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Seroprevalence of Celiac Disease Among Children with Diabetes Mellitus Type 1 in Fayoum Governorate

Samar I. R. Abd Elhalim[1*], Manal A. I. El Hawary[1], Remon M. Y. Awad[1]

[1]Pediatics Department, Faculty of Medicine, Fayoum University, Fayoum, 63514 Egypt.

*Correspondence: Samar I. R. Abd Elhalim, si1134@fayoum.edu.eg, Tel: (002) 01003064985.

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Abstract:

Introduction: Patients with diabetes are susceptible to systemic symptoms associated with celiac disease (CD), in addition to gastrointestinal symptoms. It is necessary to regularly evaluate celiac indicators in children with type 1 diabetes mellitus (T1DM) to improve diagnosis and treatment.

Aim of the Study: To assess the markers of celiac prevalence among children with T1DM in Fayoum governorate.

Subjects and Methods: 1151 adolescents and children from Children's Hospital Fayoum University's endocrinology clinics as well as a few patients from Insurance Hospital participated in this study. According to celiac antibody screening, all patients were further categorized into two groups: 1087 T1DM patients in Group I had negative CD markers. 64 T1DM cases in Group II have positive coeliac markers.

Results: 1151 patients with T1DM were included. All patients were 18 years or younger of which 590 patients (51.3%) were males. The mean age of subjects was 15.5 years with a median duration of diabetes 6.5 years. All patients were screened for CD. 64 patients with positive celiac markers out of them 14 patients with spontaneous normalization of anti-tTG IgA, 47 patients with persistent seropositive markers and 3 patients were lost to follow-up. 13 children (20%) with positive CD markers were referred for small bowel biopsy.

Conclusion: This study suggests that monitoring of CD markers is useful for CD diagnosis in children with T1DM even if children are asymptomatic.

Keywords: Type 1 Diabetes Mellitus; Celiac Disease; Gluten-Free Diet; Tissue-Transglutaminase Antibodies.

1. Introduction

Celiac disease (CD) is an immune-mediated disease that gluten consumption causes in genetically predisposed people. The disease can manifest at any age as a

range of extra-intestinal and gastrointestinal symptoms [1].

Type 1 diabetes mellitus (T1DM), a significant subtype of diabetes, is mainly found in children and adolescents and triggered by an autoimmune response [2].

The range of CD prevalence in T1DM is 0.8% to 16.4%, which is substantially greater than the 0.5–1% prevalence in the general population [3].

Two primary variables determine the cause of CD: genetic and environmental. With 40% of the genetic diversity in CD, the best well-studied genetic contribution is the human leukocyte antigen system (HLA) [4].

The signs and symptoms of CD are less distinct in the pediatric population. Individuals with CD and T1DM may not have any symptoms at all or may have minor ones [5].

The criteria set by the European Society for Pediatrics Gastroenterology, Hepatology, and Nutrition are used to diagnose CD. In cases where the diagnosis is confirmed, an intestinal biopsy is performed and tissue transglutaminase (tTG) antibodies are measured [3].

2. Subjects & Methods

2.1. Subjects and Study Design

This retrospective study reviewed data from files of children with T1DM. This study included 1151 children and adolescents from Endocrinology clinics in Fayoum University Hospital and some patients from Insurance hospitals from 1/2/2023 to 1/8/2023.

All 1151 children with T1DM were further classified into 2 groups according to celiac antibody screening:

- Group I: Cases who had T1DM with negative markers for CD 1087 cases (Total serum IgA, ATTG below 10 u/ ml).
- Group II: Cases who had T1DM with positive markers for CD 64 cases (Total IgA, anti tTG above 10 u/ ml).

Inclusion Criteria

- Children diagnosed with type 1 diabetes based on WHO guidelines.
- Age was 1 to 18 years old at the time of study.
- Both genders.

Exclusion Criteria

- Other types of diabetes (type 2 – MODY type – neonatal types).

2.2. Methods

The following information was taken from each patient's file: Date of birth, date of DM onset, length of the illness, presenting symptoms (polyuria and polydipsia, weight loss, abdominal discomfort, and vomiting), whether or not DKA is a presenting symptom of T1DM, age at celiac disease diagnosis, insulin therapy compliance, and other related problems (auto-immune diseases (thyroid disorder, auto-immune hemolytic anemia, arthritis, IBD), and Non-immune associated conditions). The previous laboratory investigations (result of last hemoglobin, thyroid profile (TSH, Free T3, and Free T4), lipid profile (serum cholesterol, TG, HDL and LDL), CBC, and celiac markers (Total serum IgA, anti-tTG) were collected, as well.

