Original article

Celiac disease in children with Type 1 Diabetes: impact of gluten free diet on diabetes management

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Abstract. *Background and aim of the work:* the coexistence of Type 1 Diabetes (T1D) and celiac disease (CD) has been long established. *Methods:* Between January 2000 and December 2009, biopsy-proven CD was diagnosed in 12 children with T1D, giving a prevalence of 4.8 % in our out-patient clinic population. For each patient with coexisting T1D and CD, two control subjects with T1D and without CD who matched for age, sex and duration of diabetes were chosen. Prospective study follow up lasted 24 months. At the enrolment time, and at 2-month intervals, time from diagnosis of T1D to diagnosis of CD, presence of gastrointestinal symptoms, HbA1c value, body mass index (BMI), Height and Weight SDS were collected by a single observer. Daily insulin requirements were also retained. *Results:* In 3 children, CD predated the onset of T1D and these children were excluded from the analysis. The 9 children who subsequently developed CD became earlier diabetic than control group (p=0.002). Eight of these children had CD diagnosis within 1 year after T1D onset. Seven out of 9 children were positive for TTG antibodies and all were positive for EMA. A significant increase in insulin requirement was found in CD children after 1 year of GFD (p= 0.02). The mean HbA1c value in CD children was higher than in the control subjects (p< 0.01).A significant increase in the insulin requirement after 1 year in the GFD compliant children was found. There was a significant improvement in height-SDS after institution of GFD in the GFD-compliant children. Families of children with both T1D and CD reported higher burden than those affected by T1D only (p= 0.001). The health care providers perceived family burden to increase with CD appearance (p< 0.05). *Conclusion:* Our study supports the importance of screening for CD in children with T1D 1. The early treatment with GFD of biopsy-confirmed CD children promotes a significant catch-up growth and prevents a growth failure during the follow-up. (www.actabiomedica.it)

Key words: Type 1 Diabetes, celiac disease, gluten free diet, metabolic control

Introduction

The coexistence of Type 1 Diabetes (T1D) and Celiac Disease (CD) has been long established (1). Genetic studies showed that these two disorders are associated, in particular, with HLA haplotype DQB1 (2). CD more occurs commonly in children with T1D (1.1-4.8%) than in the general population (0.01-0.03%) (3, 4) and these patients, being frequently asymptomatic, may be identified only through antibody screening. Serum gliadin (AGA), endomysial (EMA) and human tissutal transglutaminase (TTG) antibodies assays are the most widely used tests, and these are yearly recommended in children with diabetes in order to detect CD at an early preclinical silent stage (5). However, the optimal timing of Gluten-free diet (GFD) initiation in screening-identified children, with or without T1D, remains unclear.

In children with T1D and CD under GFD recurrent hypoglycemia and poor glycemic control were reported (6).

The patients with overt CD might permanently adhere to a GFD in order to prevent the increased risk of developing both malignant and non-malignant complications (7, 8). As concerns the role of a GFD in children and adolescents with coexisting T1D and silent CD conflicting opinions are present (7) and only little is known about the effects of this diet on metabolic control and growth in these patients (6, 9).

In the present longitudinal case-control study, the effects of a GFD after two years in terms of gastrointestinal symptoms, growth, and insulin requirement in children with T1D and biopsy-confirmed CD were investigated, and compared with paired subjects with T1D and negative celiac serology.

Subjects and methods

At the Regional Centre for Children and Adolescents with T1D of the University Hospital of Parma, Italy, all patients with T1D are regularly screened for CD by EMA and TTG tests. EMA and TTG levels are routinely assayed at diabetes diagnosis, bimonthly during the first year, and then every six months . Positive patients undergo a duodenal biopsy.

Between 1st January 2000 and 31st December 2009, biopsy-proven CD was diagnosed in 12 children with T1D, giving a prevalence of 4.8% in the out-patient clinic population which consisted of 251 children until 2009 (Table 1).

