Clinical Benefit of a Gluten-Free Diet in Type 1 Diabetic Children With Screening-Detected Celiac Disease

A population-based screening study with 2 years' follow-up

DORTE HANSEN, MD, PHD[1]
BENDT BROCK-JACOBSEN, MD, DMS[1]
ELISABETH LUND, MD[2]
CHRISTINA BJØRN, MD[3]
LARS P. HANSEN, MD[4]
CHRISTIAN NIELSEN, CS[5]
CLAUS FENGER, MD, DMS[6]
SØREN T. LILLEVANG, MD, PHD[5]
STEFFEN HUSBY, MD, DMS[1]

OBJECTIVE — This study was performed to *1*) determine the prevalence of celiac disease in Danish children with type 1 diabetes and *2*) estimate the clinical effects of a gluten-free diet (GFD) in patients with diabetes and celiac disease.

RESEARCH DESIGN AND METHODS — In a region comprising 24% of the Danish population, all patients <16 years old with type 1 diabetes were identified and 269 (89%) were included in the study. The diagnosis of celiac disease was suspected in patients with endomysium and tissue transglutaminase antibodies in serum and confirmed by intestinal biopsy. Patients with celiac disease were followed for 2 years while consuming a GFD.

RESULTS — In 28 of 33 patients with celiac antibodies, an intestinal biopsy showed villous atrophy. In 5 patients, celiac disease had been diagnosed previously, giving an overall prevalence of 12.3% (95% CI 8.6–16.9). Patients with celiac disease had a lower SD score (SDS) for height ($P < 0.001$) and weight ($P = 0.002$) than patients without celiac disease and were significantly younger at diabetes onset ($P = 0.041$). A GFD was obtained in 31 of 33 patients. After 2 years of follow-up, there was an increase in weight SDS ($P = 0.006$) and in children <14 years old an increase in height SDS ($P = 0.036$). An increase in hemoglobin ($P = 0.002$) and serum ferritin ($P = 0.020$) was found, whereas HbA_{1c} remained unchanged ($P = 0.311$) during follow-up.

CONCLUSIONS — This population-based study showed the highest reported prevalence of celiac disease in type 1 diabetes in Europe. Patients with celiac disease showed clinical improvements with a GFD. We recommend screening for celiac disease in all children with type 1 diabetes.

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It is well established that celiac disease is overrepresented in different autoimmune diseases, notably type 1 diabetes. Also celiac disease itself has features characteristic of an autoimmune disease. In numerous studies from European countries over the last 30 years, the prevalence of celiac disease in children with type 1 diabetes has been reported to be 2–8% (1). Surprisingly, no strictly population-based studies have been published, as judged from the presented material, even though two large studies from Italy (2) and Germany (3) comprise a considerable percentage of the national diabetic population.

In Denmark, the prevalence of recognized cases of celiac disease in the general population is very low compared with the prevalence in other neighboring countries (4,5). On the other hand, a high incidence of childhood type 1 diabetes has been documented (6). Therefore, it appeared to be particularly interesting to determine the prevalence of celiac disease in Danish type 1 diabetic children. In a preliminary study, we found a prevalence of celiac disease of 10% in Danish type 1 diabetic children (7). In the present study, we extended this investigation to a larger population. The study was performed in a strictly population-based design, including all type 1 diabetic children from a region representing one-fourth of the Danish population.

Despite the high prevalence of celiac disease in type 1 diabetes, the issue of routine screening of all type 1 diabetic children has been much debated (8). Many diabetic patients in whom celiac disease has been diagnosed through screening are asymptomatic or have nonspecific symptoms of celiac disease (1). The benefits of a gluten-free diet (GFD) in those patients, both in the short- and long-term, are not well established. In a few previous studies of patients with both type 1 diabetes and celiac disease, the effect of a GFD on symptoms, growth, and metabolic control has been investigated, but with inconsistent results (9–12). In the present study, the clinical course in diabetic children with celiac disease was evaluated during a 2-year follow-up period when they consumed a GFD.

