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ORIGINAL ARTICLE

Clinical profile and association of Celiac Disease in children with type-1 Diabetes Mellitus

Dilawar Khan Jokhio[1], Versha Rani Rai[1]✉, Shazia Mahar[1], Roshia Parveen[1], Uzma Salman[1], Mohsina Noor Ibrahim[1]

ABSTRACT

OBJECTIVE: To find out the clinical profile and association of Celiac Disease (CD) in children with established type-1 Diabetes Mellitus (T1DM) presenting in a tertiary care hospital of Karachi, Pakistan.

METHODS: This cross-sectional study was conducted from January-2019 to July-2019 at National Institute of Child Health, Karachi, Pakistan. A total of 126 T1DM patients of age 1-18 years were subjected to detailed history and clinical examination for CD except those in diabetic ketoacidosis and having pancreatic calcifications. Blood sample was drawn from the patients for Tissue Transglutaminase (tTg) Immunoglobulin A (IgA) and tTg Immunoglobulin G (IgG) levels and Anti-Deamidated Gliadin Peptide (anti-DGP) IgG was estimated using commercially available Enzyme Linked Immunosorbant Assay.

RESULTS: Twenty-nine (23.0%) patients were diagnosed as CD based on positive serology. The mean age of the patients was 9.31±4.40 years, 70 (55.6%) were male and 56 (44.4%) patients were female. Out of 126 T1DM patients, 29 (23.0%) were diagnosed with CD. Raised anti-DGP IgG levels were observed in 39 (30.95%) patients, raised anti-tTg-IgA levels in 35 (27.78%) and raised Anti-tTg IgG level in 36 (28.57%) cases. Other associated features included anemia (n=85; 67.46%), vomiting (n=50; 39.6%), abdominal distension (n=37; 29.3%), diarrhea (n=30; 23.81%) and abdominal pain (n=26; 20.6%).

CONCLUSION: CD is relatively common in children with T1DM, affecting both genders. Specific serological markers proved significant in CD identification. This study highlights associated features like anemia and gastrointestinal symptoms, emphasizing the need for careful consideration of CD in T1DM patients.

KEYWORDS: Celiac Disease (MeSH); Diabetes Mellitus (MeSH); Diabetes Mellitus, Type 1 (MeSH); Antibodies (MeSH); Anti Tissue Transglutaminase IgG (Non-MeSH); Anti Tissue Transglutaminase IgA (Non-MeSH); Anti-Deamidated Gliadin Peptide (Non-MeSH); Diarrhea (MeSH); Anemia (MeSH); Abdominal Pain (MeSH)

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1. Department of Pediatric Medicine, National Institute of Child Health, Karachi, Pakistan

Cell #: +92-333-3636460
Email✉: versharai.sg@gmail.com

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INTRODUCTION

Celiac disease is an immune-mediated enteropathy caused by permanent intolerance to gliadin & related proteins present in gluten part of diet in genetically susceptible individuals. Chronic diarrhea is the most common clinical manifestation of Celiac disease. The impact of season in Celiac disease being in spring is more common.[1,2]

People with Celiac disease are unable to consume gluten-containing meals because gluten trigger's autoimmune reaction in these patients, resulting in the loss of tiny intestinal villi & mal-absorption.[3]

About 10 to 15.0% of individual with Type-1 Diabetes Mellitus (T1DM) express the exact serological indicators of celiac Celiac disease, like autoantibodies to endomysium or Tissue Transglutaminase (tTg) & deaminated gliadin peptidases (DGP).[4] A complicate interaction of genetic, immunological, and environmental variables causes T1DM. Patients affect the illness prognosis, hence screening for related autoimmunity is advised.[5]

The frequency of pancreatic autoantibodies in India is lower than in other populations, which has been attributed to T1DM etiologic variability.[6] However, the frequency of celiac autoimmunity in T1DM appears to be comparable to the other studies.[7,8]

Celiac disease is a small bowel enteropathy caused by a permanent intolerance to gluten in genetically susceptible individuals. It may be difficult to recognize because of the variation in presentation and intensity of symptoms and signs and many cases may occur without symptoms. Despite similar population demographics, the frequency of Celiac Disease Anti-tTg Immunoglobulin A (IgA) and tTg Immunoglobulin G (IgG) in T1DM patients has been reported to be 8–22%.[9]

Many studies of Celiac disease frequency in T1DM patients in found in literature but most are in adult studies. Data is sparse of clinical manifestation and association of Celiac disease in T1DM children with the help of tTg-IgA, IgG, and Anti-Deamidated Gliadin

TABLE I: Clinical profile and treatment status of patients with type-1 Diabetes Mellitus

Variables		Frequency (n=126)	Percentage
Abdominal Distension	Yes	37	29.3
	No	89	70.6
Vomiting	Yes	50	39.6
	No	76	60.3
Treatment Status (patient on proper insulin therapy and regular follow up)	Yes	58	46.03
	No	68	53.97
Underweight	Yes	48	38.09
	No	78	61.91
Diarrhea	Yes	30	23.81
	No	96	76.19
Anemia	Yes	85	67.46
	No	41	32.54
Abdominal Pain	Yes	26	20.06
	No	100	79.37