For each patient with coexisting T1D and CD, two control subjects with T1D and without CD who matched for age, sex and duration of diabetes were chosen. Prospective study follow up immediately started after biopsy-confirmed CD and lasted 24 months. At the enrolment time, and at 2-month intervals, time from diagnosis of T1D to diagnosis of CD, presence of gastrointestinal symptoms, HbA1c value, body mass index (BMI), Height and Weight SDS were collected by a single observer. Daily insulin requirements were also retained. All enrolled patients were evenly treated with four-a-day insulin injections.

EMA antibodies were measured by indirect immunofluorescence on cryostat sections of lower third primate oesophagus (Alifax, Padua, Italy) and anti-TTGs were determined in serum by enzyme-linked immunosorbent assay. The TTGs results were expressed as a percentage of the positive control serum (Alifax, Padua, Italy).

Small bowel biopsy was carried out under sedation by endoscopy. Multiple biopsy specimens were obtained from the distal duodenum/proximal jejunum. The specimens were examined by a pathologist and a paediatric gastroenterologist. CD was diagnosed according Marsh classification which includes total or subtotal villous atrophy with crypt hyperplasia and increased intraepithelial lymphocytes (10). All

Table 1. Clinical characteristics of children with Type 1 Diabetes and biopsy-Confirmed Celiac disease

Patient N.	Gender	Age at the diagnosis of T1D1,y	Age at the diagnosis of CD, y	Amtiendomysial Antibody (EMA)	TTG titer	Compliance Gluten-free Diet/Symptoms	Biopsy (Marsch)
1	F	4.6	4.9	+	247.4	Yes/None	3c
2	F	4.3	4.6	+	292.8	Yes/None	3c
3	F	13.8	14.8	+	145.0	Yes/ None	3
4	M	2.7	4.7	+	n.d.	Yes/ None	3c
5	M	11	11.3	+	79.6	Yes/ Diarrhea	2
6	M	10	10.6	+	356.4	Yes/ None	3c
7	M	1.9	2.3	+	253.3	Yes/ None	3
8	M	1	2	+	n.d.	Yes/ None	3c
9	M	2.1	2.7	+	245.3	Yes/ None	2
10	F	7.9	5.3	+	22.4	Yes/Abdominal pain	2
11	F	6.6	6	+	n.d.	No/Diarrhea	2
12	M	2.4	1.4	+	n.d.	No/Abdominal pain	2

children with biopsy-confirmed CD were treated with a Gluten-Free-Diet (GFD) under supervision of a dietician. EMA/TTG levels were measured in these CD-positive patients every 6 months until negative and were retained as a marker of good dietary compliance.

HbA1c values were measured by automatic high-pressure liquid chromatography (Bio-Rad Variant, Bio-Rad Laboratories, Hercules, CA). The inter-assay coefficient of variation (CV) was 4.5% with a HbA1c level of 5.2%, and 0.9% with a HbA1c level of 12.1%. The intra-assay CVs were 3.7 and 1.9% respectively. Normal values ranged from 4.4 to 5.9% (11). The grand mean of HbA1c values in our out-patients clinic population at the time of the study was 7.6±0.9%.

The standard deviation score (SDS) for height and weight was calculated using the equation (X-mean X/SD), where X refers to individual height or weight, and "X-mean" and SD are the mean height or weight and standard deviation for sex and age respectively . BMI was calculated as weight (in kilograms) divided by height (in meters) squared.

For each patient, one parent was requested to complete a five-item questionnaire about their perception of the burden on the family related to the adolescent's diabetes. Questions were scored from 1 to 5. A lower score indicated less burden. The details of the questionnaire have been previously published (12).

The data collected were analysed using SPSS for Windows and expressed as mean ± SD. A *P* value < 0.05 was considered significant.

Mean data from the case subjects were compared with those from the two matched control subjects using a student's *t* test. The same statistical procedure was used to evaluate the influence of the GFD on HbA1c, BMI, Height and Weight SDS, and insulin requirement.