RESEARCH DESIGN AND METHODS

— In Denmark, the treatment of all children with type 1 diabetes is restricted to the pediatric departments within the hospital-based health system. The present study was performed in the region of southern Denmark consisting of

From the [1]Department of Pediatrics, Odense University Hospital, Odense, Denmark; the [2]Department of Pediatrics, Kolding Hospital, Kolding, Denmark; the [3]Deparment of Pediatrics, Esbjerg Hospital, Esbjerg, Denmark; the [4]Department of Pediatrics, Sonderborg Hospital, Sonderborg, Denmark; the [5]Department of Clinical Immunology, Odense University Hospital, Odense, Denmark; and the [6]Department of Pathology, Odense University Hospital, Odense, Denmark.

Address correspondence and reprint requests to Dorte Hansen, Department of Pediatrics, Odense University Hospital, Sdr. Boulevard 29, 5000 Odense C, Denmark. E-mail: dorte.hansen@dadlnet.dk.

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Abbreviations: AGA, anti-gliadin antibody; EMA, antibodies against endomysium; GFD, gluten-free diet; tTGA, anti-tissue transglutaminase antibody.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—*Clinical characteristics of diabetic patients with celiac disease compared with diabetic patients without celiac disease*

Characteristics	Diabetic patients with celiac disease	Diabetic patients without celiac disease	*P* value
n	33	236	
Sex (female/male)	17/16	110/126	0.710
Age (years)	9.4 (2.0–16.0)	11.1 (1.5–15.9)	0.096
Age at diabetes onset (years)	5.8 (0.7–12.7)	6.6 (0.6–14.9)	0.042
Height SDS	−0.65 (−3.5 to 2.1)	0.4 (−3.2 to 2.8)	<0.001
Weight SDS	0.1 (−1.4 to 1.4)	0.5 (−1.9 to 5.0)	0.002
Prevalence of symptoms (%)	84.8	25.4	<0.001

*Data are median (range) unless otherwise indicated.

four counties, each with one pediatric department. All children <16 years old from the pediatric departments in the four counties were included. In the county of Funen, patient identification was performed in 1997 as previously reported (7). In the remaining three counties, the children were investigated through 2002–2003.

At study entry, all patients were interviewed by the doctor about symptoms compatible with celiac disease, and a symptom questionnaire was filled out. Height and weight were registered. Blood samples were obtained and analyzed for specific antibodies. Serum anti-gliadin antibodies (IgG and IgA AGAs) were measured by enzyme-linked immunosorbent assay (13); cutoff value was 15 arbitrary units (AU). Serum anti-tissue transglutaminase antibodies (IgA tTGAs) were measured by enzyme-linked immunosorbent assay (INOVA Diagnostics); cutoff value was 20 AU. Antibodies against endomysium (IgA EMA) in serum were measured by indirect immunofluorescence using monkey esophagus tissue (INOVA Diagnostics) as substrate. The fluorescence intensity was reported semiquantitatively (0, 1+, 2+, and 3+). In patients from the county of Funen, antibody analyses were initially performed at another laboratory (7). Frozen sera from those patients were reanalyzed by the above mentioned methods, and identical results were obtained.

In patients only positive for IgG AGA, total serum IgA was determined to exclude IgA deficiency. In patients with positive IgA AGA, EMA, and/or tTGA antibodies, an intestinal biopsy was performed. Endoscopic duodenal biopsy samples were taken and examined histologically by a gastroenterological pathologist. In patients with partial or total villous atrophy, a GFD was instituted after careful instructions by a dietitian. Subsequently, patients were seen by the doctor in the outpatient clinic every 3rd month for a minimum period of 2 years. At each visit, celiac disease–related symptoms and growth parameters were schematically registered. Blood samples were taken, and measurements of celiac antibodies and other hematological parameters (hemoglobin, mean corpuscular volume, serum ferritin, folate, cobalamin, glycosylated hemoglobin, ionized calcium, and alanine aminotransferase) were performed using routine analytical methods. After 2 years follow-up with the patient consuming a GFD, another intestinal biopsy was offered to all patients with celiac disease.

