CELIAC DISEASE IN SUBJECTS WITH TYPE 1 DIABETES MELLITUS AND ITS EFFECT ON GLYCEMIC CONTROL

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ABSTRACT

Objectives: To observe celiac disease (CD) frequency in patients with diabetes mellitus 1 and its effect on glycemic control.

Methods: Type 1 diabetic patients presenting in the Sughra Diabetic clinic in Benazir Bhutto Hospital from 22 August 2011 till 22 February 2012 were included in this study. Medical history, including age of the patient at diagnosis of diabetes, duration of disease and daily insulin requirements was taken. Subjects with positive tTGAb levels had biopsy of 2nd part of the duodenum to confirm CD according to Marsh criteria on histopathological examination.

Results: The study included 125 patients with type 1 diabetes mellitus. The mean age was 30.08±8.9 years. 42 (33.6%) were males and 83 (66.4%) females. 5 (4%) of type 1 diabetics had celiac disease. All 5 had both a positive anti-tissue transglutaminase antibody (>24 U/ml) and all 5 also had histopathological changes confirming celiac disease. 4 had Marsh stage 3 (2 had stage 3b and 2 had stage 3c) and 1 had Marsh stage 4 changes on histopathology. All 5 CD-positive patients (100%) had poorly controlled diabetes whereas among CD-negative patients only 26 (2control well-controlled diabetes; this difference was p = 0.242. However, the mean HbA1c level in CD-positive patients was significantly higher than the HbA1c of CD-negative patients; p = 0.015. The mean daily insulin requirement of CD-positive patients was significantly lower than CD-negative patients; p = 0.000.

Conclusions: The frequency of celiac disease in type 1 diabetics increases as compared to general population. Because most diabetics are asymptomatic, it is better to screen all. Moreover, CD is associated with lesser daily insulin requirement and poorer diabetes control.

Keywords: Celiac Disease, Diabetes Mellitus, Type-I, Marsh Classification.

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INTRODUCTION

Coeliac disease (CD) is an autoimmune disorder causing harm to the mucosa of the small intestine due to gluten and related compounds present in cereals like wheat, barley, etc. An association between diabetes mellitus 1 and celiac disease has been recognized for more than 40 years. Most cases of CD in T1DM appear to be asymptomatic or silent and can be detected only by the

screening procedure.[1] There are 2 problems firstly the identification of CD in a large asymptomatic population and the second to halt complication. Due to high frequency of CD in diabetics and long term complications associated with CD, screening for coeliac autoantibodies in subjects with T1DM has become a widely accepted practice.[2] NICE guidelines May 2009, recommend screening in 'high risk' populations such as children and young people with type 1 diabetes by testing IgA tissue transglutaminase antibody and subsequent intestinal biopsy for histopathology.[3] In a study conducted in India in 2010, the prevalence rate of CD was found to be a much higher 11.1% amongst T1DM. Considering the results of this study and similar characteristics the of Indian and Pakistani populations, similar prevalence rates in the Pakistani population can be expected. On the literature search, it appears that the frequency of T1DM and CD has not been studied, in the Pakistani population, previously.

Previously known to be a disease of childhood but now we know that it can present between the ages of 10 to 40 years as an asymptomatic disease. Because children are on breast-feeding in their early days and later in life when they are exposed to gluten, the problems start.

Typical presentations include diarrhea with bulky, foul-smelling, floating stools, flatulence, restricted growth, weight loss, low Hb, neurologic disorders and osteopenia from deficiency of vitamin D and calcium.[4]

Now we know that many patients have very mid or no symptoms like weakness or lethargy.[5] patients without any specific symptom are detected during screening tests or perhaps during endoscopy for other complaints. It is critical to diagnose celiac disease in patients because of the following reasons: nutritional deficiencies, low-birth weight in children of affected mothers, risk of development of malignancy and presence of autoimmune disorders.

Celiac disease is a genetic disease occurs due to immune response to intestinal mucosa.[6, 7] So gluten sensitivity is not just the problem of European countries but it is also present in developing countries where wheat is major component of diet.[8] We know that due to immune mediated destruction of beta cells of pancreases diabetes I develop and now it has been shown with data that the more the contact of a celiac patient with gluten there are more chances of diabetes type I.[9] Both the diseases are correlated with genetic loci on short arm of chromosome six.[10] Because of this reason celiac disease ratio is high in Diabetes patients worlwide.[11] In past years it has been shown that ratio of celiac disease is increasing in diabetic children.[12] The objective of this study was to observe celiac disease frequency in patients with diabetes mellitus 1 and its effect on glycemic control.