The study was approved by the local University Ethical Committee; informed consent was obtained from parents, and from the children when appropriate.

Results

Two hundred and fifty one children with T1D were present in the database of our Centre registered until 2009. Children grand mean age at T1D diagnosis was 8.09±4.55 year (age range: 2-16). In 3 children, CD predated the onset of T1D and these children were excluded from the analysis. The 9 children who subsequently developed CD became earlier diabetic than control group (5.7±1.8 vs 7.7±1.2 years; t = -3.450, p=0.002). Eight of these children had CD diagnosis within 1 year after T1D onset. Seven out of 9 children were positive for TTG antibodies (79.6 to 356.4 U/mL) and all were positive for EMA.

A significant increase in insulin requirement was found in biopsy-confirmed CD children after 1 year of GFD (p= 0.02) (Table 2). In the same period of time, the mean HbA1c value in biopsy-confirmed CD children was higher (8.29±1.74 %) than in the control subjects (7.29±0.71%; p< 0.01).

At CD diagnosis, 5 out of the 9 children showed gastrointestinal symptoms on direct questioning, such as abdominal pain (5/5) or diarrhea (2/5). The other 4 children were asymptomatic. Symptoms resolved in all children after institution of a GFD except for 1 child that referred diarrhea; additional benefits such as higher physical strength and progress at school are reported in 4 children. All children referred to have been fully adherent to the GFD. Gastrointestinal symptoms were reported also by 1 out of 18 control children (5.5%); who did not report any symptoms denied having previously suffered from gastrointestinal symptoms.

Table 2. Change in Insulin Requirement over a 1-Year Period in Children With T1D1 and CD over GFD diet and in Children With T1D1 alone.

Parameters	Children With T1D1 and CD (N =9)		p	Children With T1D1 (N =18)		p
	Median Value at Diagnosis (Range)	Median Value after 1 year Follow up (Range)		Median Value at Diagnosis) (Range	Median Value after 1 year) Follow up (Range	
Insulin Requirement, U/Kg/die	0.36 (0.11-0.72)	0.59 (0.46-1.1)	.02*	0.39 (0.11-0.69)	0.59 (0.42-0.92)	.06

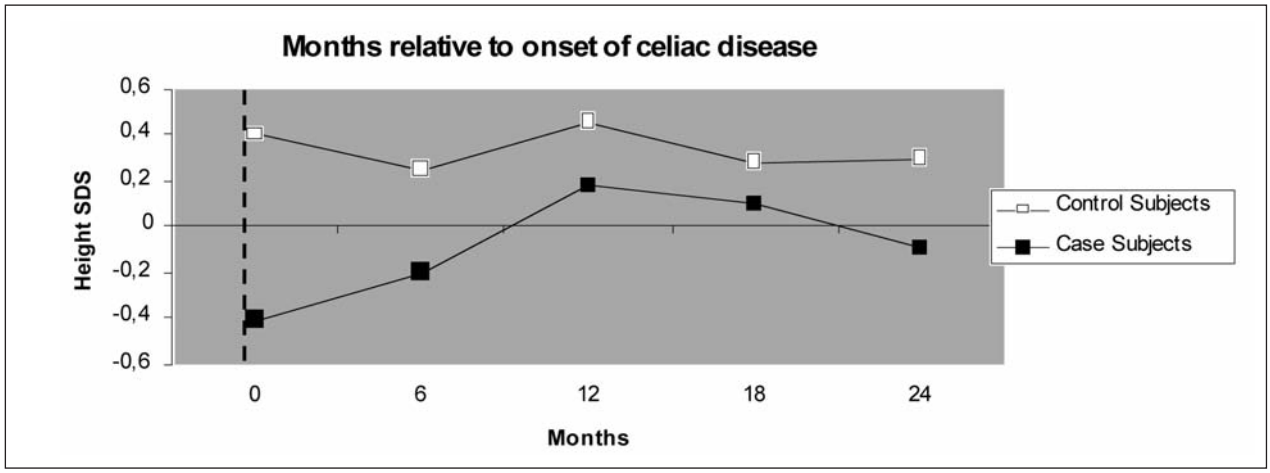

Figure 1. Height SDS means in case subjects with type 1 diabetes and celiac disease (Case Subjects) compared with control subjects without celiac disease (Control Subjects). Time 0 indicates diagnosis of celiac disease and GFD beginning in case subjects. Significant difference at this time was $P < 0.05$.

