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Original Article

Celiac disease in type-I diabetes mellitus: coexisting phenomenon

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Abstract

BACKGROUND: This study aimed to determine the prevalence of celiac disease in type I diabetic patients and to compare the symptoms and complications of celiac in patients with diabetes and celiac with patients with diabetes only.

METHODS: A total of 241 type I diabetic patients age ≥ 18 who needed insulin intake were recruited from diabetic patients attending the Diabetic Research Center in Kermanshah, Iran. Sample was screened for celiac disease by drawing 5cc blood for complete blood count (CBC), and anti-endomysial antibody test (AEA). Patients then were classified based on immunofluorescent method for the presence of AEA. Those with AEA positive underwent biopsy. The biopsy tissues were classified based on Marsh classification.

RESULTS: Twenty one patients tested positive for celiac disease based on AEA test (8.7%) and 20 (8.3%) tested positive based on the biopsy. Prevalence of celiac among diabetic patients in comparison to normal population was 8.3% vs. 0.6%; and 70% were in the stages III and IV. Weight loss was significantly more prevalent among the celiac patients, who were 4 times more likely to lose weight. Other parameters such as anemia, mucocutaneous and cutaneous hemorrhage, milk intolerance, related oral aphthous, diarrhea and steatorrhea, alopecia, dermatitis herpetiform and alopecia were higher in celiac patients but not high enough to be statistically significant.

CONCLUSIONS: There is a need to improve screening identification and treatment of celiac among all diabetic patients type I, especially in cases with uncontrolled diabetic or weight loss.

KEYWORDS: Celiac Disease, Diabetes Mellitus, Type I, Classification.

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Celiac is a genetic (the major susceptibility gene is HLA-DQ2-8) and inflammatory disease, which results from immune reactions to protein in ingested barely, wheat, and rye gluten, in the small intestine.[1-3] It can cause symptoms throughout the body including abdominal bloating and pain, chronic diarrhea, vomiting, constipation, and weight loss.[4] Gluten intolerance thus appears to be a wide spread public health problem not only in European countries but even more prevalent in the developing countries (i.e., 0.6-1%), where wheat consumption is part of the major diet.[5] Since the first report of atypical celiac disease in late 1960s,[6] many investigators have tried to recognize its presentation within other disorders including diabetics.

Type I diabetes is a disease of autoimmune destruction of a cell called "beta" in the pancreatic islets. Genetic and environmental factors play a major role in development of this disease.[7] Approximately 0.4% of people with European origin are inflicted with this disease.[8] Vaarala et al[9] suggest that consumption of gluten along with gut permeability and inflammation facilitates formation of "perfect storm criti-

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cal to the development of type 1 diabetes." Researchers have provided convincing evidence that there are certain similarities in genetic and environmental risk factors of these two disorders (i.e. a number of diabetes loci and celiac disease loci that are common in both inflammatory disorders).[7] It has been proved that the more the contact of a celiac patient with gluten, the more the chance of diabetes type I.[10]

Results of the aforementioned studies and others suggest that in the etiology of type I diabetes and celiac disease, we may find common genetic and environmental factors, which cause both diseases.[7,11] It is estimated that prevalence of celiac disease (i.e., positive test for anti-tissue transglutaminase antibodies) in diabetes children is up to 10% and 2% in adults[6,12,13] in compare with 1% in the general population[14] and diabetes is usually diagnosed first.[12] The majority of patients with celiac disease are asymptomatic or are not aware of the symptoms.[15] In fact, it is believed that symptomatic celiac patients are just the small tip of a big iceberg.[5]

Diarrhea, the hallmark of celiac, can be easily assigned to autonomic neuropathy caused by diabetes or pancreatic exocrine disorder; even mucosal atrophy might be related to one's diabetes and not celiac. In patients with celiac, it is more difficult to control blood sugar and diabetes related complications such as hypoglycemia. Mohn et al reported that episodes of symptomatic hypoglycemia were more frequent in the patients with celiac than in controls.[16]

There is no clear recommendation for celiac disease screening among diabetics, but many suggest yearly screening for the first three years of diagnosed diabetes, and every 3-5 years thereafter, and/or whenever symptoms appear.[15,17] Some tests have revolutionized diagnosing celiac disease such as serologic tests which measure anti gliadin, anti reticuline, anti endomysial, and anti tissue transglutaminase. Based on sensitivity and specificity tests the anti endomysial with the sensitivity between 85% to 98%, and specificity between 97% and 100%, and anti tissue transglutaminase with the sensitivity between 90% to 98% and specificity between 94%-97% are preferred.

