Celiac in type 1 diabetes children and youth – prevalence, metabolic control and growth parameters

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Background & Aims: To assess the prevalence of biopsy-confirmed celiac disease (CD) among children and youth with type 1 diabetes mellitus, and the implications of CD on metabolic control, nutritional status, and physical growth in type 1 diabetes patients. Methods: A retrospective study of type 1 diabetes patients at Maccabi Juvenile Diabetes Center. Those diagnosed with CD based on positive intestinal biopsy were compared to a control group compromising two patients matched by sex, age, and duration of diabetes for each CD patient. Results: Of 316 type 1 diabetes patients, 294 (93%) were screened for CD, and eleven (3.7%) diagnosed. There was no statistically significant difference in mean HbA1c levels between the CD and control groups. However, CD patients with good adherence to gluten-free diet (GFD) (n=7), had better metabolic control than those with poor adherence (n=4), without statistical significance. For patients with both type 1 diabetes and CD, and not for the control group, mean final height was significantly lower than target height (p=0.01). Among those with poor adherence to GFD, growth impairment was severe. Conclusions: Patients with both type 1 diabetes and CD had significant growth impairment; more pronounced impairment was observed in children with poor adherence to GFD.

Keywords: Gluten free diet (GFD); HbA1C


Introduction

Celiac disease (CD) has been reported to be 5-7 times more prevalent among individuals with type 1 diabetes mellitus than in the general population (2-8% and 0.5-1% respectively) [1]. The only study in Israel to investigate the prevalence of autoimmune diseases in young patients with type 1 diabetes and their first-degree relatives reported 8.3% prevalence of CD among 109 children and teenagers with type 1 diabetes [2].

Careful attention to dietary intake is important for maintaining glycemic control in type 1 diabetes. For those with CD, a gluten-free diet (GFD) is also prescribed. Strict adherence to a GFD can be challenging both on a practical and a psycho-sociological level [3, 4]. Eating in public may entail discussions and special requests, with the effect of making an invisible condition visible. The feeling of being stigmatized may result in poor compliance, particularly in adolescents [5]. The purpose of the current study was to evaluate the prevalence of biopsy-confirmed CD among children and youth with type 1 diabetes, and to compare metabolic control, growth, and nutritional parameters in children and youth with combined type 1 diabetes and CD, to those with type 1 diabetes without CD. We also explored...
whether the dietary restrictions imposed by CD may affect young people's glycemic control.

**Patients and Methods**

All patients with type 1 diabetes attending our pediatric diabetes clinic are routinely screened for CD by serological testing for celiac antibodies (antiendomysial and/or tissue transglutaminase). Antibody positive patients are referred to intestinal biopsy.

We collected data regarding patients screened for celiac disease between January 1998 and February 2007. Patients were classified into three groups: a) positive CD, as diagnosed by intestinal biopsy after positivity for endomysial and/or tissue transglutaminase antibody, b) suspected CD, including patients with positive antibodies but negative biopsy for CD; and also patients with positive antibodies who declined biopsy, and c) control group. Patients with suspected CD will not be included in the statistical analysis. For each patient with CD, two patients without CD, matched by sex, age, and duration of diabetes were selected.

Anthropometric indices (height and weight), HbA1c level, number of severe hypoglycemic and diabetes-keto-acidosis [DKA] events, laboratory tests (hemoglobin, ferritin, iron, total cholesterol, triglycerides, HDL, LDL, B12 and folic acid), prevalence of microvascular complications of diabetes (microalbuminuria and retinopathy), and adherence to GFD, were accessed. Assessment of adherence to GFD over the years was based on patient report. Patients who never consumed gluten containing foods were rated as strictly adherent; and patients who continued to consume foods not included in a GFD were considered partially adherent. The study was approved by the Institutional Review Board of Maccabi Health Care Services, Israel.

**Target Height**

Genetic target heights were calculated from midparental heights (average of mother's and father's heights) according to the following equations: for males, average parental height plus 6.5; for females: midparental height minus 6.5.

**Z Score**

The z scores for weight, height, and target height were calculated by using anthropometric software program (EpiInfo 2002, CDC 2000, Centers for Disease Control and Prevention, Atlanta, GA, USA).

**Statistical Analyses**

Statistical analyses were performed using SAS version 9.1.

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**Figure 1: Study Procedure.**
Table 1. Patients' clinical characteristics.

