Objective To evaluate the influence of biopsy-proven celiac disease (BPCD) on somatic development and metabolic parameters in children with type 1 diabetes mellitus (T1DM) in a multicenter survey.

Study design Within the Diabetes Patienten Verlaufsdokumentationssystem–Wiss project, data of 41 951 patients with T1DM, aged <20 years (52% males, mean age 13.9 years; mean duration of diabetes 5.5 years) were collected in 297 centers in Germany and Austria from 1995 to 2009.

Results The number of BPCD (0.6% in 1995; 1.3% in 2008) has increased over time. Patients with BPCD were significantly younger at diabetes onset (5.9 vs 8.3 years), had a significantly lower weight standard deviation score (SDS); (0.20 vs 0.43) and height SDS (-0.28 vs -0.03) \((P < .001, \text{each})\) compared with patients without celiac disease. No differences were found in hemoglobin A1c or numbers of severe hypoglycemia. In a subgroup of 9805 patients (183 with BPCD) significantly lower height and weight SDS \((P < .001)\) were still found after a 5-year follow-up.

Conclusions Screening for celiac disease is important in children with T1DM to prevent persistent growth failure. (J Pediatr 2011;158:589-93).

Celiac disease (CD) is a well-known comorbidity of type 1 diabetes (T1DM). Children with T1DM and CD may be symptom-free and the patients are identifiable by screening.\(^1,2\) Although symptom-free at diagnosis, the subsequent outcome years later may be malabsorption and growth failure.

Studies about anthropometric parameters in children and adolescents with T1DM and CD are inconclusive; some report no difference in height and weight;\(^2\) some found reductions in weight standard deviation score (SDS);\(^3-6\) some in body mass index (BMI) SDS\(^3,5,7\) whereas others could also show a reduction in height SDS.\(^4,5\)

The influence of CD on metabolic control is also a subject of controversy. Some studies report lower hemoglobin A1c (Hba1c) levels in patients with CD\(^6,7\) whereas others found no differences.\(^2,3,8\)

Studies have demonstrated an increase in weight\(^4,9\) and BMI\(^7,9\) after starting a gluten-free diet (GFD). Furthermore, some studies have shown a reduction in the number of hypoglycemic episodes and an improvement of diabetic control,\(^7\) particularly in those patients with malabsorption, whereas others report no effect on metabolic control\(^2,8,10\) or hypoglycemia.\(^2,6\)

In a previous study carried out by our group, 19 796 children and adolescents with T1DM have been analyzed. Patients with CD were characterized by decreased growth and height gain and lower Hba1c.\(^6\) Screening frequency for CD has increased over the last decade in Germany and Austria.\(^11\)

The aim of this follow-up study was to evaluate in a multicenter survey based on a prospective surveillance, whether with increasing screening, CD is detected earlier and to compare anthropometric parameters, metabolic control, and hypoglycemic events in patients with biopsy-proven CD to those without CD.

Based on the continuous diabetes data acquisition system for prospective surveillance (Diabetes Patienten Verlaufsdokumentationssystem), an observational study was performed.
multicenter survey was designed. Anonymous longitudinal data from patients are transmitted for central validation and analyses twice yearly. Inconsistent data are verified and reentered into the joint database. According to the guidelines of the German Diabetes Association, all centers are requested to document weight, height, BMI, blood pressure, inspection of injection sites and HbA1c levels at least once every 6 months.

Data from children and adolescents with T1DM under the age of 20, who were treated in 297 diabetes centers from Germany and Austria, were analyzed. From January 1995 to March 2009, data from 41,951 patients aged 0.1 to 20 years were included in this database. Additionally a 5-year follow-up was performed in a subgroup of 9,805 patients with complete and uninterrupted data set for the duration of 5 years.

CD Antibodies
CD was suspected if either tissue transglutaminase antibodies (tTGA) were higher than 10 U/mL with standard commercial enzyme-linked immunosorbent assay tests14,15 or endomy- sium antibodies (EMA) were positive, detected by standard commercial indirect immunofluorescence assay of monkey esophagus kits.14 Gliadin IgG and IgA were analyzed, as well using standard commercial enzyme-linked immunosorbent assay kits.