Serological testing in patients with type I diabetes can facilitate early diagnosis of celiac disease in the pre-symptomatic state.[15] Patients with affirmative results and those who have symptoms compatible with celiac disease and/or negative serology then should be referred to a gastroenterologist for further diagnostic studies. Diagnosis of celiac disease would require biopsy of the second part of duodenum through endoscopy and studying pathologic changes of the disease based on Marsh classification. Stage 0 includes the stage before mucus infiltration; stage I includes intraepithelial lymphocytic infiltration followed by lamina properia infiltration; stage II includes crypt hyperplasia; stage III villus atrophy and stage IV total mucosal atrophy.[18]

In general patients with autoantibody positive are vulnerable to mucosal atrophy and celiac disease.[19] It is also important to note that diabetics with a negative test results might become autoantibody positive in the future.[20-23] In diabetics type II, celiac is not more prevalent than common people. Timely recognition and treatment of celiac disease in diabetic patients can help to control and manage their needs for proper insulin intake and maintaining their HbA1c. For children with diabetes type I, it can also help to monitor their growth conditions. Early recognition of celiac disease can also affect diabetic complications including hypoglycemia, neuropathy, diarrhea, and controlling celiac is risky as well as irreversible complications including FTT (failure to thrive), osteomalacia, and anemia.[10,24-27] Furthermore, the occurrence of autoimmune diseases will increase when celiac and diabetes type I coexist as compared with diabetes by itself. Lack of early screening and diagnosis of celiac disease among diabetics may cause an irreversible intestinal malignancy. Therefore, timely diagnosis and treatment of celiac disease among diabetics is extremely important for achievement of favorable treatment outcome.[25]

Based on the aforementioned information and also paucity in this type of research in

Iran, the specific aims of this study are: 1) to determine the prevalence of celiac disease in diabetic patients type I referred to Kermanshah's diabetic research center and; 2) to compare the prevalence of symptoms and complications of celiac including anemia, mucocutaneous and neurologic presentations, GI symptoms, milk intolerance, uncontrolled diabetes, arthragia and low back pain and edema in diabetic patients with and without celiac disease.

Methods

This was an observational study including 241 type I diabetic patients both male and female, age 18 and over, who needed insulin intake. Patients were recruited and consented from diabetic patients attending the Diabetic Research Center in Kermanshah, a province in the western region of Iran. Upon obtaining consent, a study staff obtained complete medical history from each participating patient and performed a thorough medical examination including collecting information regarding family history of celiac and/or the patient's positive history of celiac, as well as consideration for the presence of any doubtful clinical findings. Patients' medical charts were also reviewed for examining their current prescribed regimens for diabetes treatment and management.

The selected sample was screened for celiac disease by drawing 5 cc blood for complete blood count (CBC), and anti-endomysial antibody test (AEA) IgA, which has been implicated in the pathogenesis of this disorder, was considered. Patients then were classified based on immunofluorescent method for the presence of AEA (IgA). Those with AEA positive underwent biopsy taking tissue from the second part of duodenum to confirm celiac disease. The biopsy tissues were evaluated by a pathologist and were classified based on Marsh classification. All patients had been previously checked for IgA level, and none had IgA deficiency.

