

Prevalence of Celiac Disease in type 1 Diabetes Mellitus in children and adolescents attending Children Welfare Teaching Hospital

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Summary:

Background: The association of celiac disease and type 1 diabetes mellitus is known worldwide due to shared auto immunological background, since celiac disease could present in diabetic patients with non specific symptoms or asymptotically, periodic serological screening is necessary for early diagnosis.

Objectives: To estimate the prevalence of celiac disease in children with type 1 diabetes.

Patients and methods: A total of 152 children with type 1 diabetes attending the Children Welfare Teaching Hospital; 67 boys, 85 girls with mean age of 10.3 year $\pm$ 3.7 and mean duration of diabetes 3.5 years $\pm$ 2.5, from May 2010 -May 2011 were screened for celiac disease using immunoglobulin A and G tissue transglutaminase (tTG) antibodies, immunoglobulin A endomysium antibody (EmA), and antiglutamic acid decarboxylase (Anti GAD) antibodies estimation.

Results: Anti tissue transglutaminase antibody was positive in 25 patients, more in girls (68%), duodenal biopsy was done for 15 patients, 13 had histological changes of celiac disease, making the prevalence of celiac disease 8.6%. The classical presentation of the disease was lacking in most patients, but they presented with short stature which was below the third percentile in 79% of patient with celiac disease. In most cases Celiac disease was diagnosed within the first year of the diagnosis of diabetes.

Conclusion: Annual autoantibody screening is recommended, for early diagnosis and management of patients with diabetes type 1.

Keywords: diabetes mellitus, celiac disease, anti tissue transglutaminase orogastrroduodenal biopsy

Introduction:

Celiac disease (CD), a common cause of chronic malabsorption in children is characterised by mucosal damage of the small intestine due to hypersensitivity to gluten containing food (1, 2). Clinically, the disease ranges from silent asymptomatic to active full blown picture (2), it has been reported that celiac disease is more common among patients with type 1 diabetes mellitus (DM) than among the general population (3, 4). The gold standard for the diagnosis of (CD) is duodenal biopsy (1,5), however screening for celiac disease has been recommended for specific risk factors (4,5); the anti-endomysium IgA antibody and anti-tissue transglutaminase IgA antibody (anti tTG) tests are highly sensitive and specific in identifying individuals with celiac disease. The anti-endomysium IgA antibody test is an immunofluorescent technique and is relatively expensive; interpretation is operator dependent and

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Prone to errors so that it has largely been replaced by anti-tissue transglutaminase IgA antibody tests, which are simpler to perform and have similar sensitivity and specificity. Anti-gliadin IgA and IgG and anti-reticulin IgA antibody tests are no longer recommended tests due to lack of specificity. The anti-endomysium IgA and anti-tissue transglutaminase IgA antibody test can be falsely negative with IgA deficiency, which is associated with an increased incidence of celiac disease (4, 5)

The prevalence of celiac disease in children with type 1 diabetes mellitus ranges between 1.3 to 12% worldwide and may contain high population of clinically asymptomatic and atypical cases (4, 6, 7). The association between type 1 diabetes mellitus and celiac disease was suggested to be due to sharing by seven chromosome regions between the two diseases and having the same mechanism of autoimmunity related tissue damage and dietary antigen intolerance (8, 9). The terms latent and silent celiac disease are used to refer to patients who have inherited the genes that predispose them to celiac disease but have not yet developed the symptoms or signs of celiac disease. Latent celiac disease refers

specifically to patients who have abnormal antibody blood tests for celiac disease but who have normal small intestines and no signs or symptoms of celiac disease (10). Silent celiac disease refers to patients who have abnormal antibody blood tests for celiac disease as well as histopathological abnormality in the small intestine but have no symptoms or signs of celiac disease (10). An anti-glutamic acid decarboxylase (Anti GAD) auto antibody is recognized as one of the major serological markers for type 1 diabetes and has been reported to be higher in type 1 diabetes patients (11). Positivity varies based on age, duration of diabetes and ethnicity (12). This study was undertaken to estimate the prevalence of celiac disease among patients with type one DM attending the children welfare teaching hospital in Baghdad and to study some demographic characteristics of diabetic children with and without celiac disease.

