice.

Positive results are confirmed using EMA and the biopsy of the second part of the duodenum biopsy. In the biopsy of the second part of the duodenum, at least 4-6 good samples of this part should be taken, because the lesions of the celiac disease are often irregular, fragmentary, and diffused. Pathological lesions of this disease include: a flattening of the small bowel mucosa by lymphocytic infiltration and increased lymphocytic proliferation. Although the likelihood of the diagnosis of celiac disease based on clinical symptoms and lab results increases, but intestinal biopsy is still recommended as the gold standard in the diagnostic procedure [9, 10].

Pathological changes of the small-bowel in celiac disease are divided into five major groups based on the modified Marsh classification: Marsh0: There is only an increase in intraepithelial lymphocyte, but their numbers are lower than 40 cells per 100 epithelial cells. Marsh1: Lymphocytes infiltrate the lamina propria and the number of intraepithelial lymphocytes is more than 40 lymphocytes per 100 epithelial cells. Marsh 2: The crypts become hypertrophic, but there is no atrophy of the villi. Marsh3: Atrophy of the villi is observed which includes the 3 types of A and B and C. Type A: The atrophy of the villi can be seen as partial. Type B: The atrophy of the villi is seen as subtotal. Type C: The atrophy of the villi can be seen as a total [11].

Nowadays, it has been discovered that this disease is also common in North and South America, North Africa and Southwestern Asia [12 and 13]. During the past two decades, access to sensitive serological tests with high specificity for celiac disease has changed our clinical and epidemiological data about celiac disease. At the present, it has been discovered that a significant number of patients with celiac disease don't have the clinical characteristics or typical performance of this disease. These cases are defined as latent or potential celiac disease and despite the yearly increase in the number of the diagnosed cases of celiac disease, there are still delays in the diagnosis of these patients [14].

Diabetes mellitus is divided into two types: 1 and 2. Type 1 diabetes is an autoimmune disease which is characterized by the destruction of the pancreatic beta cells and, as a result, glucose intolerance and dependence on insulin. This disease is also accompanied with increased levels of different autoantibodies and manifestations of other autoimmune diseases such as chronic thyroiditis, atrophic gastritis, and celiac disease [15,]. Over the past two decades, the global prevalence of diabetes mellitus has increased dramatically, from about 30 million cases in 1985 to 285 million cases in 2010. The prevalence of this disease is the same in most age ranges of men and women [16]. The prevalence of diabetes mellitus type 1 in Iran is 7.3 among 100,000 individuals per year [17]. Thyroid autoimmune diseasesare the most common autoimmune disorders that accompany the onset of type 1 diabetes and in various studies, the occurrence of thyroid autoimmune diseases is reported to be 15-30% in patients with type 1 diabetes [18].

Type 1 diabetes and celiac disease are disorders which have similarities in terms of the predisposing genetic factors that are accompanied with class 2 HLA antigens and autoimmune phenomena [15]. Previous studies have reported that celiac disease is present in 3-8% of patients with type 1 diabetes [19]. It has been reported that the prevalence of celiac disease in patients with type 1 diabetes in Iran is 4.2% [20]. The prevalence of celiac disease in patients with diabetes varies from 1% to 16% in different parts of the world [21,36,37].

Until recent years, celiac disease was regarded as an uncommon childhood disease. But nowadays it has been recognized that its onset may occur at any age, and in a substantial portion of the patients, after being latent for a period of time, it may be diagnosed during puberty. Various screening studies in different countries have shown that the state of our understanding of celiac disease is like an iceberg, i.e., the majority of patients with celiac disease remain undiagnosed [22].

Studies have shown that celiac disease with nonspecific symptoms or without any apparent symptoms is as common in Europe as in the Middle East. An important point in this regard that can be mentioned about celiac and its manifestations in our country is that given that wheat is the staple food of almost 95% of the Iranian population, and Iran is one of the countries which has a high consumption of wheat, it is clear that in spite of gluten consumption and considerable histological changes, a remarkable number of patients have no significant clinical changes and therefore are not diagnosed. It seems that long and continued wheat consumption and exposure to high levels of wheat proteins induce some degree of immune tolerance that leads to milder symptoms in Iranians. This point, in a sense, can be related to Simmons' theory. According to this theory, the cultivation development pattern of wheat has a selective effect on genes that predispose to celiac disease like HLAB8. On the other hand, it shows the importance of higher accuracy and precision in the diagnosis of celiac disease in Iran [23].