Data Analysis

All the collected data were analyzed using SPSS statistical package version 14. Univariate analyses were used to report the prevalence and distribution of study variables in the sample. Chi-square and Fisher Exact test, when suitable, with $p < 0.05$ and OR with 95% CI was used to compare the differences between the study groups (i.e., diabetics + celiac with the diabetes only group) in respect to the following parameters: anemia, mucocutaneous and neurologic presentations, GI symptoms, milk intolerance, uncontrolled diabetes, arthralgia and low back pain, edema, and oral aphthous lesions.

Results

There were 241 diabetics patients in the study sample including 111 male (46.1%) and 130 female (53.9%). Twenty one patients tested positive for AEA and all received biopsy from the second part of duodenum. Pathological lesions were detected for celiac disease in twenty patients. Overall, Marsh (M) I lesions were seen in two patients (10%), M II in four patients (20%), M III in seven patients (35%), and M IV in seven patients (35%). The prevalence of celiac disease in diabetics patients (n = 241) based on AEA test (n = 21) was 8.7%, and it was 8.3% in diabetic patients who received biopsy (n = 20).

Patients with both type I diabetes and positive biopsy for celiac disease (n = 20) were compared with the type I diabetic patients with no celiac disease (control group = 221) according to the prevalence of symptoms and complications implicated in both diabetic and celiac diseases (Table 1). Out of the 20 patients with the diabetes and celiac disease, 12 were female (60%) and 8 were male (40%). In the non-celiac group, the gender- based prevalence was 53.4% among female, and 46.6% among males and the difference between the two groups was not statistically significant. AEA test correctly identified 97% of diabetic patients with celiac disease who were also identified by the biopsy ($p < 0.05$).

The prevalence of following parameters where higher in the diabetics plus celiac disease group than in the diabetics only group:

Table 1. Gender, symptoms and complication, by disease status (n = 241)

Variable	Diabetics + celiac group n = 20 (8.3%)	Diabetic only group n = 221 (91.7%)	P value	OR (95% CI)
Gender: • Female • Male	 12 (60.0%) 8 (40.0%)	 118 (53.4%) 103 (46.6%)	0.57	0.52-3.24
Anemia	8 (40.0%)	71 (32.1%)	0.47	0.56-3.51
Mucocutaneous lesions and cutaneous hemorrhage	3 (15.0%)	16 (7.3%)	0.21	0.64-8.04
Neurologic symptoms	5 (25.0%)	60 (27.0%)	0.89	0.32-2.48
Milk intolerance	2 (10.0%)	21 (9.5%)	0.94	0.25-4.41
Arthralgia and low back pain	6 (30.0%)	84 (38.0%)	0.63	0.69-1.83
Edema	3 (15.0%)	35 (16.0%)	0.92	0.28-3.17
Repeated oral aphthous lesions	5 (25.0%)	26 (11.8%)	0.15	0.87-7.21
Dirrhea & steatorrhea	4 (20.0%)	29 (13.0%)	0.49	0.54-5.07
Abdominal distention	6 (30.0%)	75 (34.0%)	0.80	0.31-2.19
Recurrent abdominal pain	0 (0.0%)	49 (22.2%)	0.41	0.56-4.00
Weight loss	8 (40.0%)	32 (14.5%)	< 0.003*	1.53-10.1
Dermatitis herpetiform	1 (5.0%)	10 (4.5%)	1.00	0.73-7.29
Follicular keratosis	0 (0.0%)	7 (3.2%)	1.00	0.00-6.13
Alopecia	2 (10.0%)	5 (2.3%)	0.10	1.00-23.3
Dental hypoplasia	0 (0.0%)	4 (1.8%)	1.00	0.00-10.9

* Significant p value

anemia (40% vs. 32.1%), mucocutaneous presentations (15% vs. 7.3%), repeated oral aphthous lesions (25% vs. 11.8%), diarrhea and steatorrhea (20% vs. 13%), weight loss (40% vs. 14.5%), and alopecia (10% vs. 2.3%). However, the differences between the two groups in respect to these parameters were not statistically significant, except for the weight loss, where celiac group were 4 times more likely to lose weight [χ^2 = 8.62 (df = 1), OR = 4.3; 1.53, CI; 1.53-10.1; p ≤ 0.003].

