Celiac Disease in Syrian Children and Adolescents with Type 1 Diabetes Mellitus: A Cross-Sectional Study

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Abstract

Introduction Celiac disease (CD) is highly prevalent in patients with type 1 diabetes mellitus (T1DM). However, the rate of CD in Syrian children and adolescents with T1DM is unknown. We aimed to investigate the prevalence and characteristics of CD in our unprivileged rural community.

Methods Children and adolescents with T1DM who were regularly followed in a private endocrine clinic in Raqqa City, Syria, were evaluated from October 2018 to November 2021. Screening for CD was performed using either anti-tissue transglutaminase antibodies, antideaminated gliadin antibodies, or endomysial antibodies. Patients with positive results were referred for duodenal biopsy using Marsh classification whenever possible. The prevalence of CD was calculated for both seropositive and biopsy-proven cases.

Results Ninety-four patients with T1DM, 51 (54.3%) females, were included. The mean age was 11.6 years, and mean hemoglobin A1c (HbA1C) was 9.2%. All patients were screened for CD. Fourteen patients (14.9%) were positive, and seven (7.4%) performed a duodenal biopsy that proved positive for CD in all cases. CD seropositivity was more common in female than male patients (21.6 vs. 7%, respectively, p-value <0.05). Patients with seropositivity for CD had lower hemoglobin levels compared to seronegative patients, with a mean difference of 0.87 (95% confidence interval: 0.2–1.5; p-value <0.05). There was a statistically significant correlation between hypothyroidism and celiac seropositivity (p-value <0.05). There were no differences in age, weight, height, HbA1C, puberty status, or duration of diabetes between patients with and without CD. No correlation was identified between the incidence of hypoglycemia or diabetic ketoacidosis and the presence of CD.

Conclusion In our community, we revealed a high prevalence of CD in Syrian children and adolescents with T1DM. Our results are alarming and point to the need for establishing a national CD registry to prompt physicians for proper screening and early management in high-risk populations.

Keywords
- celiac disease
- type 1 diabetes mellitus
- adolescents
- children
- Syria

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Introduction

Celiac disease (CD) is a complex disease characterized by small bowel injury due to gluten autoimmune effects in predisposed individuals. Nonspecific signs and symptoms and distinct degrees of enteropathy, CD-specific antibodies, and genotypes define it. The CD is common, occurring in 0.5 to 1% of the general population in most countries, but is as high as 2 to 3% in certain populations.[1] The frequency of CD is considerably increased in first- and second-degree ancestors of patients with CD and in individuals with certain genetic syndromes, type 1 diabetes mellitus (T1DM), selective immunoglobulin A (IgA) deficiency, and several autoimmune conditions.[2] It has been reported that the incidence of CD among T1DM patients is between 5 and 10%,[2,3] compared to 17.4 per 1,00,000 person-years in the general population, indicating a 7 to 13-fold increased risk.[4]

The prevalence of CD in the Arab general population varies between 0.14% in Tunisia[5] and 2.7% in Saudi Arabia,[6] in compared to a higher prevalence in T1DM patients that ranges between 5.5% in Egypt[7] and 20% in Algeria.[8] There is no data on the prevalence of CD in Syrians with T1DM, but it was estimated to affect one in every 62 healthy blood donors.[9]

The coexistence of T1DM with other autoimmune disorders may complicate the management of diabetes. Patients with CD and T1DM are at increased risk of diabetic retinopathy,[10] microvascular complications,[11] worse quality of life and glycemic control,[12] and even increased risk of early albuminuria.[13]

Routine screening for CD in asymptomatic children with risk factors is debatable, with some authors recommending such an approach.[2] Conversely, other clinical practice guidelines recommend periodic screening for coexisting autoimmune disorders in symptomatic patients with T1DM.[14,15]

To the best of our knowledge, this is the first study investigating the prevalence of CD among young patients with T1DM in Syria. Additionally, this article will explore the potential relationship between CD on the one hand and patients' age and gender, clinical presentation, diabetes control, duration of diabetes, and acute diabetes complications on the other.

Patients and Methods

Settings and Design

This cross-sectional study included patients with T1DM aged 18 years or younger who were followed in a private endocrine setting. The study was conducted in Raqqa Governorate, Syria, between October 2018 and November 2021 using routinely collected data as part of standard care. All parents granted verbal permission to use the collected data. Whenever indicated, parents were asked to consent to intestinal biopsy. However, only seven out of fourteen parents approved of the procedure.

Outcome Measurements

All patients were interviewed and examined; their charts were reviewed for personal and family history, circumstances at the time of diagnosis, insulin regimens, and the incidence of acute diabetes complications, including hospitalization for hypoglycemia and diabetic ketoacidosis (DKA). We have collected the patient's weight, height, puberty status using the Tanner staging system, the occurrence of hypoglycemic episodes, and DKA since diagnosis.