The diagnosis of celiac disease patients is significant for two reasons: first, that the symptoms are alleviated by adhering to a gluten-free diet, therefore, the quality of life of the patients will be improved. On the other hand, disease complications which are associated with malnutrition are decrease or relieved .

It has been shown that the risk of autoimmune diseases and intestinal lymphomas for celiac patients is related to the duration of exposure to gluten. Therefore, the early diagnosis of celiac disease is essential to minimize complications [24]. The coincidence of celiac disease with diabetes is associated with various complications. The complications include periods of hypoglycemia and also poor diabetes control [25]. Given the absence of gastrointestinal symptoms in most cases, the diagnosis of celiac disease in diabetic patients based on gastrointestinal symptoms is unlikely. Therefore, it is recommended that routine screening for celiac disease be performed in these patients.

Materials and Methods

This descriptive analytical study was carried out on 79 patients who had previously been diagnosed with type 1 diabetes and who referred to the Adult Endocrine Clinic in the Shahid Rahimi Hospital, in Khorramabad, Iran, from April 2012 to October 2013. Individuals meeting the inclusion criteria (having an FBS more than or equal to 126 mg per dL at least twice, or symptoms of diabetes plus a random blood glucose concentration of more than 200 mg per deciliter, or glucose, a 2-hour plasma glucoseof more than or equel to 200 mg dL) were informed of the nature of the study and, after signing a consent form, they were enrolled.

For all individuals who participated in the study, a questionnaire containing demographic data and the results of paraclinical measures taken for the patients were completed. The contents of questionnaire included questions about age, gender, having a family history of diabetes, and gastrointestinal symptoms (abdominal pain, nausea, and loss of appetite ,diarrhea, bloating). As per the arrangements, the patients went to the laboratory where the tests were performed and samples were taken from each patient. For serological tests, 2cc blood was drawn from each patient from the brachial vein. The blood sample was immediately centrifuged and its serum was frozen at minus 20 degrees Celsius. The tTG IgA test was carried out using the AESKULISA kit made by AESKU, a German company,and the ELISA method. Normal values are between zero and 18, and amounts greater than 18 are considered positive. IgA deficiency and negative IgA was investigated in the participants. Then, the EMA IgA test was performed for those whose tTGIgA levels were positive using the GA (Generic Assays) kit from a German company via the ELISA method. The normal values were from zero to 20 units and values greater than 20 are considered positive. If the tTG IgA test was positive alone or together with EMA IgA, the biopsy of the smallintestine was performed after getting the consent of the patients.

Four biopsy samples were taken from each patient from the second part of the duodenum by asubspecialist in gastroenterology.The samples were sent to the pathology laboratory. Biopsy samples were examined by the pathologist cooperating with the project and their results were reported based on the Modified Marsh Classification. Finely,the obtained data were analyzed by the statistics consultant and using SPSS software.The obtained data were summarized using descriptive statistics (frequency and percentage) and nonparametric tests,such as chi-square and Fisher's exact test, and the final results were reported.

Findings

Out Of the 79 patients with type 1 diabetes that met the criteria to enter the study,33 were male (41.8%) and 46 were female (58.2%). The average age of the patients was21.4 years, the minimum age being 11 and the maximum being 39 years. In the investigation of age distribution in the two age groups of patients with type 1 diabetes, it became clear that 37 patients (46.8%) were in the age group of 20-10 years and 42 individuals(53.2%) were older than 20. Fourteen patients (17.7%) were positive for tTG IgA, among whom 3 patients (21.42%) were positive for EMA IgA, and 11 patients (78.57%) had a negative test. 65 (82.3%) individuals were negative for tTG IgA. 5 patients (6.3%) had gastrointestinal symptoms and 74 patients (93.7%) had no gastrointestinal symptoms.None of the patients had IgA deficiency.

Four patients with positive tTG IgA failed to show up for endoscopy and one person with positivetTG IgA had normal biopsy. Out of the 75 patients with type 1 diabetes who were present at all stages of the project, nine patients (12%) had celiac disease and 66 individuals were not affected by this disease. The pathologist reported that one patient was Marsh 1, 3 patients Marsh 2 and 5 patients Marsh 3. Six patients (66.66%) were 10-20 yearsold and three patients (33.33%) were older than 20. From nine patients with celiacdisease, six patients were female (66.66%) and three patients were male (33.33 percent). None of them had history of diabetes in their families.

Discussion and Conclusion

The prevalence of celiac disease varies among diabetic patients from 1% to 16% in different parts of the world [21].The prevalence of celiac disease in patients with in type 1 diabetes was reported as follow: in the United States 1.4%, in Australia 1.8%, in the UK 2%, in Finland 2.4%, in Austria 3%, in Canada 5.1%, and in Hungary 8.32% [26]. In another report, this figure was reported as 1.4% in theUK, 8.3% in Finland, and 7.8%in Italy [27]. In Sweden, thisfigure was reported as 4.8% [28].