Patients with positive markers for CD (suspected) were subjected to full clinical assessment:

- Height, weight, BMI and percentiles.
- CD gastrointestinal symptoms: (constipation, diarrhea, and abdominal pain).

Extraintestinal manifestations

- ❖ Musculoskeletal as bony pain and fractures.
- ❖ Neurological as tingling, numbness and peripheral neuropathy.
- ❖ Dermatological as skin rash and dermatitis.
- ❖ Endocrinological as hypothyroidism, hypogonadism and adrenal insufficiency.
- ❖ Recurrent episodes of hypoglycemia.
- ❖ If intestinal biopsy is done or not.
- ❖ Result of intestinal biopsy.
- ❖ Causes of excluded intestinal biopsy.
- ❖ Have a Gluten-free diet started or not.
- ❖ Compliance with gluten-free diet.
- ❖ Difficulties that they face to get a gluten-free diet.

Labs investigations

Follow up Hg A1C, and Follow up of celiac markers (Total serum IgA, anti-tTG, and anti-Endomesial Antibody (if available).

2.3. Statistical Analysis

The data was gathered, organized, and coded to enable efficient analysis. It was then entered twice into a Microsoft Access database to ensure accuracy and subsequently analyzed using SPSS software (version 22) on a Windows 7 platform. The analysis involved basic descriptive statistics, including counts and percentages for qualitative data, as well as means and standard deviations to summarize and describe the distribution of quantitative data. The study's quantitative data was first checked for normal distribution within each group using the One-Sample Kolmogorov-Smirnov test. Following this, the most appropriate inferential statistical tests were selected to further analyze the data. The quantitative parametric measures of two independent groups were compared using the independent samples test. The Mann-Whitney test was utilized to contrast quantitative non-parametric measures between two independent groups. The chi-square test was utilized to contrast between two of more than two qualitative groups. The *P*-value <0.05 was considered as statistically significant.

3. Results

1151 children with type 1 diabetes were included in the retrospective analysis, and they were further divided into two groups based on the results of the coeliac antibody test. Group I: 1087 T1DM patients who had negative CD markers. Group II: 64 T1DM cases with CD-positive markers (Table 1). The average age of our study group was (13.4±4.3) years old, ranging between 1-18 years with 51.3% being males and 48.7% being females, the mean age of DM onset in both females and males was comparable with no significant difference. All diabetic children were screened for CD, with a prevalence of 64 (5.6%) among all diabetic children.

Table 1: Demographic characters among the study group.

Variables		Frequency (n=1151)
Age (years)	Mean ±SD	13.4 ±4.3
	Range	1-18
Gender	Male	590 (51.3%)
	Female	561 (48.7%)

Anti-tTG IgA positivity was found in 45.3% of our CD cases in the first year, 34.3% between the first and fifth years, and 20.4% after the fifth year of T1DM diagnosis. The studied groups of diabetic children had other associated medical conditions (Table 2). Autoimmune diseases were found in 2.3% of cases (20 cases had hypothyroidism, four cases had Grave's disease, suspected inflammatory bowel disease (IBD) in two cases, Addison's disease in one case, and vitiligo in one case). Anemia was found in 21.4% of patients, iron deficiency anemia represented 21% of them, thalassemia in two cases, glucose-6 phosphate dehydrogenase deficiency (G6PD) in two cases, and aplastic anemia in one case. Other associated conditions (eight cases) included Wilson disease in one case, Cornelia de Lange syndrome in one case, down syndrome in one case, epilepsy in one case, obesity in two cases, nephrotic syndrome in one case and hepatitis C virus infection in one case. Complications of DM were found in two patients, in one case with optic neuropathy (DM duration was five years) and hypertension in another case (DM duration was four years).

Table 2: Associated disorders among our study group

Variables		Frequency (n=1151)
Autoimmune Thyroiditis	Hypothyroidism	20 (1.7%)
	Grave's disease	4 (0.3%)
IBD		2 (0.2%)
Addison disease		1 (0.1%)
Vitiligo		1 (0.1%)
Anemia	Thalassemia	2 (0.2%)
	Aplastic anemia	1 (0.08%)
	G6PD deficiency	2 (0.17%)
	Fe deficiency anemia	242 (21%)
Other associated conditions		8 (0.69%)

Regarding the presenting gastro-intestinal symptoms of group II majority of cases (82%) presented with abdominal distention, abdominal pain (54.1%), diarrhea (26.2%) and constipation (14.8%) (Table 3).