In patients with positive celiac antibodies, HLA typing was performed. HLA-DQB1* and -DQA1* typing was done by PCR amplification with sequence-specific primers. DRB1* alleles were detected by PCR amplification with sequence-specific oligonucleotides using the One Lambda Lab Type rSSO typing system for HLA typing.

All patients and their parents gave informed written consent, and the study was approved by the regional ethical committees. The study was performed in accordance with Helsinki Declaration II.

Statistics

The statistical package Intercooled STATA 7 was used for the statistical analyses. For comparisons between groups, the Mann-Whitney rank-sum test and Fisher's exact test were used; 95% CIs for proportions were calculated by use of the binomial distribution. The follow-up data were analyzed using the Wilcoxon signed-rank test for paired observations. *P* values <0.05 were considered statistically significant.

RESULTS — A total of 303 patients with type 1 diabetes were identified in the four counties, and 269 (89%) accepted to participate. The included patients had a median age of 10.9 years (range 1.5–16.0) and a median duration of diabetes of 3.1 years (range 0.1–14.5). Five of them had a previous diagnosis of celiac disease and were consuming a GFD.

IgA AGAs were found in 11 and IgG AGAs in 28 of the patients investigated. All patients with IgA AGAs also had EMAs and tTGAs. Sixteen patients with low titers (<30 AU) of IgG AGA had neither EMA nor tTGA. In those patients IgA deficiency was excluded, and they were not further investigated. EMAs and tTGAs were found in 33 of 269 patients, and there was an absolute correlation between the presence of these antibodies. In all but one patient, an intestinal biopsy was obtained. In 28 of 32 patients, the biopsy showed partial or total crypthyperplastic villous atrophy. In four patients, the biopsy showed normal intestinal mucosa; although in one of them, increased lymphocyte infiltration in lamina propria was noted. Thus, including the 5 patients previously diagnosed with celiac disease, a total of 33 of 269 patients (17 female and 16 male) had celiac disease, corresponding to a prevalence of 12.3% (95% CI 8.6–16.9).

Table 1 presents clinical characteristics of diabetic subjects with celiac disease compared with diabetic subjects without celiac disease. Patients with celiac disease had a significantly lower age at diabetes onset ($P = 0.042$), whereas there was no difference comparing age and sex in the two groups. The patients with celiac disease had a significantly lower height SD score (SDS) ($P < 0.001$) and weight SDS ($P = 0.002$). In the interview, they reported symptoms of celiac disease significantly more often ($P < 0.001$) than patients without celiac disease. Table 2 presents the prevalence of celiac disease–related symptoms in both groups. In four patients with celiac disease, the symptoms were first recognized in retrospect after a GFD was instituted. Only 5 of 33 (15%) patients with celiac disease had no clinical signs of the disease.

HLA genotyping, performed only in the patients with celiac disease, showed the HLA DQ2 genotype in 28 of 33 (85%) of the patients, HLA DQ8 in 12 of 33 (36%), and both DQ2 and DQ8 in 8 of 33 (24%). A single patient had neither the HLA DQ2 nor the DQ8 genotype. The four patients with celiac antibodies but normal biopsy findings all had the HLA DQ2 and/or DQ8 genotype.