Laboratory investigations included complete blood count, creatinine, glycosylated hemoglobin A1c (HbA1C), and thyroid-stimulating hormone (TSH). Screening for CD was performed regardless of the presence of symptoms, using either anti-tissue transglutaminase antibodies (anti-tTGA), anti-deaminated gliadin antibodies, or endomysial antibodies (EMA). A duodenal biopsy confirmed positive cases (defined by threefold above normal) to make a CD diagnosis.[16] Marsh criteria defined intestinal biopsy, which includes types 0, 1, 2, 3a, 3b, and 3c.[16] Total IgA was not routinely ordered due to unavailability and financial cost. Hypothyroidism was diagnosed when the TSH level was more than 10 (mU/L). Patients were considered type 1 diabetes when the diagnosis was made by the presence of T1DM autoantibodies and hyperglycemia or presenting with DKA in children or adolescents. Hypoglycemia was defined as any blood glucose level lower than 70 mg/dL. DKA was defined as plasma glucose concentration above 250 mg per dL with a pH level of less than 7.30, bicarbonate level of 18 mEq per L or less, and elevated serum/urine ketone levels.

Statistical Analysis

Data were analyzed by IBM SPSS statistics software (IBM Corp, Version 23.0. Armonk, New York, United States). Data were presented as mean, standard deviation for normally distributed variables or median, and range for non-Gaussian distributed parameters. Nominal variables were analyzed by Pearson chi-squared or Fisher's exact test. Independent sample *t*-test was used to test parametric variables with the confidence interval 95% confidence interval (CI), while comparing nonparametric variables was performed by using the Mann–Whitney U test. In all tests, a *p*-value less than or equal to 0.05 was considered statistically significant.

Results

Ninety-four patients with T1DM were included. All patients were 18 or younger in which 51 patients (54.3%) were females. The mean age of subjects was 11.6 years (95% CI: 10.7–12.5) with a median duration of diabetes 2 (0–14) years, mean HbA1C was 9.2% (95% CI: 8.7–9.7), and 47 (50%) patients used premixed insulin while the rest used basal-bolus injections (►**Tables 1** and **2**).

All patients were screened for CD. Fourteen patients (14.9%) were positive. All patients with positive screening were referred for small bowel biopsy. However, only seven patients (7.4%) accepted and underwent Marsh 3b and 3c duodenal biopsies. CD seropositivity was more common in female than male patients (21.6 vs. 7%, respectively, *p*-value <0.05). CD-positive patients had lower hemoglobin levels compared to seronegative patients, with a mean difference of 0.87 (95% CI: 0.2–1.5; *p*-value <0.05). Hypothyroidism was found in 7/85 (8.2%) patients. There was a statistically

Table 1 Study population characteristics

Characteristics	Celiac-positive	Celiac-negative	*p*-Value
Sex (female/male)	11/3 (78.6/21.4) %	40/40 (50/50) %	<0.05
Diabetes duration (y)	3 (0–14)	2 (0–14)	NS
Weight (kg)	31 (12.6–59)	30.25 (10–74)	NS
Height (cm)	138.25 (86–163)	138.75 (84–178)	NS
TSH (mU/L)	2.86 (0.2–735)	1.69 (0.37–11.08)	NS
Age (y)	11.25 ± 5	11.63 ± 4.3	NS
Hemoglobin (g/L)	12.08 ± 1	12.96 ± 1.5	<0.05
HbA1C (percentage)	9.25 ± 1.7	9.20 ± 1.6	NS

Abbreviations: HbA1C, hemoglobin A1C; NS, not specified; TSH, thyroid stimulating hormone.

Table 2 Diabetes indicators, celiac, and hypothyroidism prevalence

Variables		Number (percentage)
Treatment	Premixed insulin	47 (50%)
	Multiple-dose Injections	47 (50%)
Thyroid	Euthyroid	78 (91.8%)
	Hypothyroid	7 (8.2%)
	Unknown	9
Celiac disease	Negative	80 (85.1%)
	Positive	14 (14.9%)
Hypoglycemia	No	40 (43.5%)
	Yes	52 (56.5%)
	Unknown	2
DKA	No	41 (44.6%)
	Yes	51 (55.4%)
	Unknown	2
HbA1C testing	Not done	53 (56.4%)
	Done once	23 (24.5%)
	Many times	18 (19.1%)
SMBG	Not done	48 (51.1%)
	Regular	46 (48.9%)

Abbreviations: DKA, diabetes ketoacidosis; HbA1C, hemoglobin A1C; SMBG, self-monitoring body glucose.

significant correlation between hypothyroidism and celiac positivity (*p*-value <0.05; ►**Table 3**).

There were no observed differences in age, weight, height, HbA1C, puberty status, or duration of diabetes between patients with and without CD. At least one episode of hypoglycemia was reported by 71 (54.2%) subjects. There was no correlation between the incidence of hypoglycemia and the presence of CD. Additionally, DKA was reported at least once in 69 (52.7%) patients; however, that did not correlate with CD.