Table 3: Clinical symptoms of CD in group II

Variables		Frequency (n=61)
Gastrointestinal symptoms	Diarrhea	16 (26.2%)
	Constipation	9 (14.8%)
	Abdominal pain	33 (54.1%)
	Abdominal distention	50 (82%)
Extraintestinal manifestations	Skin rash	11 (18%)
	Hypothyroidism	2 (3.3%)
	Arthralgia	11 (18%)

Extraintestinal manifestation found among group II cases included dermatological as skin rash, dermatitis and erythema multiform were presented in 18% of cases, endocrinologic two cases presented with hypothyroidism, musculoskeletal manifestations in 18% of cases presented with arthralgia, neurological manifestations in one case with delayed motor and mental (the MRI finding was bilateral occipito-parietal areas of encephalomalacia), and none of the cases had cardiac, hepatic, renal or respiratory symptoms (Table 4).

Table 4: Description of Follow-up laboratory investigations among children in group II

Variables (n=61)		Mean ±SD	Range	
Level of Celiac Antibodies	Total IgA (mg/dL)	173.6 ±83.1	80-534	
	Anti- tTG IgA (u/mL)	45.8 ±60.1	12-201.8	
	>10 Folds	**7** (11.5%)		
	<10 Folds	54 (88.5%)		
	Hemoglobin A1c (%)	9.7 ±2.6	6.5-16	
Hemoglobin A1c	Good Control	2 (3.3%)	7 ±0	*P* =0.04*
	Poor control	56 (96.7%)	12.5 ±4.03	

**statistically significant with p <0.05.*

Table 5 showed that the mean level of celiac markers during follow-up among group II were (173.6 ±83.1) and (45.8 ±2.6) for Total IgA and Anti TTG IgA respectively, and only one case did Anti EMA. We found that seven cases (11.5%) of the CD group had levels > 10 folds of Anti TTG IgA. Regarding HbA1C, (96.7%) of cases with CD showed poor controlled DM. Hypoglycemic episodes were reported in 27 cases of the CD group (44.3%). Only 13 children of group II had intestinal biopsies. Intestinal biopsy findings included increased intra-epithelial lymphocytes (two cases), mild duodenitis (five cases), moderate duodenitis (seven cases), villous atrophy (seven cases), epithelial apoptosis (one case) and crypt hyperplasia (one case). According to the MARSH classification, one patient was stage 3a and another one was stage 3b. 23% of cases in group II had intestinal biopsy. In 25.5% of cases parents refused to do a biopsy, 14.9% of them had more than 10 folds anti-tTG IgA antibody while 59.6% of cases were not advised to do a biopsy. We found that 32.8% of cases in group II followed a gluten-free diet regimen, but only 3.3% of them were compliant with it. The following conditions were associated with CD in patients of group II, Hypothyroidism in 3.3% of cases and anemia (55.7% of them had iron deficiency anemia and thalassemia in one case). Table 6 showed that patients of group II had a significant decrease in Anti TTG IgA level at follow-up time (p =0.001).

Table 5: Compliance on GFD among children in group II and difficulties encountered

Variables		**Frequency (n=61)**
Gluten-free diet	No	41 (67.2%)
	Yes	20 (32.8%)
Compliance with the gluten-free diet	No	18 (90%)
	Yes	2 (3.3%)
Difficulties encountered with GFD	Expensive	11 (18%)
	Un available	2 (3.3%)
	Not palatable for children	1 (1.6%)
	Not started yet	47 (77%)

Table 6: Comparison of antibody levels at baseline and follow-up among group II.

Variables	Among Group II (n=61)		*P*-value
	Baseline	Follow-up	
Total IgA (mg/dL)	170.5 (80-908)	156.8 (80-534)	0.29
Anti- tTG IgA (u/mL)	33.2 (47- >200)	15.3 (12-201.8)	0.001*

**statistically significant with p <0.05.*

Group II showed a significantly high level of total IgA at follow-up time among cases who did not do intestinal biopsy (*p* =0.04). Although no significant p-value in anti-tTG IgA, that may be due to high levels of celiac antibodies in patients who were not advised to do an intestinal biopsy. While there was in statistically significant difference in antibodies at baseline assessment (Table 7).