Table 2—*Prevalence of celiac disease–related symptoms reported by the diabetic patients before screening for celiac disease was performed and by patients with celiac disease after 2 years of consuming a GFD*

Symptoms*	Patients without celiac disease	Patients with celiac disease	*P* value	Patients consuming a GFD
n	236	33		
Abdominal pain	23 (9.7)	16 (48.5)	<0.001	0†
Loose and/or frequent stools	15 (6.4)	7 (21.2)	0.010	2 (6.5)
Bloating	24 (10.2)	9 (27.2)	0.021	3 (9.7)
Constipation	2 (0.8)	3 (9.0)	0.014	0
Arthralgias	10 (4.2)	7 (21.2)	0.002	1 (3.2)
Tiredness	6 (2.5)	8 (24.2)	<0.001	0
Frequent hypoglycemia	1 (0.4)	2 (6.0)	0.040	0
Aphthous ulcers	1 (0.4)	1 (3.0)	0.230	0
Tooth enamel defects	8 (3.4)	3 (9.0)	0.139	—
Hemoglobin <6.5 mmol/l	—	4 (12.1)	—	0
Serum ferritin <15 μg/l	—	9 (27.2)	—	1 (3.2)
Thyroid antibodies	13 (5.5)	3 (9.0)	0.425	—
Dermatitis herpetiformis	0	1 (3.0)	0.122	—
Autoimmune hypothyroiditis	0	4 (12.1)	<0.001	—

Data are *n* (%). *A few patients with celiac disease first reported symptoms in retrospect after experiencing the relief with the GFD (three patients reported abdominal pain, a single patient reported abdominal pain, diarrhea, and tiredness, and another patient reported arthralgias). †Some patients reported abdominal pain at breach of the diet.

A GFD was initiated in 31 of 33 patients with celiac disease, whereas 2 asymptomatic patients refused to start the diet. In 24 of 31 patients, the celiac antibodies disappeared, confirming the diagnosis of celiac disease according to the revised European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) criteria (14). In seven patients with variable compliance to the GFD, the celiac antibodies declined during follow-up but never became negative (Fig. 1). In many patients, the decrease in celiac antibody titers was slow, and the antibodies became negative after 1–2 years on a strict diet. Almost all of the symptomatic patients experienced relief of symptoms while consuming the GFD (Table 2), whereas three asymptomatic patients experienced no changes. Table 3 demonstrates the development of different clinical and biochemical parameters at 6, 12, 18, and 24 months of follow-up compared with baseline. After 2 years of follow-up, there was a significant increase in weight SDS ($P = 0.002$), whereas the increase in height SDS ($P = 0.073$) did not reach significance. However, when patients who were >14 years old at the onset of the study were excluded, there was also a significant increase in height SDS ($P = 0.036$). There was a significant increase in hemoglobin ($P = 0.001$), mean corpuscular volume ($P = 0.020$), and serum ferritin ($P = 0.012$). A significant increase in serum folate was found after 6, 12, and 18 months, but the increase did not reach statistical significance at 24 months ($P = 0.076$). No significant change in HbA_{1c} (A1C) was seen during the 2 years of follow-up. In 18 of 33 patients, a second intestinal biopsy was performed after they consumed a GFD for 2 years. In 14 patients, the intestinal mucosa had normalized, whereas in 4 patients, who did not follow a strict diet, the mucosa had only partially recovered.

CONCLUSIONS — In the present study, we investigated a total of 269 children <16 years old, representing 89% of all children with type 1 diabetes in this age-group in an area representing ~25% of the Danish population. In this population, we found a prevalence of celiac disease of 12.3% (95% CI 8.6–16.9). The prevalence of celiac disease might be even higher. A single patient who had no biopsy sample taken still has very high celiac antibody titers. Four patients with celiac antibodies, all HLA DQ2 and/or DQ8 positive, had normal biopsy findings but may have latent celiac disease. A single patient, who was antibody negative at the primary screening, later developed symptoms of celiac disease, and the diagnosis was confirmed by celiac antibodies and intestinal biopsy. Finally, patients with celiac disease might have been missed because of false-negative serology results (15). The high prevalence of celiac disease among Danish diabetic patients is surprising in view of the low prevalence of recognized celiac disease in the general population in Denmark (4). A similar screening study in the general population might possibly reveal a prevalence of celiac disease of ~1% as found in many other European countries (16).