Small Bowel Biopsy
Findings of small bowel biopsy were interpreted using criteria defined by Marsh.16 A normal biopsy corresponded to Marsh 0, increased intraepithelial lymphocytes to Marsh 1, crypt hyperplasia to Marsh 2, and villous atrophy to Marsh 3.16 Criteria for the diagnosis of CD were positive CD-specific antibodies and Marsh criteria ≥ 1 in small bowel biopsy.

Glycemic Control
HbA1c was measured as a marker of glycemic control. To correct for different laboratory methods, HbA1c levels were mathematically standardized to the Diabetes Control and Complications Trial reference range of 4.05% to 6.05% to correct for different laboratory methods, HbA1c levels were mathematically standardized to the Diabetes Control and Complications Trial reference range of 4.05% to 6.05% with the MOM (multiple of the mean) transformation.17

Hypoglycemic Events
Severe hypoglycemia was defined as episodes with moderate or severe symptoms (Grade 2 and 3 according to ISPAD Consensus Guidelines 2000).18 Centers where hypoglycemia has never been documented were excluded from analysis of hypoglycemia frequency.

Demographic Data
BMI and BMI SDS: BMI, derived from weight in kilograms divided by square of height in meters, is an accepted measure of overweight and obesity in children, adolescents and adults. Using recent German reference values,19 BMI-SDS were calculated with the LMS method described by Cole.20

Statistical Analysis
Data were analyzed with the SAS software (Version 9.1; SAS Institute Inc., Cary, North Carolina). Data are presented as mean ± standard deviation (SD) for normal distributed variables or median and range for non-Gaussian distributed parameters. For group comparisons, nonparametric statistical tests (Kruskal-Wallis) were used, with adjustment for multiple comparisons by use of the method of Holm.

Results
The Diabetes Patienten Verlaufsdokumentationssystem–Wiss database comprised 41,951 patients with T1DM <20 years (52% male), with a mean (±SD) age of 13.9 ± 4.3 years, a duration of diabetes of 5.5 ± 4.2 years and age at diabetes onset of 8.4 ± 4.2 years. The mean daily insulin dose was 0.8 ± 0.3 IE/kg and the mean HbA1c was 8.2 ± 1.8%.

Trends in CD Antibody Measurement and Biopsy over the Last Decade
Annually measurements for CD antibodies (tTGA or EMA) increased from 0.1% in 1995 to 55% in 2008. Duration from diabetes onset to diagnosis of CD decreased from 9.3 years in 1995 to 2.8 years in 2008. The number of biopsy-proven cases of CD in the whole group increased from 0.6% in 1995 to 1.3% in 2008.

Description of Patients with versus Patients without CD
Analyzing the most recent treatment year, 22,273 of 41,951 patients have been screened for CD (tTGA or EMA or Gliadin antibodies), and 20.4% were positive. Overall, 15,075 of the patients have been screened for more specific CD antibodies only (tTGA or EMA), and 10.8% were positive.

Of all patients screened for CD, 17,661 have been classified as CD negative (either normal biopsy result or negative CD-specific antibodies), and in 411 patients, CD was confirmed by small bowel biopsy. A total of 394 had biopsy-proven total CD (Marsh 3), 17 had partial CD (Marsh 1-2). Forty-eight patients have undergone biopsy and had a normal mucosa.

Comparing 17,661 patients without CD to 411 patients with biopsy-proven CD, we found that CD was more prevalent in girls (58%) (P < .001), that patients with biopsy-proven CD were significantly younger at onset of diabetes (5.9 vs 8.3 years) (P < .001), and that they had a significantly longer duration of diabetes (7.7 vs 5.4 years) (P < .001) (Table).

With regard to anthropometric parameters, we found that patients with biopsy-proven CD had a significantly lower weight SDS (0.20 vs 0.44) and height SDS (−0.28 vs −0.03) (P < .01). In contrast, there was no statistically significant difference in BMI SDS (Table). Analyzing diabetes complications and metabolic control, we found no differences
in diabetes complications neither acute (severe hypoglycemic events or diabetic ketoacidosis) nor late complications (retinopathy, microalbuminuria or dyslipidemia), nor in metabolic control (Table).