Patients and methods:

A total of 152 patients, 67 males and 85 females with type 1 diabetes mellitus attending the department of diabetes and endocrinology in Children Welfare Teaching Hospital were enrolled in this study over a period of one year (May 2010 - May 2011). Diagnosis of type 1 DM was made according to WHO criteria (13). Full history and complete physical examination were performed for all patients. Patients' records were reviewed for registering information including age of onset of DM, duration of the disease, date of presentation of gastrointestinal symptoms suggestive of celiac disease like diarrhoea, abdominal distension, loss of weight or failure to gain weight, anorexia, constipation and stunted growth. Anthropometric parameters were measured for all patients including height and weight and plotted on growth charts. Laboratory investigations, specific for celiac disease, like anti-tissue transglutaminase (anti tTG) IgG & IgA class, and anti-endomysial (EmA) antibodies, anti-glutamic acid decarboxylase (Anti GAD) antibodies by Elisa. Total IgA level and hemoglobin Alc (HbA1c) were not estimated for all patients because of lack of the availability of the material. Duodenal biopsy was done for 15 patients who had given the consent out of 25 patients with seropositive anti-tissue transglutaminase antibodies in order to document the characteristic morphologic features according to Marsh staging criteria (14). Marsh stage 0: Normal mucosa; Marsh stage 1: Increase number of intraepithelial lymphocytes, usually exceeding 40% Entrocytes. Marsh stage 2: Proliferation of the crypts of Lieberkuhn. ; Marsh stage 3: 3a partial villous atrophy. 3b subtotal

villous atrophy 3c Total villous atrophy; Marsh stage 4: hypoplasia of small bowel architecture. The guidelines followed for the diagnosis of CD in this study was according to the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) criteria (15).

Statistical analysis:

Data was gathered; organized, tabulated using Microsoft Office Word 2003, and percentages and tables were done by Microsoft Office Excel 2003. Discrete variables presented as numbers and percentages and continuous variables presented as mean $\pm$ SD (standard deviation). Chi square test for independence used to test the significance of association between discrete variables. Student t test for two independent samples used to test the significance in observed difference in mean of continuous variables. Findings with P value less than 0.05 considered significant.

Results:

A total of 152 patients with type I Diabetes Mellitus were included in the study, 67(44.1%) males and 85(55.9%) females. The age ranges from (1-18) years with a mean of 10.3 years $\pm$ 3.6 SD, and mean duration of diabetes 3.5 $\pm$ 2.5, with no statistical difference between boys and girls (Table (1)). anti tissue transglutaminase antibody test Results showed that only 25 patients (32% boys & 68% girls) tested positive compared to 127 patients with negative results(46.5% boys & 53.5% girls), yet the association were statistically not significant. ($\chi^2 = 1.8$, df=1, p value > 0.05) (Table(1)). Of the Fifteen diabetic patients with positive celiac screen test who underwent duodenal biopsy after taking their consents, 13 of them showed positive histopathological changes of celiac disease (5 boys (38.5%) and 8 girls (61.5%)), all of them were of Marsh stage 3 (silent CD), and two were negative (latent CD). The prevalence of biopsy confirmed CD was 8.6%. Table (2) showed the distribution of study group by age and duration of diabetes both in patient with and without celiac disease. It was found that both, patients with and without celiac disease, were almost at the same age. Table (3) showed the distribution of patients by duration of DM at time of CD diagnosis, it was found that celiac disease presented shortly after the diagnosis of diabetes in 46.1% of cases. On studying the anthropometric measurement, it seemed that the height was above the 3rd percentile in most of those without Celiac Disease (97%), whereas most of those with Celiac Disease were far below the 3rd percentile (79.9%), and the differences were statistically significant (χ^2

= 11.5, df =1, p value < 0.05).(Table(4)). Most of patients with CD were asymptomatic, only two patients present with anemia and abdominal distension. Regarding anti GAD test, there was no

statistically significant association in patients with CD and non celiac ones as shown in (Table (5)).

Table (1) Distribution of the Study Group by Age, Gender, Duration of DM (in years) and Celiac Screen Antibody test Results

Variables		Males		Females		Total	
Patients studied	No. %	67	44.1	85	55.9	152	100
Age (in Years)	Range Mean $\pm$ Sd*	1-16	9.9 $\pm$ 3.8	3.5-18	10.6 $\pm$ 3.5	1 – 18	10.3 $\pm$ 3.6
Duration of DM (in year)**		3.6 $\pm$ 2.7		3.3 $\pm$ 2.4		3.5 $\pm$ 2.5	
Celiac Screen Antibody***							
Positive		8 (32%)		17 (68%)		25 (16.5%)	
Negative		59 (46.5%)		68 (53.5%)		127 (83.5%)	

* Difference is statistically not significant (T test, df = 150, p value > 0.05)

** Difference is statistically not significant (T test, df = 150, p value > 0.05)

*** The association is statistically not significant (χ^2 = 1.8, df =1, p value > 0.05)

Table (2) Distribution of the Study Group by Age, Duration of DM (in years) and Presence of CD

Variables	DM with CD (+ve OGD) (13)		DM without CD (139)		Total (152)	
Age (in Years) Range Mean $\pm$ Sd*	8-15	10.3 $\pm$ 2.4	1-18	10.3 $\pm$ 3.8	1 – 18	10.3 $\pm$ 3.6
Duration of DM (in year)**	3.3 $\pm$ 2.4		3.5 $\pm$ 2.6		3.4 $\pm$ 2.5	