The prevalence of milk intolerance (10% vs. 9.5%), and dermatitis herpetiform (5% vs. 4.5%) between the two groups (diabetics + celiac vs. diabetics only) were nearly the same and not statistically different. However, in reference to several parameters, there was either no recurrent or lower prevalence in the diabetics + celiac group vs. control group, although none were statistically different. These parameters include neurologic symptoms (25% vs. 27%), arthragia and low back pain (30% vs. 38%), edema (15% vs. 16%), and abdominal distention (30% vs. 34%). Moreover, dental hypoplasia, alopecia, and follicular keratosis were not found in celiac patients but were detected in 1.8%, 2.3%, and 32% of the non–celiac diabetic patients, respectively. We also did not detect any positive family history in celiac patients.

Discussion

In this study, the prevalence of celiac disease in patients with type I diabetes was 8.3%. The prevalence of celiac disease in healthy blood donors is reported as 0.6%.[28] It means that the prevalence of celiac in our diabetic patients was 14 times more frequent than what is detected in the normal population. In a similar study conducted among 250 diabetic patients who were recruited from a diabetes clinic in Iran during early 2000, the prevalence of celiac was reported 3.4%.[29]

In a meta analysis of 15712 patients from 1984 to 2001, the prevalence of celiac disease, using auto-antibody test, was reported be-

tween 0.6% to 16.4%.[8] In similar studies, the prevalence of 4.6% in the United States, 7.7% in Canada, and 6.4% in Spain have been reported.[28] In the current study, out of the 20 diabetic patients with celiac, 35% were in stage III and another 35% in stage IV, while 20% of these patients were in stage II and 10% in stage I, according to Marsh pathologic classification. This means that 70% of these patients were already in advanced stages and were missed early disease diagnosis due to the lack of clinical findings. Findings of other studies conducted in Iran Diabetic Center and Italy suggest that the longer the duration of diabetes in a patient, the higher is the risk of being diagnosed with higher stage of celiac disease.[29] In the current study, the prevalence of uncontrolled diabetes was 85% in the celiac patients and 66.5% in non-celiac patients. The difference between the two groups was not statistically significant ($p = 0.09$). However, we believe this might be due to low sample power. Further studies with larger samples are needed to substantiate the results of the current study.

Weight loss was significantly more prevalent among the celiac patients in our study ; patients in the diabetes + celiac group were over four times more likely to show weight loss. Similar finding has been reported in previous studies.[27-30] Other parameters such as anemia, mucocutaneous lesions and cutaneous hemorrhage, milk intolerance, repeated oral aphthous lesions, diarrhea and steatorrhea, alopecia, and dermatitis herpetiform were higher in celiac patients than the control group, but were not high enough to be statistically significant.

Conclusions

Out of the 241 diabetic patients in the study, 21 tested positive for celiac disease based on AEA test (8.7%) and 20 (8.3%) tested positive based on biopsy of the second part of duodenum. This finding points to the potential capability of AEA as a screening test for celiac among diabetics, which has also been suggested previously.[25] Also, the high prevalence of celiac among diabetic patients in compare to normal population (8.3% vs. 0.6) and higher presentation of the diabetic patients in the more advanced stages of celiac disease (70% in the stages III and IV) suggests necessity of some suitable strategies for improvement in screening identification, and treatment of celiac among all type I diabetic patients, especially in cases with uncontrolled diabetes or weight loss. It is also recommended to closely monitor insulin needs and blood glucose control during the early phase of instituting a gluten-free diet.[15]

Conflict of Interest

Authors have no conflict of interests.

Authors' Contributions

HB contributed in the development of research protocol, implementation of the research, and draft of the manuscript. HM supervised acquisition and scientific integrity of data collection and revision of the manuscript. AK contributed in the interpretation of data and revising the manuscript. AH participated in the design of the study and interpretation of data. AA contributed in the critical review, intellectual content, interpretation of data, and revision of the manuscript. SBH was involved in critical review, intellectual content, and revisions of the manuscript. All authors have read and approved the content of the manuscript.

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