Five-Year Follow-Up of Patients with Biopsy-Proven CD Compared with Patients without CD

In a 5-year follow-up of a subgroup of 9805 patients with complete, continuous data (183 of them with biopsy-proven CD), we found after 1 year a slightly lower weight SDS in patients with CD in comparison with patients without CD and T1DM (0.20 ± 0.90 vs 0.29 ± 0.91) without statistical significance. The difference became increasingly more pronounced within the 5-year follow-up and was statistically significant after 4 years (0.23 ± 0.93 vs 0.43 ± 0.90) (P = .02) (Figure 1).

Height SDS was also slightly lower in patients with biopsy-proven CD after 1 year (0.03 ± 1.08 vs 0.16 ± 0.95) without statistical significance, but the difference in height SDS became statistically significant (P = .03) in the second year of follow-up (−0.08 ± 0.10 vs 0.15 ± 0.95) and remained significant thereafter within the 5-year follow-up (Figure 2). There were no differences in BMI SDS and HbA1c between patients with and without CD after 1 year (BMI: 0.27 vs 0.28; HbA1c: 7.2% vs 7.1%) nor after 5 years (BMI: 0.41 vs 0.53; HbA1c: 7.6% vs 7.8%).

Five-Year Follow-Up of CD-Specific Antibodies in Patients with Biopsy-Proven CD

In the 5-year of follow-up we found after 1 year 15% of the patients having still positive CD antibodies (tTGA or EMA antibodies). CD antibody positivity increased over time to 18% after 3 years and 27% after 5 years. Patients with positive CD antibodies in the follow-up had a decreased weight and height SDS compared with patients with negative CD antibodies, but the difference was not statistically significant (data not shown).

Table. Summary of clinical and laboratory data from the most recent treatment year in young patients with T1DM and biopsy-proven CD compared with patients with T1DM without CD (either CD antibody negative or normal biopsy)

<table>
<thead>
<tr>
<th></th>
<th>Patients without T1DM and CD (n = 17 661)</th>
<th>Patients with T1DM and biopsy-proven CD (n = 411)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males/females (%)</td>
<td>52/48</td>
<td>42/58</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>13.7 (13.6; 13.8)</td>
<td>13.6 (13.2; 14.1)</td>
<td>.99</td>
</tr>
<tr>
<td>Diabetes onset (yrs)</td>
<td>8.3 (8.2; 8.4)</td>
<td>5.9 (5.5; 6.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetes duration (yrs)</td>
<td>5.4 (5.3; 5.5)</td>
<td>7.7 (7.3; 8.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Height SDS</td>
<td>−0.03 (−0.05; −0.02)</td>
<td>−0.28 (−0.39; −0.17)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Weight SDS</td>
<td>0.44 (0.42; 0.45)</td>
<td>0.20 (0.10; 0.31)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI SDS</td>
<td>0.53 (0.52; 0.55)</td>
<td>0.42 (0.34; 0.51)</td>
<td>.19</td>
</tr>
<tr>
<td>Insulin dose/kg/day</td>
<td>0.9 (0.86; 0.87)</td>
<td>0.8 (0.86; 0.93)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.2 (8.17; 8.22)</td>
<td>8.05 (7.89; 8.22)</td>
<td>.99</td>
</tr>
<tr>
<td>Severe hypoglycemia</td>
<td>12.9</td>
<td>9.8</td>
<td>.99</td>
</tr>
<tr>
<td>DKA</td>
<td>5.3</td>
<td>4.6</td>
<td>.99</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>29%</td>
<td>24%</td>
<td>.99</td>
</tr>
<tr>
<td>Retinopathy %</td>
<td>1.0%</td>
<td>1.9%</td>
<td>.99</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>10%</td>
<td>6.5%</td>
<td>.99</td>
</tr>
</tbody>
</table>

Severe hypoglycemia, Events/100 patient years; DKA, diabetic ketoacidosis.
Values in bold significant.
Data are presented as mean and confidence limits or percentage.