* Difference is statistically not significant (T test, df = 150, p value > 0.05)

** Difference is statistically not significant (T test, df = 150, p value > 0.05)

Table (3) Distribution of Patients with CD by Duration (in years) of DM at the time of CD diagnosis

Study Groups	No.	%
< 1 year	6	46.1
1 – 5 years	4	30.8
> 5 years	3	23.1
Total	13	100

Table (4) Distribution of the Study Group by Height

Height	DM without CD		DM with CD	
	No.	%	No.	%
Below 3rd percentile	42	30.2	10	79.9
Above 3rd percentile	97	69.8	3	23.1
Total	139	100	13	100

* The association is statistically significant (χ^2 = 11.5, df = 1, p value <0. 0.05)

Table (5) Distribution of the Study Group according to Anti GAD test Results*

Anti GAD Test	DM without CD		DM with CD	
	No.	%	No.	%
+ ve	32	23	6	46.2
- ve	107	77	7	53.8
Total	139	100	13	100

* The association is statistically not significant (χ^2 = 3.4, df =1, p value > 0.05)

Discussion

The current study showed a prevalence of CD in type 1 DM to be 8.6 % (biopsy confirmed), this result was lower than what was found by El-Saadany et al. (16) from Egypt (11.2%), higher than what was found in Iran (6.2%)(17), and nearly the same

prevalence was found by many other researchers from Greece (8.6%)(18), Kerala-India (8%)(19), Canada(7.7%), and Cerutti study (6.8%)(20). Very low prevalence rates were found in Germany (1.4%)(21), US (22) and Scotland (5.8%)(23). There was no significant difference in anti- tTG IgA Ab test results between boys and girls, although out of 25 patients, who tested positive, girls were higher (68%) than boys (32%) same conclusion was reached by the Kostas et al. (18) and Cerutti et al. study (20) while in the Egyptian study the girls: boys ratio was nearly equal (24). The age of the onset of DM was nearly the same in both groups (with or without CD), and most of those who suffered from celiac disease developed the disease after short period of having DM, same results were reached by other worker as in the Kostas et al. study (18) and disagreed with that of Jacob & Kumar study (19) and Cerutti study (20) in which diabetic children with celiac disease developed DM at a significantly younger age than those without celiac. Furthermore other researchers found that initial negative serology does not rule out CD as confirmed by patients having positive OGD with normal anti-tTG Gholam-HossenFall et al(17) in the current study two patients with positive anti-tTG, showed normal OGD this might be explained by the possibility of having silent or latent CD. Patients with positive serology need close follow up to elicit early diagnosis of CD.Height was significantly above the 3rd percentile in most diabetics without CD compared to those with CD where most of them were below 3rd

percentile, same result was obtained by the El-Saadany et al(16), Indicating the importance of tracing patients with type1DM for the possibility of having CD because nowadays the classical presentation of CD like abdominal distension flatulence, anorexia and steatorrhea or constipation is not considered a clear evident any more making periodic screening for CD especially within the first five years after diagnosing type1DM in these children essential(25), other studies noticed a decline in linear growth in patients with type1 DM and CD with a frequency ranging from 30% to 96%(26, 27), this emphasized that all diabetic children specially having stunted growth should be screened for CD, although there are other causes for stunted growth (2, 5) The anti GAD positivity, there was no statistically significant association among diabetic patients with celiac and without celiac disease, same conclusion was reached by Kostas et al (18), this might reflects the possibility of loss of antigenic stimulation due to cell depletion by time. Despite attempts to make screening convenient and free, many diabetic patients were apprehensive about CD testing. For patients and families, diabetes is a challenging condition that requires daily effort to balance meals, activity, and insulin administration to maintain adequate metabolic control. The effect of an additional chronic disease, such as CD, may substantially affect the quality of life in diabetic patients. Unfortunately, we are not aware of studies that address the psychosocial effect of CD screening in asymptomatic diabetic patients (28, 29) Although the gold standard for diagnosis of CD is the intestinal biopsy, the fact that the biopsy is an invasive procedure is an obstacle to its acceptance as a diagnostic method for investigation(1), furthermore, the wide spectrum of CD and its non specific clinical presentations makes the identification of patients needing investigation difficult and problematic ,many studies have been done with aim of identifying serological screening methods with proper sensitivity and specificity that could in the future be a substitute of biopsy for the diagnosis of CD (22, 30, 31).

Conclusions:

The prevalence of CD among children with type 1 DM was 8.6%, diabetics with CD tend to have stunted growth compared to those without the disease and CD usually appear relatively after short period from diagnosis of DM in children. Because celiac disease can present either asymptotically or with non specific symptoms in type1 diabetes mellitus patients, periodic screening for celiac disease should be part of routine investigation.

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