Discussion

The prevalence of CD varies widely by geographical location,[1] population age,[17] and screening methods.[18] The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) recommends screening for CD with anti-tTGA combined with total IgA levels. Confirming the diagnosis requires a duodenal biopsy if anti-tTGA levels are less than ten times the upper limits of normal (ULN). However, if these levels are more than ten times the ULN, then only a positive EMA test in a separate sample is needed to confirm the diagnosis, which would obviate the need for a biopsy.[19] This approach has led to recognition of two potential entities: the seropositive CD and the positive biopsy-proven CD.

The prevalence of CD in T1DM is estimated to range between 5 and 10%[2,3] in Western populations and 5.5 and 20% in Arab countries.[7,8] We found a high prevalence of seropositive CD at 14.9% in our patients, similar to results found in Saudi Arabia at 15.9%,[6] higher than rates in other studies[20] but lower than 20.8% described by Sharma et al.[21] This high prevalence in our community can be explained by many factors, including the practice of gluten-rich dietary patterns at an early age and the genetic predisposition as described by Murad et al who reported that HLA-DQ2 and HLA-DQ8 alleles are more common in Syrian children with CD compared with the general population.[22] Those identical alleles are also associated with type 1 diabetes.[23,24] In our study, seven patients underwent endoscopy, and their histopathology showed advanced enteropathy consistent with CD. Some investigators have demonstrated that higher anti-tTGA titers were seen in biopsy-positive CD patients and suggested that antibody titers of more than ten times the ULN may be used as an alternative diagnosis criterion when the biopsy is not feasible.[25] However, 12 out of 14 patients in our study had anti-tTGA levels more than ten times the ULN. However, biopsy refusal limited any further exploration of such a relationship.

Consistent with the literature, only 2 out of 14 of our patients were symptomatic, signifying the importance of screening for CD early after diagnosing T1DM in children and adolescents. It is wise to consider celiac screening at the time of T1DM diagnosis and 2 to 5 years after diagnosis. Screening for CD is indicated in all T1DM patients with suggestive symptoms.[15]

Like many studies, we report a female preponderance of CD in our patients.[20,21,26,27] Factors that may explicate this tendency include variances between male and female immune systems, effects of sex hormones, genetic susceptibility, parental inheritance, and level of exposure to external factors and their impact on epigenetics.[28]

Table 3 Celiac positivity associations with study population's variables

variables		Celiac disease		*p*-Value
		Positive	Negative	
Hypoglycemia	No	5 (35.7%)	35 (44.9%)	NS[b]
	Yes	9 (64.3%)	43 (55.1%)	
DKA	No	4 (28.6%)	37 (47.4%)	NS
	Yes	10 (71.4%)	41 (52.6%)	
Sex	Female	11 (78.6%)	40 (50%)	0.048[a]
	Male	3 (21.4%)	40 (50%)	
Treatment	Premixed insulin	10 (71.4%)	37 (46.3%)	NS
	MDI	4 (28.6%)	43 (53.8%)	
Hypothyroidism	No	10 (71.4%)	68 (95.8%)	
	Yes	4 (28.6%)	3 (4.2%)	0.013[a]
Puberty stage	Tanner (1–3)	11 (78.6%)	53 (67.1%)	NS
	Tanner (4,5)	3 (21.4%)	26 (32.9%)	
Diabetes onset	Less than 5 years	6 (42.9%)	22 (27.5%)	NS
	More than 5 years	8 (57.1%)	58 (72.5%)	

Abbreviations: DKA, diabetes ketoacidosis; MDI, multiple dose injections.
Percentages are numbers within the celiac disease
[a]Statistically significant using Fisher's exact test.
[b]No relation.

In contrast to many publications that found an increased prevalence of CD with the recent onset of T1DM and a longer duration of diabetes,[26,27] we did not find such correlations similar to many studies.[21,29] However, the small sample size and a short follow-up may have contributed to this observation.

Although autoimmune thyroid disorders were not mainly investigated in our study, TSH was tested as a routine workup in T1DM; hypothyroidism was present in 8.2% of cases. Our data confirm a significant correlation between hypothyroidism and CD, consistent with the literature.[18,30,31]

The limitations of this study are many, including the small sample size, screening only once during the study period, using variable screening tests, the refusal to undergo a small bowel biopsy, the lack of resources to follow ESPGHAN recommendations in a non-biopsy approach, and referring patients to different laboratories. Nevertheless, our data sheds the first light on the prevalence of CD in this high-risk group of patients and calls for increasing official and public awareness.

Conclusion

In our community, we revealed a high prevalence of CD in Syrian children and adolescents with T1DM. Our results are alarming and point to the need for establishing a national CD registry to prompt physicians for proper screening and early management in high-risk populations.

Authors' Contributions

I.A. has full access to all the data presented and takes responsibility for the integrity and accuracy of the content. All patient's data are available upon request as SPSS sheet. Both authors contributed to the conception and writing of the manuscript, literature search, revision, and approval of the final version. I.A. runs a private clinic of endocrinology in Raqqa governorate besides his affiliation with Damascus University; patient's data were collected during his work in Raqqa.

Compliance with Ethical Principles

The study was based on routinely collected data as part of standard care. All parents granted verbal permission to use the collected data.

Financial Support and Sponsorship

None.

Conflict of Interest

None declared.

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