<table>
<thead>
<tr>
<th></th>
<th>CD (n=11)</th>
<th>Control Group (n=22)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>6 (54.6%)</td>
<td>12 (54.6%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>5 (45.4%)</td>
<td>10 (45.4%)</td>
<td></td>
</tr>
<tr>
<td>Age at end of study (Mean ± SD)</td>
<td>16.1 ± 6.0</td>
<td>17.6 ± 6.8</td>
<td>0.56</td>
</tr>
<tr>
<td>Age at diabetes diagnosis (Mean ± SD)</td>
<td>5.0 ± 4.0</td>
<td>6.6 ± 4.6</td>
<td>0.33</td>
</tr>
<tr>
<td>Years with diabetes (Mean ± SD)</td>
<td>11.1 ± 5.1</td>
<td>10.9 ± 5.5</td>
<td>0.92</td>
</tr>
<tr>
<td>Age at celiac diagnosis (Mean ± SD)</td>
<td>10.2 ± 5.8</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Years with celiac (Mean ± SD)</td>
<td>5.4 ± 4.2</td>
<td>-</td>
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</table>

Figure 2. HbA1c levels in CD patients. a: comparing CD patients and control group from diagnosis of diabetes. b. comparing CD patients with good and poor compliance to GFD before and after diagnosis of CD.

(SAS institute Inc., Cary, NC, USA). Descriptive statistics are presented as numbers (percentages) and mean values ± standard deviation (SD). Categorical variables were compared by the chi-square test or Fisher exact test, and continuous variables by student's t-test. All tests were two-sided and p-values <0.05 were considered statistically significant. For longitudinal follow-up, mean values of study parameters for each patient were used in analyses. These observations reflect the means of all values measured during each year.

All differences between mean values were analyzed with the generalized estimating equations (The SAS GENMOD procedure). This procedure allowed us to account for effects of within person correlation and matching study design.

**Results**

Figure 1 depicts the study procedure and results of CD screening. Of 316 type 1 diabetes patients in our clinic (mean age 10.2 years), one was diagnosed with CD prior to diabetes diagnosis. Two hundred ninety-three tested for endomysial and tissue transglutaminase antibody. Of the 18 with positive results, 16 underwent an intestinal biopsy, which confirmed CD in eleven (6 boys, 5 girls) (3.7%). Ten patients were diagnosed with CD following diabetes diagnosis. Eight patients (2 boys, 6 girls) were classified as "suspected CD" (2.7%). For six (2.0%), this was based on positive results from a CD screening test but with a negative biopsy. Two others (0.68%) screened positive for CD but refused to undergo a biopsy. Patient clinical characteristics are presented in Table 1. As seen matching by age, gender and duration of diabetes the two study groups were similar. The average age at CD diagnosis was 10.2±5.8 years. Duration of CD at the time the study was conducted was 5.4±4.2 years. The mean onset age for type 1 diabetes among CD patients was younger than the mean age of the entire cohort of all patients excluding CD patients (305 patients) 5.2 and 10.2 years respectively.

**Metabolic control**

There was no difference in mean HbA1c levels between the CD group (n=11) and the control group (n=22) (p=0.85) (Figure 2a). However, CD patients with good compliance to GFD (n=7), had better metabolic control throughout the entire follow-up than CD patients with poor compliance to GFD (n=4), without statistical significance (p=0.45) (Figure 2b).

**Weight and Height**

**Weight**

We found no difference between the mean weights of CD and control group patients throughout the entire follow-up.
(p=0.16) (Figure 3a). We observed that several years after diagnosis of CD, weight continuously declined in patients with low adherence, while remaining stable in patients with high adherence to a GFD, without statistical significance.

**Height**

Comparing z scores for mean heights of CD and control group patients showed no statistical difference during 12 years of follow-up (p=0.51) (Figure 3b). Comparing the difference between height of patients and their target height z-score showed CD patients to be below their genetic target height (p=0.01), while patients without CD reached their genetic target height (Figure 4a). Furthermore, among patients with CD and poor compliance to GFD (n=4), the difference between height of patients and target height z-score decreased throughout the follow-up period; such trend was not observed among those with strict compliance to GFD (n=7) (Figure 4b). Six of the 11 (55%) CD patients reached their final height, compared with 8 of the 22 (36%) in the control group. However, the mean final height was, on average, 5 cm lower than the mean target height for CD patients; yet 2.4 cm higher than the mean target height for control patients (range: -5:+16).

There were no statistically significant differences in any of the other laboratory parameters (hemoglobin, ferritin, iron, total cholesterol, triglycerides, HDL, LDL, B12, and folic acid) between the CD patients and the control group. Fewer severe hypoglycemia events were reported for CD patients than for controls (2/11, 18.1% and 10/22, 45.4%, respectively, p=0.25) and DKA episodes (none in CD group and 4/22, 18.2% respectively, p=0.28), yet neither of these differences reached statistical significance. Similarly, there were no statistically significant differences in mean microalbuminuria levels (2/11 (18.1%) vs. 2/22 (9.1%), respectively, p=0.59) or in the prevalence of retinopathy (none in both groups).

**Discussion**

This is the largest study in Israel to assess the prevalence of CD in patients with type 1 diabetes. The prevalence rate of 3.7% for biopsy-confirmed CD in type 1 diabetes patients is 6 times that detected in the general population in Israel (0.6%) [6], affirming increased prevalence of CD in patients with type 1 diabetes. The results are similar to of Leeds et al [7], who found a prevalence of CD in patients with type 1 diabetes of 3.3%. Importantly, this study is based on the screening of 93% of the 315 patients in our medical center who were not diagnosed with CD at the onset of type 1 diabetes. The only other study to assess CD in type 1 diabetes patients in Israel was based on 109 patients from a number of medical centers [2].