METHODS

It was cross sectional study conducted in the outpatient clinic of Sughra Diabetes Clinic, Medical Unit 2, Benazir Bhutto Hospital, Rawalpindi. Study was carried out over 6 months from 22 August 2011 till 22 February 2012.A total of 125 patients with diagnosed type 1 diabetes of any duration were included in the study.

Sampling technique was consecutive non-probability sampling.

Inclusion criteria:

Diagnosed T1DM patients presenting in Diabetic clinic on OPD basis, both genders with age $\geq$ 13 years. (Both old and newly diagnosed patients).

Exclusion criteria:

- Type 2 diabetics
- Patients on gluten free diet
- Seriously ill patients
- Pregnancy

After taking consent from patients presenting in Sughra Diabetic clinic who fulfilled the above-mentioned criteria for diagnosis of T1DM were included in this study. Medical history, including age of the patient at diagnosis of diabetes, duration of disease and daily insulin requirements was taken. Lab investigations included capillary fasting glucose, HbA1c and IgA tTGAb levels. Subjects with positive tTGAb levels had biopsy of 2nd part of duodenum. Celiac disease was defined as having positive titers of Ig A anti tissue transglutaminase antibodies using ELISA technique and biopsy taken from the descending part duodenum by endoscopy showing histological findings compatible with Marsh criteria.

Table 1– MARSH Classification

MARSH stage	Histopathology
Stage 0 (Pre-infiltrative)	Normal Mucosa
Stage 1 (Infiltrative)	Increased intraepithelial lymphocytes, greater than 30 lymphocytes per 100 enterocytes.
Stage 2 (Hyperplastic)	Hyperplasia of crypts
Stage 3 (Destructive)	Variable degree of villous atrophy.
Stage 3a	Partial villous atrophy
Stage 3b	Subtotal villous atrophy
Stage 3a	Total villous atrophy
Stage 4 (Hypoplastic)	Villous atrophy and hypoplasia of crypts.

Diabetes mellitus type 1 was diagnosed as individuals with age < 25 years at diagnosis having fasting glucose

levels ≥126 mg/dL as per ADA diagnostic criteria. Glycemic control was assessed in terms of HbA1c levels. Normal HbA1c level was taken as ≤ 6.5%. A good control was the one in which HbA1c was ≤ 6.5%.

All data was entered on SPSS (Statistical package for social sciences) 17 version. Then Frequencies and % were observed for diarrhea, effect on HbA1c levels, CD in T1DM, and type of CD on histopathology.

RESULTS

Demographic characteristics:

The study included 125 patients with type 1 diabetes mellitus. The age ranged from 13 to 46 years with a mean age of 30.08±8.9 years. The median and mode ages were 30 and 35 years respectively. The study included 42 (33.6%) males and 83 (66.4%) females.

The daily insulin requirement ranged from 22 to 100 units with a mean of 60.2±17.8 units. The HbA1c ranged from 5 to 12.2% with a mean of 8.1±1.6%. 29 (23.2%) had diabetes duration < 1 year, 55 (44%) had diabetes duration 1-5 years, 37 (29.6%) had diabetes duration 10-20 years and 4 (3.2%) had diabetes duration > 20 years.

Celiac disease among type 1 diabetics:

Five (4%) of type 1 diabetics had celiac disease. All 5 had both a positive anti-tissue transglutaminase antibody (>24 U/ml) and all 5 also had histopathological changes confirming celiac disease like atrophy, crypt hyperplasia, and increased intraepithelial lymphocytes. 4 had Marsh stage 3 and 1 had Marsh stage 4 changes on histopathology.

Celiac disease prominent features were present only in one patient and only one patient had lactose intolerance.

The mean age of CD-positive patients was 36±9.6 years whereas that of CD-negative patients was 29.8±8.85 years; p = 0.131.

Among 5 CD-positive patients 2 (40%) were males and 3 (60%) were females whereas among CD-negative patients 40 (33.3%) were males and 80 (66.6%) were females; p = 0.757

All 5 CD-positive patients (100%) had poorly controlled diabetes whereas among CD-negative patients only 26 (21.6%) had well controlled diabetes; p = 0.242.

Mean HbA1c level of CD-positive was 9.8±1.17% whereas that of CD-negative patients was 8±1.6%; this was statistically significant; p = 0.015.

Mean daily insulin requirement for CD-positive patients found was 31.6±8.64 units whereas that of CD-negative patients was 61.4±17.1 units; this difference was statistically significant; p = 0.000.