Table 7: Comparison of antibody levels in different Intestinal biopsy groups.

Variables		Intestinal biopsy		*P*-value
		Not done (n=48)	Done (n=13)	
Baseline assessment	Total IgA (mg/dL)	198.6 ±147.8	173.9 ±75.9	0.9
	Anti- tTG IgA (u/mL)	222.2 ±1042.6	95.2 ±88.6	0.19
Follow-up	Total IgA (mg/dL)	184.8 ±84.9	135.9 ±65.8	**0.04***
	Anti- tTG IgA (u/mL)	49.6 ±62.6	33.2 ±51.1	0.8

statistically significant with p <0.05*.**

As shown in Table 8, the children of group II, who were compliant with a gluten-free diet, had a statistically significant high percentage of intestinal biopsy (*p* =0.05), with no difference in total IgA level, anti-tTG IgA level at follow-up or HbA1C level.

Table 8: Comparison of variables in different Gluten-free diet-compliant groups.

Gluten-free diet	Non-compliant (n=59)		Compliant (n=2)		*P*-value
	Median	Range	Median	Range	
Total IgA (mg/dL)	156.8	80 -534	179.5	129-230	0.55
Anti - tTG IgA (u/mL)	15.3	12-201.8	42.2	12.1-72.3	0.74
HbA1c (%)	9.20	6.5-16	11.9	9-14.7	0.33
Hypoglycemic attacks	26	44.1%	1	50%	0.99
Intestinal biopsy	11	20.3%	2	100%	**0.05**

**statistically significant with p < 0.05.*

4. Discussion

A lot of people are becoming aware that T1DM and CD are related, especially in light of the regular CD screening that T1DM patients undergo. Approximately 5% of patients who have both diseases co-occurring, usually with T1DM developed before CD. The co-occurrence of these two illnesses has historically been linked to the presence of shared high-risk HLA genotypes (DR-DQ) [6].

We carried out our investigation in the Fayoum governorate to find the seroprevalence of coeliac markers in children with type 1 diabetes. 1151 children and adolescents from the endocrinology clinics at Fayoum University Hospital as well as a few patients from Insurance Hospital were included in this retrospective analysis.

The average age at which our patients developed T1DM was 10.4, and the average duration of time they had the disease was 6.2 years. There were 51.3% men among our patients. Although the disease can strike at any age, research by Norris et al. (2020) and Vojislav et al. (2020) revealed that the incidence of T1DM increases with age, peaking around the age of 10–14 [7, 8].

This study reveals a rising trend in the incidence of T1DM among children and adolescents, which is in line with previous research. For instance, a US-based study found a 10% increase in T1DM incidence among those under 20 years old over 20 years, accompanied by a 47% rise in prevalence. Similarly, European data shows an average annual increase of 3.4% in T1DM among adolescents between 1989 and 2013, with varying rates across countries, ranging from 1% in Spain and Italy to 6% in Poland, Romania, and Lithuania. In Germany, the prevalence of T1DM among teenagers has also seen a significant increase, from 1.4 per 1000 in 2002 to 2.5 per 1000 in 2020.

In our study, the frequency of DKA was statistically higher among children with CD. This was in contrast to research conducted by Aljulifi et al. (2021) and Kurien et al. (2015), which found no statistically significant difference in the number of DKA admissions between seropositive and seronegative CD patients [9, 10].

It is well known that maintaining metabolic control is crucial for diabetes patients to reduce their medium- and long-

term risk of problems. For patients who also have CD, this is especially true. The metric used to measure long-term glycemic management is called glycated HbA1c. This value is an indication of total glucose exposure since it considers blood glucose levels during fasting and after meals. It shows the average blood glucose levels over a span of two to three months. International guidelines suggest measuring HbA1c frequently to assess glycemic control since they provide information about long-term glycemic states. It was shown that just 9.6% of the patients exhibited adequate glycemic control. Furthermore, we found that age over 12 and insufficient control were significantly correlated [11].