In previous studies, most of which are from other European countries, the prevalence of celiac disease in type 1 diabetic children has generally been lower than that in the present study (1). Genetic and environmental factors might account for some of the regional differences. However, the higher celiac disease prevalence in the present study might also be explained by differences in study conditions: *1*) this study was population-based, whereas previous studies have been based on outpatient clinics with no detailed reports of demographic data; *2*) we used sensitive and specific celiac antibody tests

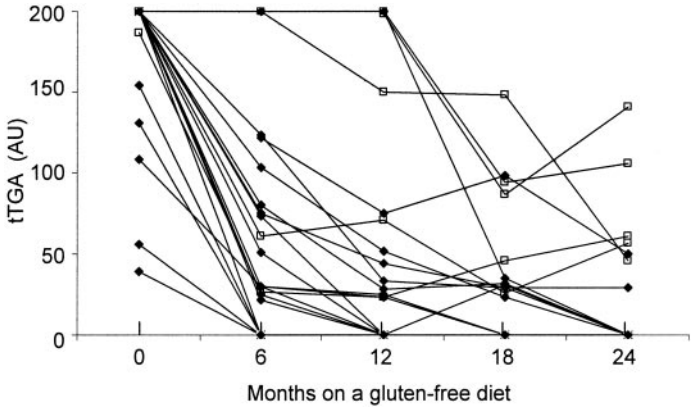

Figure 1—*The development of tissue transglutaminase antibodies in children with type 1 diabetes and celiac disease, measured 0, 6, 12, 18, and 24 months after starting a GFD. ◆, patients adherent to GFD; □, patients not strictly adherent to GFD.*

Table 3—*Development of different clinical parameters in patients with type 1 diabetes and celiac disease measured before and after 6, 12, 18, and 24 months of starting a GFD*

		Duration of the GFD					
	n	Baseline	6 months	12 months	18 months	24 months	*P* value
Weight SDS	27	−0.12	0.11	0.25*	0.30*	0.35*	0.002
Height SDS	27	−0.46	−0.37	−0.31	−0.24	−0.26	0.073
A1C (%)	28	8.6	9.0	8.8	8.7	8.4	0.300
Hemoglobin (mmol/l)	25	7.6	8.4*	8.3*	8.4*	8.3*	0.001
Mean corpuscular volume (fl)	25	81.6	83.0	83.8	83.5	84.4*	0.020
Ferritin (μg/l)	26	26.0	31.1	39.8*	44*	37.9*	0.012
Folate (nmol/l)	24	489	606*	637*	639*	581	0.076
Cobalamin (pmol/l)	25	387	416	415	395	379	0.872
Calcium (mmol/l)	23	1.24	1.26*	1.26*	1.26*	1.26*	0.044
ALAT (units/l)	26	24.9	27.2	21.0	19.7*	20.6	0.062

Data are means of the group. At 24 months follow-up, the corresponding *P* values are also presented. Only a few follow-up data were available from patients with celiac disease diagnosed before this study. The increase in hemoglobin was not caused by the increase in hemoglobin seen in male puberty. Paired comparisons were performed by Wilcoxon signed-ranked test. *Significant changes from baseline.

(IgA EMAs and tTGAs) (17); *3*) in contrast with many other studies, all but one of the celiac antibody-positive patients in the present study did consent to intestinal biopsy; and *4*) we also included patients with previously diagnosed celiac disease. Our conclusion is that the much lower prevalences of celiac disease in type 1 diabetes found in some European countries might be underestimates of the true prevalence in the population.

In the present study, patients with celiac disease had a significantly earlier onset of diabetes compared with diabetic subjects without celiac disease (Table 1). This observation is in agreement with some (3,18,19) but not all (20–22) previous studies. In a recent Italian multicenter study in which 4,322 young patients with type 1 diabetes were investigated, a threefold higher risk for celiac disease was found in children <4 years old at the onset of diabetes than in those >9 years old (2). In Denmark, an increase in the incidence of type 1 diabetes in children <5 years old has been observed during recent years (6). If the association between young age at diabetes onset and the development of celiac disease is consistent, an increase in the number of patients with both diseases might be expected.