TABLE II: Laboratory data of patients with Celiac Disease

Variables		Frequency (n=126)	Percentage
Raised Anti-Deamidated Gliadin Peptide (DGP) IgG level	No	87	69.05
	Yes	39	30.95
Raised Anti Tissue Transglutaminase (TTG) IgA level	No	91	72.22
	Yes	35	27.78
Raised Anti- TTG IgG level	No	90	71.43
	Yes	36	28.57
Celiac Disease (both TTG IgA and TTG anti DGP positive)	No	97	76.98
	Yes	29	23.02

Table III: Stratification of celiac disease patients regarding age and clinical features

Total (n=126)		Celiac Disease		P value
		Yes (n=29)	No (n=97)	
Age (years)	≤ 10	17 (58.6%)	40 (41.2%)	0.14
	> 10	12 (41.3%)	57 (58.7%)	
Underweight	Yes	18 (62%)	30 (30.9%)	0.004
	No	11 (37.9%)	67 (69.0%)	
Duration of Type-1 diabetes Mellitus (years)	≤ 10	16 (55.1%)	55 (56.7%)	0.98
	> 10	13 (44.8%)	42 (43.2%)	
Anemia	Yes	18 (62.0%)	67 (69.0%)	0.50
	No	11 (37.9%)	30 (30.9%)	
Diarrhea	Yes	15 (51.7%)	15 (15.4%)	0.003
	No	14 (48.2%)	82 (84.5%)	
Abdominal Pain	Yes	13 (44.8%)	13 (13.40%)	0.0001
	No	16 (55.1%)	84 (86.5%)	
Abdominal Distension	Yes	12 (41.3%)	25 (25.7%)	0.00
	No	17 (58.6%)	72 (74.2%)	
Vomiting	Yes	15 (51.7%)	35 (36.0%)	0.32
	No	14 (28.2%)	62 (63.9%)	

Peptide (anti-DGP) IgG in T1DM pediatric population worldwide generally and specifically.

As local data on Celiac disease in T1DM pediatric population is very limited, this study was planned to find out the clinical profile and association of Celiac disease in children with established T1DM presenting in a Tertiary Care hospital of Karachi, Pakistan.

METHODS

This cross-sectional study was conducted from 2nd January 2019 – 2nd July 2019 at National Institute of Child Health, Karachi, Pakistan after taking ethical approval from the institutional ethics committee. Sample size 126 was calculated with 95% confidence interval and 5% margin of error by taking expecting 11.1% T1DM of Celiac disease in children.

Patients of both genders with T1DM of age 1 to 18 years were included. Patients with diabetic ketoacidosis (a venous pH less than 7.3 or serum bi-carbonate concentration less than 15.0 mmol/L, serum glucose concentration greater 200mg/dL together with ketonemia & ketonuria confirmed through the blood and urine test, evidence of pancreatic calcifications (confirmed through the abdominal x-ray; hyper dense foci in front of T2 and L1 vertebral body) were excluded from the study.

Informed consent was taken from the parents. All patients were subjected to detailed history and clinical examination for T1DM and Celiac disease. Blood sample 10cc was drawn from the patients TTG IgA levels. TTG IgG and Anti-DGPs IgG were estimated using available commercially ELISA kits from Diametral Diagnostics.

Value of TG IgA was considered raised if > 12U/ml, value of TTG IgG was considered raised if >12 U/ml and anti DGP was considered raised if >12 U/ml. At least two serological tests were included to label patient celiac positive, hence avoiding duodenal biopsy.

The data was entered in SPSS software version 10. Age, Weight, BMI, duration of T1DM were presented as mean and

SD. Gender, treatment status, underweight, diarrhea, abdominal pain, residential status was presented as frequency and percentages. Data was stratified age, weight, duration of T1DM, gender, underweight, diarrhea, abdominal pain, residential status to see the effect modifications. Post stratification chi-square test was applied. P-values less than 0.05 were considered significant.

RESULTS

A total of 126 patients enrolled. The mean age, weight & duration of Type-1 DM was 9.51±4.08, 18.76± 7.87 and 2.0±0.8. There were 70 (55.6%) male and 56 (44.4%) female. Seventy-seven (66.11%) patients were from urban areas and 49 (38.89%) were from rural areas.

Abdominal distension was present in 37 (29.3%) and vomiting in 50 (39.6%) patients. Treatment status in the form of proper insulin therapy and regular follow up was present in 58 (46.03%) and not present in 68 (53.97%). A total of 48 (38.09%) patients were found underweight and 78 (61.91%) were of normal weight. Anemia was present in 85 (67.46%) patients. Diarrhea was present in 30 (23.81%), and abdominal pain was present in 26 (20.6%) patients. A total of 48 (38.09%) patients were found underweight and 78 (61.91%) were of normal weight. Anemia was present in 85 (67.46%) patients. Diarrhea was present in 30 (23.81%), and abdominal pain was present in 26 (20.6%) patients (Table I).