In a study on the prevalence of celiac disease in patients with diabetesin Egypt, it was reportedthat 28% of patientshad positive serologic evidence, and 15.2% had pathological evidence in favor of a diagnosis of celiac disease [29].In studies conducted in Africa,the prevalence of celiac disease among type 1 diabetes patients was remarkable. For example, in Libya 21.3% of diabetic patients had positive serologicevidence and 10.25% had celiac disease [30].The prevalence of positive serology results was reported as 20.9%, and the prevalence of celiacdisease as 10% in a study in Saudi Arabia [31]. In a study in Algeria, the prevalence of celiac disease in patients with type 1 diabetes was reported as 16.4% [26].In Iran in a study which was conducted by Dr. Shahbazkhani in 2003, the prevalence of positive serology results was reported as 2.4% and the prevalence of celiac was 2.4%. In the study of Dr. Daryani et al. in 2001, the prevalence of positive serology results was reported as 3.8% and the prevalence of celiac was 2.5%.Also Dr. Larijani reported the prevalence of celiac disease in patients with type 1 diabetes in 2003 as approximately1.9%. It should be noted that these studies have been conducted in Tehran. Many of the above studies have been conducted based on the anti-gliadin antibody test that is not very accurate.Some of the above studies have also been conducted using the EMAIgA screening test.Although this test is highly accurate, but it is not better than the tTG IgA test [32]. The present study was conducted using the tTGIgA screening test.For patients who had positive test results,theEMAIgA test has also been conducted. Based on the results obtained from this study, among patients with type I diabetes who referred to the endocrine clinic 17.7% had positive tTGIgA test results, among whom21.42% had positive EMAIgA test results. Four patients with positive tTG IgA failed to show up for endoscopy.On the whole, out of 75 patients with type 1 diabetes, 12% had celiac that was confirmed by biopsy and also one subject had normal biopsy results.The prevalence of celiac disease in this study is almost similar to the study which was carried out by Dr.Hassan Vosoughinia and his colleagues in 2012 in the Mashhad University of Medical Sciences on 87 type 1 diabetes patients. In that study, 32.2% of diabetic patients had positive serology results and 10.3 % of the patients had celiacas confirmed by biopsy [33].

In present study, 66.66%of the patients were 10-20 years old at the time of the diagnosis of celiac disease and 33.33%of the patients were older than 20. This difference was not statistically significant, and given the small sample size,an accurate interpretation is not possible. On the other hand, in the study which was conducted by Dr. Ghergherehchi et al. in 2009 in Tabriz, there was no relationship between the age of onset of diabetes and celiac disease [34].

Different studies have shown that the prevalence of celiac disease in women is higher than in men. In the present study, 66.66% of the patients were female and 33.33% of the patients were male which can be justified by the fact that the prevalence of autoimmune diseases is higher in women compared to men. However, there was no significant relationship between gender and the occurrence of celiac disease in this study.

In terms of a family history of diabetes among patients with celiac disease, none of them had a positive family history. There was no statistically significant relationship between a family history of diabetes with the occurrence of celiac disease.It should be noted that both diseases are autoimmune diseases and are affected by genetic and environmental factors.

In a multicenter study, gastrointestinal symptoms in patients with diabetes type 1 and celiac was reported as 24% [35] and in Dr.Shahbazkhani's report in2000, half of the patients experienced abdominal pain [32].

In the present study, out of the 79 patients with type 1 diabetes who were investigated, 5 patients (6.3%) had gastrointestinal symptoms (abdominal pain, nausea,diarrhea ,bloating, loss of appetite), 100% of whom had positive tTGIgA and 40% had positive EMAIgA. Statistical results showed a significant relationship between the results of serological tests and gastrointestinal symptoms.It should be noted that lack of gastrointestinal symptoms does not necessarily indicate that the results of serological testsare negative. On the other hand, given the lack of gastrointestinal symptoms in most cases, the diagnosis of celiac disease in patients with type I diabetes is unlikely just based on gastrointestinal symptoms.

Suggestions

Given that the risk of developing autoimmune diseases and intestinal lymphomas for celiac patients is related to the duration of their exposure to gluten, it is suggested that celiac disease screening tests be performed for all diabetic patients routinely. It should also be noted that the lack of gastrointestinal symptoms does not rule out the possibility of celiac disease.

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