According to the Israel Pediatric Endocrine Society and the Israel Center for Disease Control (ICDC), 0.5% of patients with type 1 diabetes are diagnosed with CD prior to diagnosis of type 1 diabetes [8]. Similarly, in the current study, in only one of 294 patients with type 1 diabetes, CD was diagnosed prior to diabetes (0.34%). Previous studies have also shown that CD diagnosis generally presents months, and even years, after type 1 diabetes onset [9, 10]. Rates of undiagnosed CD, as well as of other autoimmune diseases, have been reported higher in individuals with type 1 diabetes than in the general population [11]. This highlights the importance of periodic screening tests for CD.

One of the most important findings of the current study is the growth impairment observed among patients with both type 1 diabetes and CD, compared to patients with type 1 diabetes alone. Our data show that, on average, control subjects reached their target height, whereas patients with CD were, on average, significantly shorter than their genetic target height potential. Furthermore, poor adherence to GFD resulted in continuous growth impairment, compared with steady improvement among those with good adherence to a GFD (Figure 4b). Among patients who reached their final
target height, in those with poor adherence to a GFD, the gap between their final height and their genetic target height was, on average, wider. We found that two years following diagnosis of CD, heights of patients with poor adherence to a GFD deteriorated continually, while those with good adherence to a GFD improved continually. Our findings concur with a previous study [12] that did not show a significant improvement in mean height Z score in 7 patients with type 1 diabetes 12-24 months after diagnosis of CD. Several studies have examined the effects of a GFD on patients with type 1 diabetes. Saadah et al. [13] reported growth improvement following diagnosis of CD in patients with type 1 diabetes, and growth impairment in those who do not adhere to a GFD. Sanchez-Albuisa et al. [14] found height Z scores to improve subsequent to GFD adherence. However, Westman et al. [15] showed no effect of GFD adherence on growth parameters in 20 patients with type 1 diabetes and CD. Goh et al. [16] showed that one year after diagnosis of CD, children with asymptomatic CD and type 1 diabetes do not have significant changes in BMI, height Z-score or metabolic control.

The observation that the mean final height of CD patients was 5 cm lower than their mean target height emphasizes the need for a high index of suspicion for CD in subjects with type 1 diabetes for early diagnosis. Moreover, a decline in height Z score among patients with CD and type 1 diabetes calls for assessing adherence to a GFD.

We did not find a statistically significant difference in HbA1c levels between patients with CD and those without. Our study supports previous reports [13, 16], but differ from those of Amin et al. [17] in which patients with CD had better metabolic control as assessed by HbA1c levels. It is possible that the difference between these two studies is due to a difference in adherence to GFD among CD patients. Indeed, in our study, HbA1c levels in those who adhered to a GFD improved with time, compared to those who did not. It is possible that those who were not adherent to a GFD may have been less strict about their diabetes control, resulting in higher HbA1c levels. It is also possible that the dietary restrictions imposed by CD reduce patient ability to abide by their diabetes diet. Alternatively, the decreased insulin sensitivity documented among patients not adherent to GFD, may explain their poorer metabolic control [17].

Although we detected height impairment between patients with type 1 diabetes and CD, we did not find differences in diabetes control, absorption of micronutrients, or body weight. A recent study showed increased prevalence of positive antibodies against pituitary hormones among CD patients, causing growth-hormone deficiency [18]. We therefore recommend further investigation of this population.

This study is limited by the small number of patients with CD, and by its retrospective design. Finally, not all patients reached their final height. Strengths of the study include the screening of 93% of the patients with diabetes in one medical center, a biopsy-confirmed CD diagnosis; assessment of several laboratory parameters, and long-term follow-up of weight and height parameters. This compares with previous studies, which lacked a control group [15, 17] or follow-up data [4, 12]. Larger studies are needed to investigate if the severe height impairment in CD individuals with poor adherence to a GFD may in fact be related to their glycemic control.

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None of the authors have conflicts of interest.

Author contribution

A.A. conception and design of the study, generation, collection, assembly, analysis and/or interpretation of data, drafting or revision of the manuscript, approval of the final
version of the manuscript. G.H. analysis and/or interpretation of data, statistical analysis, drafting or revision of the manuscript. V.B. analysis and/or interpretation of data, statistical analysis, drafting or revision of the manuscript. C.G.B. drafting or revision of the manuscript. L.L.G. analysis and/or interpretation of data, drafting or revision of the manuscript. O.P.H. conception and design of the study, generation, collection, assembly, analysis and/or interpretation of data, drafting or revision of the manuscript, approval of the final version of the manuscript.

References