Most patients with celiac disease diagnosed through screening are described as having subclinical celiac disease (23). In the present study, only 5 of 33 (15%) of diabetic subjects with celiac disease had the diagnosis before our screening even though the majority of the patients with celiac disease reported symptoms of celiac disease in their interview. Only 5 patients with celiac disease presented with no symptoms or biochemical signs of celiac disease. This observation supports recommendations of screening for celiac disease in type 1 diabetic patients. Despite an increased clinical awareness from the physicians, celiac disease may remain undiagnosed in many patients with type 1 diabetes if regular screening is not performed.

Although a considerable number of screening studies have been performed, only a few studies described the effects of a subsequent GFD in patients with type 1 diabetes and celiac disease. In the present study 31 of 33 patients with both diseases were followed while they consumed a GFD for at least 2 years. During follow-up, the symptomatic patients experienced increased well-being. In a few patients with variable compliance to the diet, minor symptoms remained (Table 2). The majority of patients became celiac antibody negative after 3 to 24 months after starting the GFD. At diagnosis of celiac disease, we found that patients were stunted in their growth, with both height and weight SDSs being affected, compared with diabetic patients without celiac disease (Table 1). After 2 years of consuming a GFD, patients with celiac disease had a significant increase in weight SDS. In patients <14 years old, a significant increase in height SDS was also seen, reflecting the potential for growth in younger patients. In accordance with this finding, some previous researchers have reported an impairment of growth in patients with celiac disease and type 1 diabetes compared with diabetic control subjects (3,9). In longitudinal studies of diabetic patients consuming a GFD, Amin et al. (9) found an increase in BMI SDS, Saadah et al. (10) showed an increase in weight-for-age *z* scores, and Sanchez-Albisua et al. (12) found an increase in height SDS in patients with good dietary compliance. On the other hand, Rami et al. (11) and Westman et al. (24) found no improvement in neither BMI SDS or height SDS on a GFD. However, most follow-up studies have been small, and interpretation of the results is difficult because of variable dietary compliance in the patients investigated.

In the present study, we evaluated hematological markers, often affected in patients with celiac disease. Iron deficiency anemia is a frequent symptom in children with celiac disease (23). In our patients, we found a significant increase in hemoglobin, mean corpuscular volume, and serum ferritin after 2 years of consuming a GFD. Acerini et al. (25) measured the same parameters longitudinally in a small group of seven diabetic patients consuming a GFD but could not demonstrate any significant changes. An important aspect in patients with type 1 diabetes and celiac disease is the metabolic control with a GFD. In the present study, A1C was almost unchanged in patients consuming a GFD. In a few studies, a decrease in A1C was seen in diabetic subjects after a GFD (9,12), whereas others could not demonstrate any improvements (10,11,25,26). However, A1C may not by itself reflect the metabolic control in diabetic subjects consuming a GFD. In the present study, two patients experienced fewer episodes of hypoglycemia after the start of the GFD. Mohn et al. (27) also described fre-

quent episodes of hypoglycemia in diabetic children with celiac disease with a reduction in the hypoglycemic risk with a GFD. Continuous blood glucose monitoring and careful registration of insulin requirements before and after the start of the GFD would give further valuable information about the metabolic control.

In summary, in a population-based study of Danish children with type 1 diabetes, we found a high prevalence of celiac disease. The occurrence of celiac disease was associated with young age at diabetes onset. Patients with celiac disease were stunted in their growth, and many had unrecognized symptoms of celiac disease. Longitudinal follow-up after consumption of a GFD in this cohort of patients demonstrated symptom relief and improvements in growth parameters, but no significant changes in metabolic control. The data lend support to recommendations of regular screening for celiac disease in all children with type 1 diabetes.

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