Out of 126 diabetic patients, only 29 (23.0%) were diagnosed with Celiac Disease. Raised Anti-DGPs (IgG) level was rise in 39 (30.95%) patients, Raised Anti-TTG IgA level 35 (27.78%) and Raised Anti- TTG IgG level in 36 (28.57%) (Table II).

Celiac Diseases were present in 17 (58.6%) children from < 10years and 12 (41.3%) children were greater than 10 years of age. Anemia was observed in 18(62.0%) children, diarrhea & vomiting in 15 (51.7%) children whereas abdominal pain was present in 13 (44.8%) patients as shown in Table III. There was significant association with underweight, diarrhea and abdominal pain with Celiac Disease (P<0.050)

DISCUSSION

In this study, prevalence of Celiac disease diagnosed on serological basis in children with Type-1 Diabetes was 23%. Serologic screening for Celiac disease is not recommended in routine patients with Type-1 DM, as the clinical signs and symptoms (if any) specific to the Celiac disease are mostly mild.[10] Moreover, the association between the time of onset of these two disease states and the timing of the emergence of Celiac disease after establishment of DM diagnosis is not known.[11,12] In 2020 study, the prevalence of biopsy-proven Celiac disease in children with Type-1 DM was 4.4%, which was approximately 9 times higher than the prevalence of Celiac disease in the general population.[13-15]

In our study performed using anti-TTG IgA antibodies, we detected serologic positivity in 16 (7.3%) cases. A study conducted in Turkey, TTG IgA positivity was noted in 13.5% of patients with Type-1 diabetes. One study detected a higher incidence (16.4%) of serologic antibody positivity in patients with Type-1 DM while studies performed using Tissue Transglutaminase antibodies demonstrated serologic positivity ranging from 5% to 10%.[16] In another study, detected serologic positivity in 21 (21/234; 8.9%), Celiac disease in 10 (10/234; 2.4%), and latent Celiac disease in nine (9/234; 3.9%) of cases with Type-1 DM, respectively.[17] In 2015 study, the average incidence of Celiac disease was 11.2% based on TTG IgA examines & the outcomes of bowel biopsies. Celiac disease was seen in5% of participants with Type-1 diabetes.[3]

Out of 29 Celiac Disease, anemia was observed in 18 (62.0%) children, diarrhea & vomiting in 15 (51.7%) children whereas abdominal pain was present in 13 (44.8%) patients. Raised Anti-DGPs (IgG) level in 39 (30.95%) patients, raised Anti Tissue Transglutaminase IgA level in 35 (27.78%) and raised Anti Tissue Transglutaminase IgG level in 36 (28.57%). As compared to study done in Egypt, 11 (44%) patients among 25 patients with refractory iron deficiency anemia, 23 patients (34.3%) among 67 patients with non-endocrinal short stature, and 6 patients (3%) among 200 patients with Type-1 Diabetes Mellitus were diagnosed by jejunal biopsy as having coeliac disease.[18]

Many studies have shown strong association of Celiac Disease with Type-1 diabetes on basis of positive serology.[19] Local study conducted on small number of patients (68 type-1 Diabetic children) out of which 8.8% were celiac positive on basis of raised Tissue Transglutaminase IgA levels.[20] In another local study Clinical spectrum of Celiac Disease and follow-up after gluten free diet was studied in 61 patients with the help of only single serological test. Tissue Transglutaminase IgA and interestingly intestinal symptoms diarrhea was most common manifestation, and it was recommended in low-income countries where biopsy is not frequently possible serology alone can be very helpful.[21]

CONCLUSION

This study provides insights into the prevalence and clinical characteristics of Celiac Disease among T1DM patients. Around 23.0% of T1DM patients had Celiac Disease based on serology, affecting both genders. Specific serological markers including including anti-DGP IgG, Anti-tTg IgA, and Anti-tTg IgG, proved significant in Celiac Disease identification. The study highlights associated features such as anemia and gastrointestinal symptoms like vomiting, abdominal distension, diarrhea, and abdominal pain, emphasizing the need for careful consideration of Celiac Disease in T1DM patients. These insights contribute to informed diagnosis and management, improving patient outcomes.

This research contributes to the growing body of knowledge regarding the intersection of CD and T1DM, underscoring the need for heightened clinical suspicion and appropriate serological screening in patients with T1DM. Such insights are essential for

informed decision-making in the diagnosis and management of these intertwined conditions, ultimately leading to improved patient outcomes and quality of life.

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

DKH: Concept and study design, analysis and interpretation of data, drafting the manuscript, approval of the final version to be published

VRR & SM: Acquisition of data, drafting the manuscript, critical review, approval of the final version to be published.

RP: Acquisition, analysis and interpretation of data, drafting the manuscript, approval of the final version to be published.

US: Analysis and interpretation of data, drafting the manuscript, approval of the final version to be published.

MNI: Concept and study design, critical review, approval of the final version to be published

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST

Authors declared no conflict of interest

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The data that support the findings of this study are available from the corresponding author upon reasonable request

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KMUJ web address: www.kmuj.kmu.edu.pk
Email address: kmuj@kmu.edu.pk