Over the past two decades, there has been a notable increase in the prevalence of CD due to the use of sensitive and precise serological tests and a more thorough understanding of the condition by doctors. 64 children (5.6%) with diabetes who tested positive for CD markers had 14.7% BPCD (Biopsy Proven CD) among our diabetic children. Taczanowska et al. (2021) confirmed comparable findings in the SWEET registry, indicating a 4.5% frequency of CD among their cases [12]. Additionally, the Craig et al. (2017) investigation discovered that among T1DM children and adolescents, the CD frequency varied between different countries by 1.4% to 16.4% [13]. Our findings, however, were not as high as those of Alali and Afandi (2023), who reported a high incidence of seropositive CD in their patients of 14.9%. These results highlight the therapeutic challenges of addressing both illnesses concurrently and highlight the significance of CD screening in children with T1DM.

Our study's mean age at CD diagnosis was 5.6 years, which is consistent with Wessels et al. (18) who reported a propensity for the group with CD to have CD at a younger age. Aziz et al. (19) found a similar range for the mean age at CD diagnosis, 3.7-9.5 years.

According to our research, intestinal manifestations of CD in children with coeliac positive indicators included diarrhea (26.2%), constipation (14.8%), abdominal distention (82% of cases), and abdominal colic (54.1%). This is in line with the findings of Reilly et al. (20) and Caio et al. (21) who discovered that diarrhea, abdominal distention, appetite loss, and failure to thrive were intestinal symptoms of CD.

Our study found that hypothyroidism was more prevalent than hyperthyroidism among diabetic patients, with 1.7% and 0.3% incidence rates, respectively. This is consistent with previous research, which suggests that thyroid disease is more common in individuals with T1DM compared to the general population [14]. Studies have shown that autoimmune thyroid disease (AITD) affects approximately 3-8% of children and adolescents with T1D, with hypothyroidism being the most common form. Furthermore, research has found that up to 29% of individuals with T1DM develop anti-thyroid antibodies shortly after diagnosis, which is a strong predictor of AITD, particularly hypothyroidism.

Our study showed that only 13 children (20%) with positive celiac markers had intestinal biopsies but in 25.5% of cases their parents refused to do a biopsy, and 14.9% of them had levels more than 10 folds of celiac antibodies. Due to the invasive nature of the treatment, the majority of our cases did not get intestinal biopsies, even though over half of them were not advised to. Our results are consistent with those of Wessels et al. (2020), who discovered that 33.3% of children with CD and T1DM underwent duodenal biopsies [15].

The only treatment for CD that is now accessible is a GFD; only 32.8% of our patients followed a gluten-free diet, and only 3.3% of them adhered to the GFD. Our findings are significantly less than those of Myléus et al. (2020) who discovered that children with CD adhered to a gluten-free diet at a rate that varied significantly, from 23% to 98% [16]. Comparably, greater GFD compliance rates (68% and 85–96%) were found by Söderström et al. (2021) and Webb et al. (2015) [17, 18].

In our investigation, anti-tTG IgA levels were significantly lower in coeliac cases at follow-up, and anti-tTG IgA levels were lower in patients following a GFD than in those who did not. This may indicate that these levels will keep falling until they return to normal. According to a study by Söderström et al. (2021) 23% of the children who had their tTG IgA levels normalized took two years or longer to achieve normalization, compared to 77% who did so in just one year [17]. According to the former study, a considerable proportion of CD and T1DM children need more than a year to reach normal tTG IgA. This finding

may be important to consider when assessing a child's compliance with a GFD.

5. Conclusion

With a frequency of 5.6%, we revealed a strong correlation between T1DM and CD in our cases. In terms of Hb A1C, 96.7% of our T1DM and CD patients had inadequate DM disease management.

When T1DM was diagnosed, about 50% of the individuals had CD, and 40% of those cases were diagnosed in the first five years. When coeliac serology spontaneously normalizes, serological follow-up is necessary in alternative to an urgent duodenal biopsy or the initiation of GFD therapy in patients with modest anti-tTG IgA antibody levels and no symptoms. The existence of CD at the time of the T1DM diagnosis did not affect metabolic management. Of CD patients, anemia, primarily iron deficiency, was observed in 50.8% of cases, and hypothyroidism in 3.3%. Children compliant with GFD in our study were only 3.2%.

Ethical committee approval: The Faculty of Medicine Research Ethical Committee reviewed this study. The researcher provided the participants with information regarding the study's objectives, the examination, and the investigation that was conducted. Additionally, the researcher informed them of their right to decline participation and the confidentiality of their information.

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