Table 3. Comparison of case and control subjects at the diagnosis of CD

	Case subjects	Control subjects
Height-sds	-0.41± 0.15*	0.13 ± 0.27
Weight-sds	0.11 ± 0.09	0.4 ± 0.13*
BMI-sds	0.23 ± 0.03	0.20 ± 0.14

Data are means ± SEM. *P = 0.001

At diagnosis of CD, the mean height-SDS resulted significantly lower in CD-positive patients compared with control patients ($p<0.05$) (Figure 1). One year after the institution of GFD a significant improvement in height-SDS in the GFD-compliant children ($P=0.001$) was observed (Table 3 and Figure 1). No significant improvement in weight-SDS and in BMI-SDS was shown (Table 3).

Families of children with both T1D and CD reported higher burden (38±11) than those affected by T1D only (21±12; $t= 3.64$, $p= 0.001$). As with parents, the health care providers perceived family burden to increase with CD appearance ($p< 0.05$).

Discussion

Clinicians are more aware of co-morbidities of diabetes and their complications, and screening frequency for CD has increased over the last decade as previously reported (13). More specific and sensitive antibodies to detect CD (TTG or EMA) are now available (14) and the use of these antibodies has increased over the last years. In addition, the rate of small bowel biopsy has also spread and, as a consequence, latent period between T1D and CD diagnosis has significantly shortened, resulting in an early CD detection and in a possible prevention or delay of CD-related complications (15).

Celiac disease is reported to be associated with Down and Turner syndromes and other conditions that have autoimmune features, such as T1D and autoimmune thyroid disease. Studies on children and adolescents with T1D have found a 6.2% to 7.7% prevalence of CD (16-18). The rationale for screening children with T1D for CD includes reducing hypoglycemia events, maximizing growth, bone health, and nutrition, and reducing long-term malignancy risks and mortality rates (19).

This 2-year retrospective follow-up study has provided additional evidence that children with T1D1 may have few classical symptoms of CD but are identified with screening. Moreover the increase of number of screening tests during the first year after diagnosis of CD is the major goal providing a better metabolic control and a relevant benefit in celiac disease symptoms.

Our results showed an increase in insulin requirement in T1D children on GFD after 1 year of CD diagnosis that is not evident after 2 years of CD diagnosis yet (Table 2). This probably could be related to the gluten free diet introduction. It is known that some gluten free foods have a higher glycaemic index. Another explanation could be due to a transitory psychological stress to have simultaneously two pathologies like T1D1 and CD.

We found that celiac autoimmunity was associated with lower weight and BMI even if not statistically significant, which may result from still delayed diagnosis and inadequate GFD.

We did not see differences in HbA1c and other metabolic parameter, consistent with many other studies (20, 21). No differences in episodes of severe hypoglycemia were also shown.

With regard the significant difference that we found about SDS-height between children with both CD and T1D and children with only T1D at the diagnosis, we show that it is abolished after 1 year of GFD. We hypothesize that a catch-up growth after starting a GFD in the first year is present. The catch-up growth is more pronounced and significant in height than in weight and BMI, even if some differences between the two groups of children are evident.

The appearance of CD increases family burden, and the data is confirmed by the health professional scores. This is reliable to the coexistence of a second disease that affects the quality of life of both parents and children.

In conclusion, optimal timing of screening and treatment of celiac autoimmunity remains to be determined. Therefore our study supports the importance of screening for CD in children with T1D 1. The early treatment with GFD of biopsy-confirmed CD children promotes a significant catch-up growth and prevents a growth failure during the follow-up.

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