Table 2– Comparison of diabetes control; celiac disease vs no celiac disease diabetics

Celiac disease	Diabetes control		P value
	Well controlled	Poorly controlled	
Yes	0	5	0.242
No	26	94	
Total	26	99	

Table 3– Comparison of daily insulin requirement; celiac disease vs no celiac disease diabetics

Celiac disease	N	Mean	Std. Deviation	Std. Error Mean	P value
Yes	5	31.6	8.64	3.86	0.00
No	120	61.4	17.10	1.56	

DISCUSSION

Celiac disease is a chronic immune-mediated disease-causing damage to small intestinal mucosa. An association has been recognized for more than 40 years between celiac disease and diabetes I. Despite of this association investigation for CD in diabetic is not happening routinely.[13]

We carried out a study to estimate the frequency of celiac disease in diabetes I and it effect on glycemic control. 125 type 1 diabetic patients presenting in the Sughra Diabetic clinic in Benazir Bhutto Hospital from 22 August 2011 till 22 February 2012 were included in this study. Subjects with positive tTGAb levels had biopsy of 2nd part of duodenum to confirm CD according to Marsh criteria on histopathological examination. The mean age was 30.08±8.9 years. 42 (33.6%) were males and 83 (66.4%) females. 5 (4%) of type 1 diabetics had celiac disease. All 5 had both a positive anti-tissue transglutaminase antibody (>24 U/ml) and all 5 also had histopathological changes confirming celiac disease. 4 had Marsh stage 3 (2 had stage 3b and 2 had stage 3c) and 1 had Marsh stage 4 changes on histopathology. No significant variation was found related to age or gender, distribution between CD- positive and CD-negative patients; p = 0.131 and p = 0.757 respectively. All 5 CD-positive patients (100%) had poorly controlled diabetes whereas among CD-negative patients only 26 (21.6%) had well controlled diabetes; p = 0.242. However, mean HbA1c level of CD-positive was significantly higher than HbA1c of CD-negative patients; p = 0.015. The mean daily insulin requirement of CD-positive patients was significantly lower than CD-negative patients; p = 0.000.

Frequency of celiac disease in diabetes I patients is high. In our study what we found was frequency of 4% of celiac in diabetes I which is compatible to the data.

In our study 4 out of 5 patients were asymptomatic or not aware of symptoms. When patients restrict gluten in their diet their health improves this is the reason why some patients have good health. About 1/ 3 patients have unexplained reason for failure to have good health.[14]

According to data frequency of CD in type 1 diabetes is from 1.4% to 5.1% in children and in adults it is from 3.5% to 6.0%.[15]Now the question is, is CD affects blood glucose control or not. In our study the mean HbA1c of celiac disease diabetics was significantly higher. The lower insulin requirement in CD-positive diabetics may be due to the lower weight because of malabsorption and because of tendency to lower blood sugar because of diarrhea.

Data has shown that celiac disease patients have hypoglycemic episodes and less insulin requirement prior to diagnosis.[16, 17]This may be because of malabsorption leading to hypoglycemia therefore early detection of celiac disease in diabetes is important. frequency of CD is just less than 1% in general population and most is clinically silent. Our work also shows higher frequency of celiac disease in diabetes but its effect on glycemic control is not clear however some studies do show better glycemic control.[18, 19 In] our study also celiac disease patients had less insulin requirement.

In a study conducted in Iran frequency of celiac disease in diabetes was 8.3% as compared to normal populatio 0.6%, 70% were having stages III and IV and weight loss was also 4 times more common in celiac patients.[20]

We used IgA tTGAb and positive histopathology for diagnosis of CD. Since all our patients had either subtotal or total villous atrophy therefore all had positive serology.[21]

Data on frequency of celiac disease among type 1 diabetics is lacking in our country however studies in general population show a prevalence of < 1%. According to a study carried out in CMH Lahore[22] and CMH Rawalpindi, showed a prevalence of coeliac disease to be 0.18%. Mean age found was 6.1 years and different clinical symptoms were diarrhea, anemia, reduced growth, abdominal distention, abdominal pain and vomiting.

CONCLUSION

Frequency of celiac disease was found high in diabetes I in comparison to general population. All diabetics should be seen for celiac disease as most celiac patients are asymptomatic. Moreover, CD is associated with lesser daily insulin requirement and poorer diabetes control.

ETHICAL APPROVAL

The study was approved by the Ethical Committee of Benazir Bhutto hospital, Rawalpindi.

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AUTHOR'S CONTRIBUTIONS

MN: Manuscript writing, Concept, Planning
HBS: Revision of the Manuscript
KDA, RA: Critical revision
MTS, SK: Manuscript writing