Discussion

Data from this study support and extend previous findings documenting a higher prevalence of CD in females with T1DM,6 that patients with CD are significantly younger at diabetes onset,6,11,21 and that they have a significantly longer duration of diabetes at the time of diagnosis of CD.6,11,21 Clinicians are more aware of comorbidities of diabetes and their complications, and screening frequency for CD has increased over the last decade as reported previously from our group.11 More specific and sensitive antibodies to detect CD (tTGA or EMA) are now available,22 and the use of these antibodies have increased over the last decade in Germany and Austria. In addition, the rate of small bowel biopsy has also increased and, as a consequence, time between diagnosis of T1DM and CD has significantly decreased, resulting in an earlier
In conclusion, we can demonstrate that screening frequency for CD and frequency of biopsy has increased over the last decade and no difference in metabolic control, and severe hypoglycemia could be found between patients with and without CD. There is still a significant difference in height and weight SDS, which may result from still delayed diagnosis and inadequate GFD. Therefore our study supports the importance of screening for CD in children with T1DM and close follow-up of patients with CD to prevent growth failure.

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References


Detection of CD and possibly a reduction of CD-associated complications. Compared with our previous study the number of patients with CD specific antibodies has increased within the last decade from 6.7% to 10.8%, which might reflect either a real increase in the prevalence of CD or the result of increasing screening frequency or the result of the use of more specific and sensitive antibody tests.

There are several studies with smaller numbers of patients evaluating the influence of either biopsy proven CD or CD antibody positivity on somatic development in children with T1DM and CD. These studies report reductions in weight and height SDS but also in BMI SDS. In this large multicenter study we confirm findings from a previous study from our group that patients with CD have still a significantly lower height and weight SDS compared with patients without diabetes and CD. In contrast, we found no difference in BMI SDS any longer. As the majority of the patients in our study with CD had total villous atrophy (394 compared with 17 patients with partial CD), the significant difference in weight and height SDS in patients with CD might be explained by malabsorption caused by CD, especially in patients with total villous atrophy. Furthermore, there are still some patients included in our database from former years, where there has been a longer delay between diagnosis of T1DM and CD. Another reason for the lower height and weight SDS might be that not all patients have been screened at diabetes onset, and, hence, there might be a delay in diagnosis.

In assessment of the subgroup of patients in a 5-year follow-up, we found after 1 year only a slight reduction in weight and height SDS, without statistical significance in patients with CD. We hypothesize that there is a catch-up growth after starting a GFD in the first year. The catch-up growth is more pronounced in weight than in height. The difference in weight SDS became more pronounced within 5 years and was statistically significant not before 4 years. In contrast, height was already significantly lower in patients with CD after 1 year of follow-up, indicating that the gain in weight is not sufficient enough to reduce the difference in height.

Another explanation for the difference in weight SDS during the follow-up might be due to inadequate compliance to GFD. As we demonstrated in a subgroup of patients in the 5-year follow-up, CD specific antibodies remained positive in 15% of the patients with CD after one year and increased within the 5 years up to 27%. Patients, especially those with silent CD, may not accept the second disease. Thus long-term dietary compliance seems to be problematic and patients diagnosed because of clinical manifestations have higher compliance rates than those identified through screening. We did not find any difference in HbA1c levels between patients with CD compared with patients without CD; this is in contrast to our previous study. One explanation is that lower HbA1c levels in patients with CD have been found especially in patients with total villous atrophy, being an indicator for impaired absorption of nutrients. Because of an earlier diagnosis of CD, the damage of intestinal mucosa might have been reduced. Several studies have shown that CD and even subclinical CD in children with diabetes may increase the risk of hypoglycemia, and early identification and treatment may reduce the risk. In this study we found no difference in severe hypoglycemic events between patients with BPCD compared with patients without CD; this might also be the result of earlier detection and treatment of CD.

Figure 2. Changes in height SDS over a 5-year follow-up in patients with T1DM and biopsy-proven CD (black squares) compared with patients with T1DM without CD (white triangle). Asterisk indicates significant difference (P < .05).


Appendix

Anthropometry, Metabolic Control, and Follow-Up in Children and Adolescents with Type 1 Diabetes Mellitus and Biopsy-Proven Celiac Disease